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Cellulose an ageless renewable green nanomaterial for medical applications: An overview of ionic liquids in extraction, separation and dissolution of cellulose

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Contents

Abstract

Cellulose is a renewable natural fiber, which has gained enormous and significant research interest and evolved as the prime and promising candidate for replacing synthetic fibers. The various sources of cellulose, which is one of the world's most ubiquitous and renewable biopolymer resources, include trees, plants, tunicate and bacteria. The renewable biomaterial in the form of nanocellulose and its composites have been included in this review having the broad range of medical applications, viz; tissue engineering, cardiovascular surgery, dental, pharmaceuticals, veterinary, adhesion barriers and skin therapy. These grafts are being fabricated from biodegradable materials. Bacterial cellulose is also an emerging renewable biomaterial with immense potential in biomedical field. The fabrication methods, characteristic properties and various overwhelming applications of cellulosic composites are explicitly elucidated in this review. The crux of this review is to exhibit the latest state of art, development in the field of cellulosic nanocomposite science and technology research and their applications towards biomedical field. Among the fourteen principle of green chemistry the two key principles i.e. using environmentally preferable solvents and bio-renewable feed-stocks covers in dissolution of cellulose in ionic liquids (ILs). In addition, this review covers about the comprehensive extraction and dissolution of cellulose and nanocellulose using ILs.

1. Introduction

Sustainability is briskly moving from the wings to the focal point of the researchers. Overutilization of nonrenewable and sustainable assets, and also the collateral creation of waste has to lead the world to a point of crisis. Green chemistry, along with other advanced sciences must play a prominent role in realizing a feasible society. This review will bear some significance with scholastics, scientists, experts, business pioneers, strategy creators, and students, and in addition, people who need to know the fundamentals of the science and innovation of sustainability. The present century has validated extraordinary progress in green technology in the field of materials science through the development of biocomposites due to eco-sustainability issues.

The hydrophilic attributes of microfibrillated cellulose (MFC) have lead the greater part of the research to be centered around nano-composites in light of hydrophilic matrices as they witness potential advantages like low cost and low density per unit volume, reduced tool wear and acceptable specific strength besides their renewable and degradable characteristics. However, certain drawbacks such as incompatibility with the hydrophobic polymer matrix, the tendency to form aggregates during processing and water-swellable nature of cellulose, especially in its disordered regions, greatly reduce the potential of natural fibers to be used as reinforcement in polymers. Moreover, properties of cellulosic fibers are strongly influenced by their origins as well as different parts of a plant.

Presently, academia and industries are investigating the use of cellulose nanostructures as reinforcements in order enhance the thermal, mechanical, dimensional stability and other types of functional properties (electrical /electromagnetic shielding/ barrier/fire retardant/triggered biodegradability/solvent resistance) of the composite materials with the added advantages of eco-friendliness for various advanced applications [1-4]. In the present review, the focus will be on the conventional and advanced extraction techniques of renewable cellulosic nanostructures and its application in the medical field.

Increase in the number of the annual number of scientific publications in the area of cellulose nanocomposite with the medical application and radial graphs with the number of scientific works in web of science categories since 2006 has been shown below in **Fig. 1**.
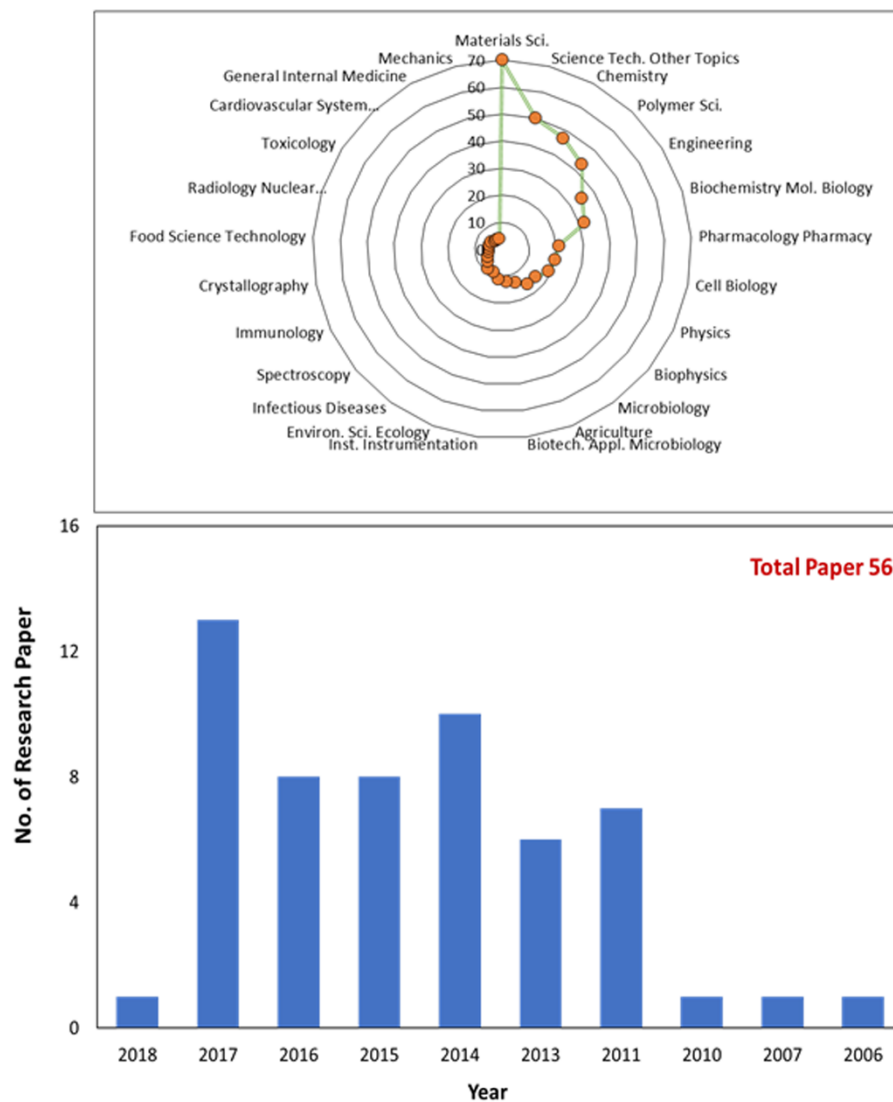
Fig. 1. Illustration of the annual number of scientific publications since 2006, using the search terms "Cellulose nanocomposite and further refined by word 'Medical' in web of science on 31 March 2018. The radial graphs display the number of scientific works in web of science categories.

Recently, cellulosic nanocomposites were reviewed by pioneering researchers regarding their production and the effect of the source of biomass on the morphological characteristics of the nanostructures, as well as the chemical functionalization that can be accomplished from the hydroxyl radicals on their surface. In addition, the chemical and physical properties of nanocellulose were connected with their applications in the perspective of energy, biomedicine, in nanocomposites and particularly for environmental issues [5-14]. Furthermore, research on

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advancements of nanoscience and nanotechnology encourage researchers to develop nanomaterials from renewable bio-resources, which have progressively lowered environmental impact. Seabra et al [6] reviewed about cellulose nanocrystals as carriers in medicine and their toxicities. Capron et al [8] reported the behaviour of nanocelluloses at gas/liquid and liquid/liquid interfaces and explained how they allow the design of materials with tailored properties. In addition, they also proposed that controlling of nanocelluloses at interfaces might be one of the solutions to enable a generalized method towards the development of materials.

Although the researchers in the field of nanocellulose made pioneering observations, still there is a space for current research. Cellulose and nanocellulose contain a class of nanostructures with different biological, physicochemical and morphological properties. In this regard, more detailed up to date discussions and explicit explanations must be required for the members of this class. This review is a collection of the literature that exist until the date on the cellulose nanocomposites. The pivotal aim of this review is to provide an overview of physico-chemical properties, reinforcement of nanocellulose, processing and extraction techniques of cellulose and nanocellulose including new development areas and their biomedical applications. In addition, we have provided information about the importance of Ionic liquids for the comprehensive extraction and dissolution of cellulose and nanocellulose using ILs.

2. Cellulose fibers

Cellulose being the most abundant polysaccharide on the biosphere are being used as an attractive reinforcing materials in the form of cellulose fibers on account of so many advantages viz. low weight, ubiquitous, biodegradable, cost-effective, renewable, low abrasive nature, interesting specific properties, since these are waste biomass and exhibit good mechanical properties [15, 16]. Cellulose fibers also have some disadvantages such as moisture absorption, quality variations, low thermal stability and poor compatibility with the hydrophobic polymer matrix. The main admonition is that cellulose nanofibres are dependably part of a complex biocomposite in the plant cell divider and must be legitimately separated and individualized keeping in mind the end goal to be exploited in planned applications. On the basis of their dimensions, functions, and preparation methods, which in turn depend mainly on the cellulosic

source and on the processing conditions, nanocellulosics are classified into three main subcategories as shown in **Table 1**.

Table 1. The family of nanocellulose materials classified into three main subcategories.

Type of nano-cellulose	Selected references and synonyms	Typical sources	Formation and average size
Microfibrillated cellulose (MFC)	microfibrillated cellulose [17], nanofibrils and microfibrils, nanofibrillated cellulose	wood, sugar beet, potato tuber, hemp, flax	Defibrillation of wood pulp by mechanical treatment before and/or after chemical or enzymatic processes diameter: 5-60 nm length: several micrometers
Nanocrystalline cellulose (NCC)	cellulose nanocrystals, crystallites [18], whiskers [19], rodlike cellulose microcrystals [20]	wood, cotton, hemp, flax, wheat straw, mulberry bark, ramie, Avicel, tunicin, cellulose from algae and bacteria	Chemical treatment in the form of Acid hydrolysis of cellulose, diameter: 5-70 nm length: 100-250 nm (from plant celluloses); 100 nm to several micrometers (from various sources of celluloses
Bacterial nano-cellulose (BNC)	bacterial cellulose [21], microbial cellulose [22], biocellulose [22]	low-molecular-weight sugars and alcohols	Synthesized by Bacteria diameter: 20–100 nm; various types of nanofiber networks

2.1 Cellulosic molecular basis

Cellulose is the ubiquitous type of polysaccharide biomaterial [23] and has applications in various fields of present-day industry. Presence of cellulose as the common material of plant cell walls was first perceived by Anselm Payen in 1838. Cellulose is considered to be a long chain polymer with monomeric units of D-glucose. Cotton fiber happens to be almost the purest form of cellulose [24].

Normally, in wood, plant leaves and stalks, cellulose is found in a blend with different materials, for example, lignin and hemicelluloses. Albeit, cellulose is mostly thought to be a plant material, however, a few microscopic organisms are additionally found to produce

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cellulose. Cellulose is chemically a long chain of small repeating units linked by glycosidic linkages. These repeating units in the cellulose chain consist of sugar, ß-D-glucose [25]. The linkage of the sugar units is based on the condensation of the water molecule by the combination of the H and –OH group. Cellobiose is formed by the linkage of just two of these units thereby produces a disaccharide. The basic glucose units are structurally 6-membered rings, called pyranoses. They are linked by single oxygen atoms (acetal linkages) between the C-1 of one pyranose ring and the C-4 of the adjacent ring. Since the condensation of a water molecule due to the reaction of an alcohol and a hemiacetal to form an acetal, on account of which the glucose units in the cellulose polymer are named as anhydroglucose units.

In case of glucopyranose ring, the spatial arrangement of the acetal linkages is vital. The cellulose units have all the groups bigger than hydrogen sticking-out from the periphery of the rings (equatorial positions). The stereochemistry at carbons 2, 3, 4 and 5 of the glucose molecule are fixed, but in pyranose form, the hydroxyl at C-4 can advance towards the carbonyl at C-1 from either side, hence giving rise to two different stereochemistry at C-1. The glucose molecule has two stereoisomers which include α and β-configuration. In the α- form, the hydroxyl group at the C-1 (anomeric center) is on the opposite face to the -CH$_2$OH group, while in the β- form, the hydroxyl group at the anomeric center is on the same face as the -CH$_2$OH group. These configurations are also called as anomers as their configuration can be changed in the solution. The β-configuration, with all its functional groups positioned in equatorial directions, causes the molecular chain of cellulose to extend in approximately straight line, thereby making it a good fiber-forming polymer [26].

The hydroxyl groups along the equatorial positions of the cellulose chain which protrude laterally are easily available for the hydrogen bonding. The crystallization of the cellulosic chains is caused by the hydrogen bonds between the chains. Since the chains are typically longer than the crystalline regions, they are understood to go through many diverse crystalline locales, with regions of disorder in the middle ("fringed-micelle" model) [27]. On account of the strength of the inter-chain hydrogen bonds in the crystalline part of the cellulosic chain, the resultant fiber has excellent strength and insolubility in many solvents. They additionally keep cellulose from

liquefying (non-thermoplastic). In the amorphous regions, the chains are further distanced and more accessible for hydrogen bonding with other molecules, such as water due to which majority of the cellulose structures are hygroscopic in nature. Hence, cellulose swells but does not disperse in water [26].

Three types of anhydroglucose units can be found in a cellulose molecule which includes the reducing end with a free hemiacetal (or aldehyde) group at C-1, the non-reducing end with a free hydroxyl at C-4 and the internal rings linked at C-1 and C-4. Due to long chain length, the reactivity of the internal alcoholic groups predominates and are not affected by the reaction conditions. Cellulose reactions are typically controlled by the steric factors on account of the inherent reactivity of the hydroxyl groups. The reaction prone sites in cellulose are C-2, C-3 and C-6 hydroxyls and C-H groups for the modification or surface treatment. Modification through grafting with hydroxyl group has been reported to be best suited at C-2 and C-3 rather than at C-6 [26].

2.2 Physico-Chemical Properties and Hierarchal Structure of Cellulose Fibers

The classification of cellulosic fibers has been done on the basis of their source and classified into leaf: pineapple, sisal, banana, abaca, cantala, date palm, henequen curaua; seed: cotton; bast: jute, ramie, flax, hemp; fruit: coir, kapok, oil palm; grass: bagasse, bamboo, alfa, and stalk: straw (cereal) [28]. The fibers which are commonly being used in composite applications are bast and leaf (the hard fibers) [29-31]. Typically, plant fibers used for the composite preparation are flax, ramie, sisal, coir, cotton, jute, hemp, henequen and kapok. Tanzania and Brazil are the two countries which are the largest producers of sisal in the world [32].

Cellulose fibers, a constituent of plant fibers are composed of cellulose microfibrils which are helically wound and joined together with disordered lignin matrix. The binding material lignin retains the water in the fibers; acts as a resistant against biological attack and as a stiffener to give stem its protection against gravity forces and wind. One of a constituent in the natural fibers is hemicellulose which acts as a compatibilizer between the lignin and cellulose [32]. There is homogeneity in the membrane of the cell wall in a fiber [33]. The layered structure of the fiber is complex consisting of a thin primary wall which is the first layer deposited during cell growth surrounding a secondary wall [34]. The mechanical properties of the fiber depend on

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the thick middle layer of the secondary wall which is made up of three layers. The helically wound series of long-chain cellulosic molecules forming microfibrils constitutes the middle layer. The angle between the fiber axis and the microfibrils is called the microfibrillar angle. The specific value of microfibrillar, angle which is an angle between the fiber axis and the microfibrils, varies from one fiber to another. The diameter of these microfibrils usually varies in the range of about 10–30 nm and normally contains 30–100 cellulose molecules in extended chain conformation and are a reason to the mechanical strength of the fiber.

Various factors affect the characteristic properties of the cellulose fibers which include decortications, disintegration (physico-mechanical, ultra-sonication), type, climate, harvest, maturity, retting degree, fiber modification, textile, and technical processes [35]. The mechanical, physical, and chemical properties of natural fibers plays an important role in order to interpret the properties of natural fiber-reinforced composite materials. The strong fiber among all the known fibers is flax fibers. The tensile strength at 3 mm clamp length for elementary and technical flax fibers was reported in the region of 1500 MPa and about 800 MPa respectively [36-38]. The diameter of the elementary fibers determines the modulus of the fibers and was observed to be in the range of 39 GPa to 78 GPa for fibers having a diameter approximately from 35 μm to 5 μm respectively. It was concluded that the variation in the modulus of flax fibers was due to the variation in relative lumen size between fibers having a different diameter. On an average, the Young's modulus of single flax fibers was reported to be 54 GPa and the results were found to be within the range of moduli measured on technical fibers. The mechanical, chemical, and physical properties of plant fibers are also affected by the processing of fiber such as retting, scotching, bleaching, and spinning [39].

The cellulose fibers as compared to other natural fibers have high stiffness, high strength and low density [40]. The cellulose fibers from soft-wood-Kraft-fibers and flax are characteristically close to the E-glass fibers. The area of growth, its climate and age of the plant greatly influence the properties of the fibers [41]. The structure and the characteristics of the fibers depend on the Technical digestion as well. The process typically used for Cellulose fibers with moduli up to 40 GPa can be extracted from wood by chemical-pulping process. Those fibers which are within the elastic modulus of 70 GPa fibers are further subdivided into microfibrils. The true value of elastic moduli of cellulose chain has been fixed up to 250 GPa [32]. The

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specimen test length determines the tensile strength of natural fibers and thereby reinforcing efficiency [42] and the same can be observed in case of flax fiber whose tensile strength is significantly based on the fiber length [43]. While it has been observed that the tensile strength of pineapple fiber is meagerly dependent on the length, but on the standard deviations of the measured values. Flax fibers are considered to be possessing reasonably high-specific strength and stiffness.

The chemical composition and the internal structure of the fibers adjudicate the certain important properties viz; electrical resistivity, density, ultimate tensile strength, and initial modulus [40]. The most apt characteristics for fibers are high durability, low bulk density, excellent tensile strength and modulus, good recyclability and moldability.

2.3 By-products of Cellulose

The industrial products wherein cellulose derivatives are an important component are packaging, films, lacquers, plastics, textiles and explosives. Lately, solubilized form of cellulose derivatives in water or dilute alkali have been prepared. The study is going on to find ways of using these derivatives as thickening agents for foods, creams, ointments and pastes, finishing and sizing agents for textiles, as absorbable surgical gauze, protective colloids, adhesives and in printing, paper, pharmaceutical, and other industries. The annual production of wood cellulose is several million tons which is a primary raw material for cellulose derivative products. The other good source of cellulose for the cellulose bye products is cotton linters. Cotton linters (chemical cotton) which are typically used in cellulose acetate preparation can find its application in plastics or high-tenacity rayon. The other major applications of cellulose acetate, made from wood cellulose are shown in **Fig. 2.**
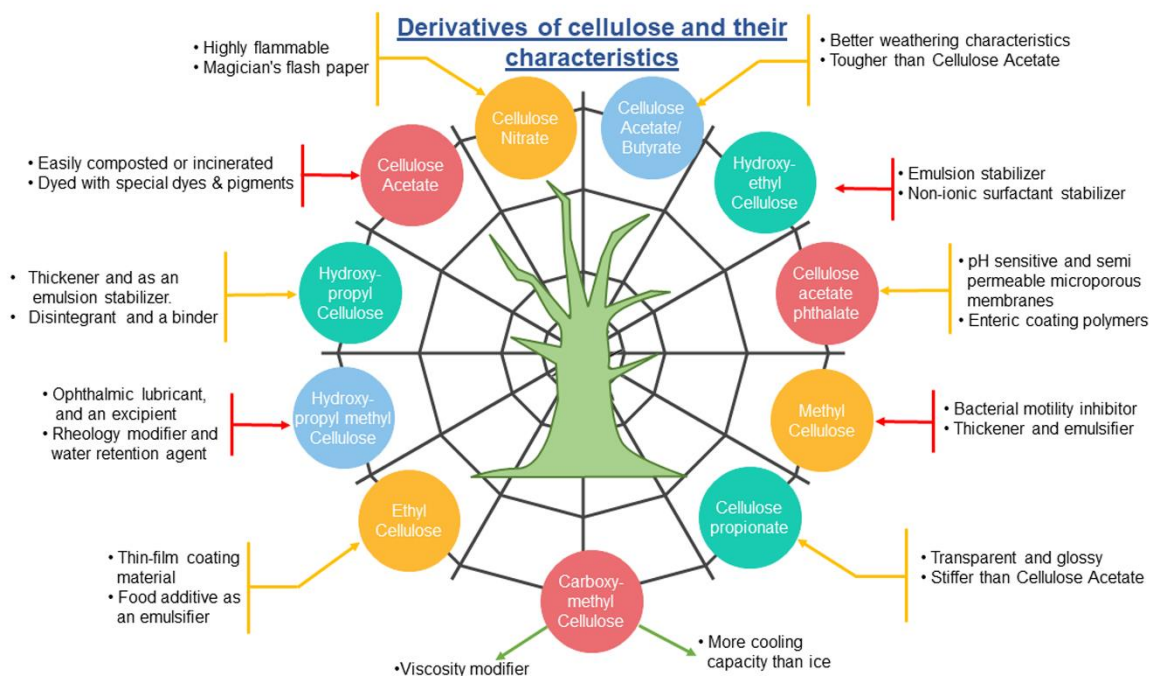
Fig. 2. Derivatives of cellulose and their characteristics.

3. Reinforcement of nanocellulose

The major role of the cellulose nanofibers is to be used as reinforcement in the development of nanocomposites and proved to have a great potential in this regard. The researchers are actively involved in the separation and characterization of cellulose nanofibers from various sources. Cellulose nanofibers can be isolated from the cell walls broadly by simple mechanical methods or a combination of both chemical and mechanical methods.

3.1. Cellulose Nanofibers Synthesis from Wheat Straw and Soy Hull

The chemical treatment has been reported to be used to extract cellulose nanofibers from wheat straw leading to purified cellulose [44]. The disintegration and defibrillation of chemically treated nanofibers from the secondary wall of the cell wall was further carried out by the application of mechanical treatment [44]. The diameters of the cellulose nanofibers from wheat straw were reported to be in the range of 10–80 nm and lengths of a few thousand nanometers. While the diameter of the cellulose nanofibers from the soy hull had been found to be in the range of 20–120 nm and shorter lengths as compared to the wheat straw nanofibers. Various sources have been used for the extraction of nanofibrillated cellulose (NFC) at the maximum

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possible lengths and diameters less than 100 nm by mechanical dispersion and high pressure homogenization processes (approx. 1500 bar) [45]. This mechanical treatment leads to nanoscaled fibril networks. Wang and Sain [46] were successful in the separation of the cellulose nanofibers from soybean stock by chemo-mechanical treatments as shown in **Fig 3**.
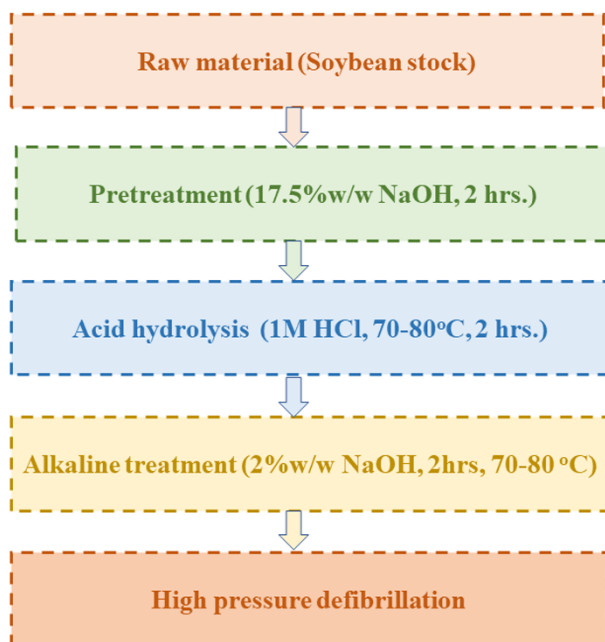

Fig. 3. Isolation of nanofibers by chemomechanical treatment [47].

The extraction of cellulose nanofibrils from wheat straw has also been carried through the steam explosion, acidic treatment, and high shear mechanical treatment. The wheat straw fibers were first treated with an alkaline solution and then the obtained alkaline-treated pulp was drenched in 8% solution of H_2O_2 (v/v) and kept overnight. An excess amount of H_2O_2 present in the pulp was then removed with excess distilled water. The acidic solution of 10% HCl (1N) was added to the bleached pulp and dispersed using ultrasonicator at a temperature of $60 \pm 1°C$ for $5\,h$. Lastly, the fibers were removed and washed many times with distilled water for the neutralization of the final pH and then dried. Further, fibers were soaked in water and continuously agitated with a high shear homogenizer for a quarter hour. The fiber agglomerates when subjected to high-shearing action of the homogenizer gets defibrillated and thereby result in the extraction of nanofibrils as shown **Fig. 3.** [48].

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3.2. Structural characterization of cellulose nanofibers

The structural characterization of the cellulosic nanofibers is being typically being carried out by transmission electron microscopy (TEM), atomic force microscopy (AFM), wide-angle X-ray scattering (WAXS), field-emission scanning electron microscopy (FE-SEM), and NMR spectroscopy [49]. The information about the diameter of the cellulose nanofiber is generally being determined by the combination of microscopic techniques with image analysis however determination of the lengths of cellulose nanofiber is strenuous on account of the entanglements and difficulties in identifying both ends of individual nanofibers. The general perception and reports often considers micro fibrillated cellulose (MFC) suspensions as not uniform and that they consist of cellulose nanofibers and nanofiber bundles [50].

The suspensions of white and colored nanofibers were obtained by the acid hydrolysis by Teixeira et al. [51]. The white and colored nanofibers were found to have possible differences among them in morphology and other properties. The diameter of 6-18 nm and a length of 85-225 nm have been reported on the basis of the morphological study of the cotton nanofibers. It was also observed that there were no major morphological differences among the nanostructures from various types of cotton fibers. The major distinction between the white and the colored nanofibers include sulfonation effectiveness, thermal stability under dynamic temperature conditions and slightly higher yield of the white nanofibers. While, the colored nanofibers were reported to have a better thermal stability as compared to the white in isothermal conditions at 180°C.

Alemdar and Sain [44] analyzed the structure of the cellulose nanofibers from agricultural residues. The chemical treatment which also led to the partial removal of hemicelluloses and lignin from the fibers were characterized by FTIR spectroscopic analysis. It was reported that the chemical treatment enhanced the crystallinity of the fibers and was revealed by XRD results. Further TGA technique was used to study the thermal properties of the nanofibers and was observed to increase dramatically. The mechanical process for the fibrillation/preparation of cellulose nanofibers from two commercial hard- and softwood cellulose pulps was carried out by Stelte and Sanadi [52]. The atomic force microscopy (AFM), light microscopy (LM) and scanning electron microscopy (SEM) instrumentation were used to study the degree of fibrillation.

3.3. Nanocomposites based on cellulose nanofiber

The marketing potential of nanocomposites in many areas of research and application is quite promising and enthralled good investments. The nanoparticle /reinforcing particle in case of nanocomposite industry, must be having at least one of its linear dimensions lesser than 100 nm. The nanoparticles can be separated from this naturally occurring polymer due to the hierarchical structure and semicrystalline nature of cellulose. Long thin filaments of natural cellulose fibers are basically built up of smaller and mechanically stronger fibers which are called as the microfibrils consisting of alternating crystalline and non-crystalline domains. Multiple mechanical shearing actions are generally used to fibrillate more or less individually these microfibrils. The as-synthesized cellulosic fibers are usually called microfibrillated cellulose (MFC) as shown in **Fig. 4**. The dissolution of amorphous domains is being carried out by longitudinal cutting of these microfibrils by subjecting the biomass to a strong acid hydrolysis treatment. The preparatory method and sources of cellulose ensures the dimension of the nanoparticles (rod-like nanocrystals or whiskers) [53-56]. The important characteristics which makes cellulose nanocrystals as the ideal reinforcement for the development of polymer nanobiocomposites are its abundance, low weight, excellent mechanical properties and reinforcing capability and biodegradability [22, 57-59]. Impressive mechanical properties with a Young's modulus of about 150 GPa and an extended surface area of several hundred $m^2 \cdot g^{-1}$ [60], cellulose nanocrystals have the potential to substantially reinforce polymers at low filler loadings. This reinforcing material has a great potential as is evident from tens of scientific publications and the research being carried out by experts in this field of study although most of the studies is focused on their mechanical properties as reinforcing phase and self-ordering characteristics of their liquid crystal. Moreover, for any reinforcing nanoparticle, the main issue is their homogeneous dispersion within a polymeric matrix.
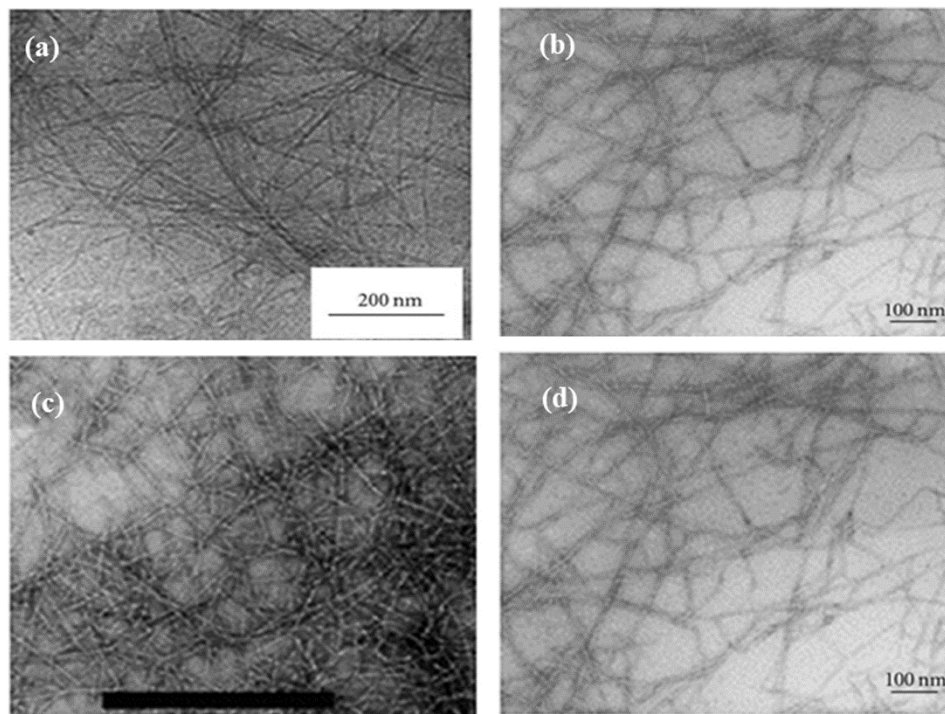
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Fig. 4. Transmission electron micrographs from dilute suspension of cellulose nanocrystals from: (a) ramie [61], (b) bacterial [62], (c) sisal [63], (d) microcrystalline cellulose [21].

4. Cellulose nanofibrillar extraction techniques

4.1 Mechanical extraction by homogenization

The microfibrillated cellulose which is simply nano-order unit woven like structure can be obtained by the fibrillation of pulp fiber using a mechanical treatment, comprising of refining and high-pressure homogenization processes. The equipment used for the refining process typically being used in the paper industry is called a refiner. The methodology of using disk refiner includes the forced introduction of the dilute fiber suspension to be treated through a gap between the rotor and stator disks, which possess surfaces fitted with bars and grooves, wherein the fibers are exposed to repeated cyclic stresses. This morphological modification and size reduction of the fibers takes place through this mechanical treatment and thereby brings about irreversible changes in the fibers. This process of refining is followed by the homogenization process, wherein dilute slurries of cellulose fibers pre-treated by refining are forced at high pressure and allowed to pass through a spring high pressure loaded valve assembly. The fibers

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are subjected to a large pressure drop with shearing and impact forces by the opening and closure of this valve in rapid succession. As a result of this combination of forces high degree of microfibrillation of the cellulose fibers is promoted, thereby producing microfibrillated cellulose [64].

The homogenization process is generally being preceded by the refining process in order to carry out the external fibrillation of fibers by steadily peeling off the external primary and S1 layers of the cell wall (*P* and *S*1 layers) and hence exposing the *S*2 layer of the secondary cell wall. This leads to the internal fibrillation and enables to loosen the fiber wall, thereby preparing the pulp fibers for subsequent homogenization process [65, 66]. It has been observed that the mechanical characteristics of high strength cellulose composites are substantially dependent on the degree of fibrillation of pulp fibers. The study also reported that there is specific point in the fibrillation stage wherein there is a sudden enhancement in the mechanical properties of the composites rather than superficial fibrillation which is not effective in improving composite strength, though there is a distinct point in the fibrillation stage at which an abrupt increase in the mechanical properties of composites occurs. It has also been reported that the passes in the range of 16 to 30 passes through the refiner greatly enhance the mechanical properties of the fibers especially their bending strength. This increment in the mechanical strength of the bulk of the fibers was ascribed to the complete fibrillation. It was further reported that the high pressure homogenization-treated pulps, linearly increases the composite strength against water retention values and reached maxima at 14 passes through the homogenizer, which describes the cellulose's exposed surface area.

4.2 Mechanical isolation by steam explosion

There are many methods that can be applied to isolate highly purified microfibrils from the plant cell wall of different plant fiber sources. Typically, successive chemical and mechanical treatments are being employed. One of the promising mechanical pretreatment methods is steam explosion treatment which is presently being comprehensively studied. The steam explosion technology is used to fragment the lignocellulosic biomass materials into biopolymer constituents. Many scholars have studied the treatment of several biomass resources by steam

explosion [67-72]. This technique was first introduced to fragment wood into fiber for the production of the board [73]. This technique allows the raw fiber to be exposed to the steam at high pressure which is followed by the rapid dip in the pressure which eventually leads to the significant break down of the lignocellulosic framework, hydrolysis of the hemicellulose portion, depolymerization of the lignin fractions and finally defibrillization [74, 75]. The steam explosion was considered as an auto hydrolysis process by Marchessault [76]. The following are the outcome of this process on the biomass which includes:

i. Accessible glycosidic links gets Cleaved

ii. β-ether linkages of lignin gets Cleaved

iii. Cleavage of lignin–carbohydrate complex bonds

iv. Lignin and carbohydrates undergo minor chemical modification.

This technique has an advantage of producing nanocellulose with high aspect ratio and percentage yield as compared to other conventional methods [77].

4.3 Defibrillation by high-intensity ultrasonication

This technique comprises of a combination of chemical pretreatment and mechanical treatment (**Fig. 5.**). The wood fibers are first cleaned in the chemical pretreatment stage in order to prepare the cellulose fibers as per general methods [78, 79]. This process begins with the removal of lignin by the use of acidified sodium chlorite solution at a temperature of 75 °C for an hour and the process is then the treatment is repeated five times until the product became white. Further, the samples are typically being treated in 3 wt% potassium hydroxide at 80 °C for 2 h and subsequently in 6 wt% potassium hydroxide at 80 °C for 2 h to remove hemicellulose, residual pectin and starch. The samples are finally being filtered and washed with distilled water until neutralization after a series of chemical treatments. The samples are being preserved in a water-swollen state during the whole process in order to prevent the formation of strong hydrogen bonds between the nanofibers after the elimination of the matrix.
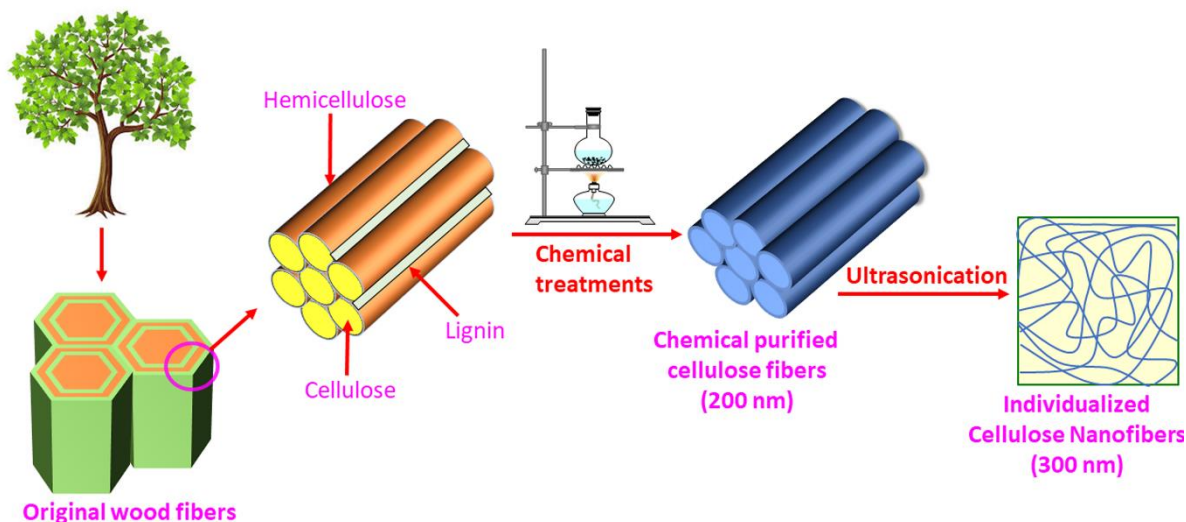
Fig. 5. Procedure for the individualizing cellulose nanofibers

The cellulose fiber solution thus obtained after the chemical pretreatment, is being then implanted in a typical ultrasonic generator at a concentration of 120 ml having a frequency range of 20–25 kHz assembled with a cylindrical titanium alloy probe tip of 1.5 cm in diameter. The isolation of cellulose nanofibers takes place by subsequent ultrasonication carried for 30 min. The output power of the ultrasonication is conducted at various power supply viz. 400, 800, 1000, and 1200 W in order to analyze the effect of ultrasonic intensity on the nanofibrillation of the chemical-purified cellulose fibers. This treatment is being carried out in an ice/water bath, and the ice is kept throughout the whole ultrasonication time.

4.4 Extraction by electrospinned technique

This technique is considered as the cost-effective method especially for polymer fibers by attaining the fiber diameters in the range of a few nanometers from micrometers and hence this technique has highly been acknowledged by the researchers. In this technique, the polymer solution is fed through a capillary, Wherein the solutions form a pendant drop at the tip of capillary. This is followed by a high voltage between the capillary and a grounded collection target. The process is dependent on the electric field strength which overcomes the surface tension of the droplet, thereby forming a polymer solution jet and accelerates towards the collection target. On way to the collection target, the polymer jet solution travels through the air while the solvent evaporates and finally a non-woven polymeric fabric is formed on the target.

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Since the obtained non-woven fabrics mostly simulates the superstructure features of the natural extra cellular matrix, these non-woven fabrics has therefore achieved a great interest in tissue engineering applications as immobilized enzymes, scaffold materials for tissue regeneration, and wound dressing articles and catalyst systems. Furthermore, these three dimensional network due to their high specific surface area and high porosity facilitate their use in tissue cultures and high density cell. The solution composition, applied voltage, collector distance, and collector type are some of the conditions which greatly effects the diameter and morphology of the resulting fiber in the electrospinning process [80].

In many aspects, the electrospinning technique has exemplified the history of conventional cellulose fiber spinning by the formation of nano- and micro-scale fibers from cellulose fibers. The first electrospun fiber was patented way back in 1934 by Formhals [81]. Many direct solvents for cellulose and have been used in wet- or dry-jet wet spinning processes have been discovered over the last five decades. These direct solvents include lithium chloride/dimethyl acetamide (LiCl/ DMAc) and N-methyl-morpholine N-oxide/water (nNMMO/H_2O) [82] have also been studied for electrospinning cellulose. Moreover, recently ionic liquids and ethylene diamine/salt as cellulose solvents have also been reported for electrospinning cellulose fibers [83]. The great difficulties of employing this technique directly on cellulose from a solvent without derivitization are quite proven in electrospinning as in wet- and dry-jet wet spinning and many scholars have followed the route of spinning more easily soluble cellulose derivatives and then immediately converting the derivatives back to cellulose. Thus, till date, it has been well reported that the electrospinning technique allows easy reinforcement of particles with different structures, like 1-dimensional carbon nanotubes, 2-dimensional layered silicates or 3-dimensional SiO_2 nanoparticles and various others, into the nanofibers.

4.5 Cellulosic nanofibers by bacterial synthesis

The common source of cellulose has been mostly plants. Since, mechanical treatments/pretreatments of plant cellulose generally require tough, aggressive processing to remove non-cellulose materials such as hemi-cellulose and lignin. Luckily, there is an alternative method of producing cellulose wherein no mechanical refining or chemical treatment is needed. An alternative to plant cellulose which has been synthesized with the help of bacterias is

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bacterial cellulose (BC). BC being a promising nanofibre biomaterial can be formed into any size or shape for developing composites due to its various characteristics which includes high crystallinity, high tensile strength, high water-holding capacity, and fine web-like network structure [84-87].

The cellulose fibre structure as in the case of paper provides good mechanical properties on account of the degree of hydrogen bonding between the fibers in the network. The paper material becomes stronger as the hydrogen bonding increases. Since the BC is synthesized extra-cellularly by the *Acetobacter xylinum and* is of nano-size, due to which hydrogen bonding between fibrils is greater as compared to that in plant cellulose. The properties like high water-holding capacity, high degree of crystallinity and high tensile strength of fibrils are basically due to the hydrogen bonding present between the hydroxyl groups.

The distinctive properties of BC have made it a prospective candidate to be used as a scaffold for tissue engineering, which includes high water-holding capacity, high hydrophilicity, and a fine fibre network which can be easily shaped into three-dimensional structures during synthesis [88, 89]. BC is considered as a natural medium for the cell growth as the porosity of BC typically helps to support cell ingrowths and effective mass transport of tissue like cartilage. BC has been reported to be suitable for various applications on account of its outstanding mechanical properties, the capability to form uniform membrane sheets after drying under specific synthesis conditions and an ultra-fine network structure [84]. BC fibers are also used as reinforcing agent in composites due to its property of being relatively inert [62]. Hence the process of producing BC has been developed with the targets of enhancing yield, structure and various desired physical properties [90, 91]. The pH level, medium used for culture, and the source of nitrogen and phosphate are some of the important conditions which acts as the main foods for *Acetobacter xylinum* have all been studied [92].

It has been ensured through previous research that the *Acetobacter xylinum* does not go through genetic mutation [93]. Medium inoculated with *Acetobacter* xylinum is usually being protected from mutation the addition of 20 wt. % malt extract with as a cryo-protectant [94]. Because of the mutations there are high chances of the growth of a wild variety organism which can decrease *Acetobacter xylinum*'s ability to produce cellulose. The mutation also effects the physiological and morphological of BC and a regression in the Young's modulus of the bacterial

cellulosic sheet produced due to the growth of a acetan which is a byproduct in the process [95]. To ensure a high productivity of BC from the *Acetobacter xylinum,* many biosynthesis-related processes have been employed which includes expression of sucrose, in which UDP-glucose is efficiently formed from sucrose [96], the addition of polyacrylamide-co-acrylic acid [97], and addition of 1% ethanol in the medium [98]. The most latest was by cloning of the *Acetobacter xylinum* whereby the final yield of BC was quite higher than that produced by the original bacteria itself [99, 100].

4.6 Extraction and dissolution of cellulose and nanocellulose using ionic liquids

As neoteric green solvents, ionic liquids (ILs) refers to a specific class of molten salts which are liquids at temperatures of 100 °C or below which shows numerous attractive properties including negligible non-flammability, recyclability, low vapor pressure, and high thermal stability [101, 102]. Varying the structure of the cations or anions of the ILs, the physicochemical properties of ILs can be tuned [102-109] accordingly depending on the application in various field such areas as extraction [110, 111], catalysis [112, 113], electrochemistry [114-116], and organic synthesis [117]. Traditional cellulose extraction and dissolution processes are facing challenges because of the energy and environmental problems [118-123]. Therefore, to make full use of cellulose resources, it is necessary to develop ''green'' cellulose extraction methods and suitable cellulose dissolution approaches. Here we will discuss the rapidly expanding use of ILs in the dissolution of cellulose and focus on the ability of various reported ILs to dissolve cellulose. Significant increase in the number of publication for dissolution of cellulose in the green solvent i.e. ILs is not only due to abundance of biomass and green solvent IL but also due to increase application of nanocellulose and its composite in medical field. The **Fig. 6.** below shows increase number of publication of dissolution of cellulose in ILs with years. The reported IL in the literature till date for dissolution of cellulose has been summarized in the **Table 2**.
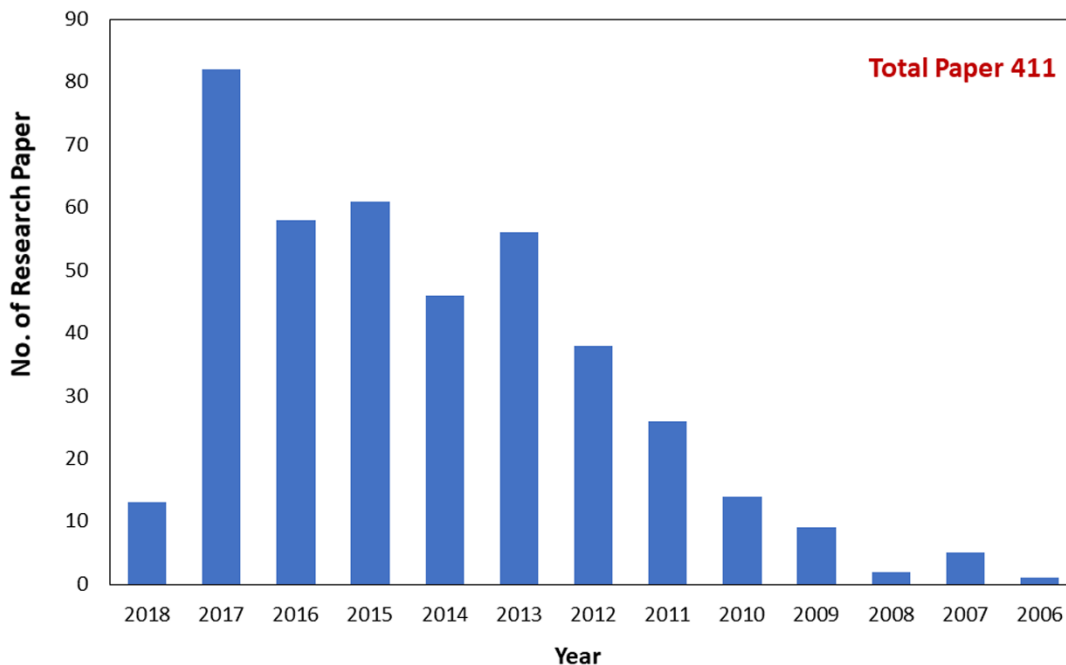
Fig. 6. Annual number of scientific publications since 2006, using the search terms 'Cellulose' and further refined by word 'extraction' and 'ionic liquids' dated 03 April 2018.

Cellulose consists of β-(1→4)-linked glucose repeating units and with close chain packing via numerous intermolecular and intramolecular hydrogen bonds, it is extremely difficult to dissolve cellulose in water and common organic solvents. However, organic solvent system such as N-methylmorpholine oxide, dimethylsulfoxide, tetrabutylammonium fluoride, N,N-dimethylacetamide/lithium chloride and N,N-dimethylformamide/ nitrous tetroxide [124, 125] have been reported to dissolve cellulose but still have some drawbacks such as toxicity, high cost, difficulty in solvent recovery, or harsh processing conditions [126]. The dissolution mechanism of cellulose in ILs [127] involves the oxygen and hydrogen atoms of cellulose-OH in the formation of electron donor-electron acceptor (EDA) complexes which interact with the ionic liquid (**Fig. 7.**). For their interaction, the cellulose atoms serve as electron pair donor and hydrogen atoms act as an electron acceptor. In corresponding fashion, the cations in ionic liquid solvents act as the electron acceptor center and anion as electron-donor center. The two centers must be located close enough in space to permit the interactions and to permit the EDA complexes to form. Upon interaction of the cellulose-OH and the ionic liquid, the oxygen and

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hydrogen atoms from hydroxyl groups are separated, resulting in opening of the hydrogen bonds between molecular chains of the cellulose and, finally, the cellulose dissolves.
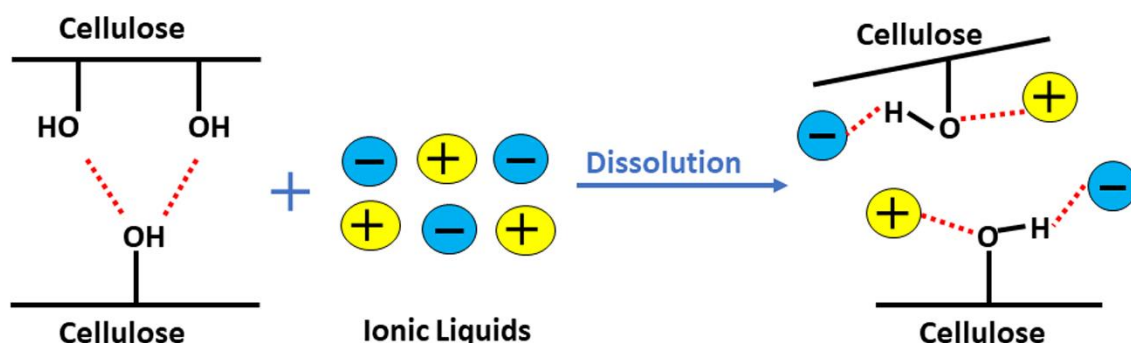
Fig. 7. Dissolution mechanism of cellulose in ionic liquids [128].

The imidazolium based ILs were among the first to show processing of biomass with the dissolution of pure cellulose using imidazolium ILs. Since then, studies on the application of ILs in biomass chemistry have made great progress and now many ILs have been found to be able to dissolve cellulose [126, 128-135] [136-142] and prominently IL can be recycled and reused which makes IL an economical reagent. Thus, ILs opens a door for the wide utilization and dissolution of cellulose in IL. Swatloski et al. [118] found that some hydrophilic ILs 1-butyl-3-methyl imidazolium chloride ($[C_4mim][C1]$) are efficient candidates for the dissolution of cellulose and also reported the effects of ILs with varying structures of cations and anions on the dissolution properties of cellulose. Furthermore, Vitz et al. [143] studied various imidazolium based IL for the dissolution of cellulose and reported 1-ethyl-3-methylimidazolium diethyl phosphate ($[C_4mim][(Et)_2PO_4]$) as best suitable IL. Kuroda et al. [144] reported extraction of cellulose from wheat bran by using 1,3-dimethylimidazolium methyl sulfate ($[C_1mim][MeSO_4]$), 1,3-dimethylimidazolium methl acetate ($[C_1mim][MeAc]$) and 1,3-Dimethylimidazolium methyl methylphosphonate ($[C_1mim][(MeO)(Me)PO_2]$). Wang and coauthors [145] used 1-allyl-3-methylimidazolium chloride ($[Amim][Cl]$), to extract cellulose from Chinese parasol, pine, poplar, and catalpa wood chips. 67%, 66% and 54%, yield at 120 ^{0}C temperature. Also, the recycle and reuse of IL [Amim][C1] were determined to ensure the cost efficiency of the use of ILs to recover cellulose. Later, Li and coauthor [146] also used the same IL [Amim][Cl] for extracting cellulose from Zoysia japonica. They reported that cellulose extraction rate was 71%

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under optimized conditions, and the yield of cellulose was >99% by [Amim][Cl]. Liu *et al.* [147] reported cellulose regeneration rate of Zoysia japonica by ammonia fiber expansion (AFEX) using the IL [Amim][Cl] and accomplished a maximum of 97% when the ultrasonic power was 110 W. His further analysis using FTIR and NMR states that regenerated cellulose was like microcrystalline cellulose. Kosan *et al.* [129] used 1-ethyl-3-methylimidazolium acetate ([C$_2$mim][Ac]), 1-ethyl-3-ethylimidazolium chloride ([C$_2$mim][Cl]), 1-butyl-3-methylimidazolium chloride ([C$_4$mim][Cl]), and 1-butyl-3-methylimidazolium acetate ([C$_4$mim][Ac]) ILs to dissolve cellulose. Stanton *et al.* [148] evidenced the successful fabrication of regenerated silk-cellulose films from various ILs, by demonstrating the direct relationship between the intermolecular interactions in films and the anion structure of the ionic liquids. Rinaldi reported that the addition of imidazolium ILs, [C$_4$mim][Cl] or ([C$_4$mim][Ac], to polar aprotic solvents caused the effective dissolution of cellulose [149].

Froschauer *et al.* [150] separated cellulose and hemicellulose from wood pulp by 1-ethyl-3-methylimidazolium acetate [C$_2$mim][Ac]/Cosolvent (water, ethanol, or acetone) systems. Zhuo *et al.* [151] synthesized SO$_3$H$^-$functionalized acidic ionic liquids used as catalysts for the hydrolysis of cellulose in [C$_4$mim][Cl]. They stated that compared with acidic inorganic acids/ ionic liquids reported in the literature, the acidic ILs with the shorter side-chain [(CH$_2$)$_3$] at C-1 on the imidazoline ring and HSO$_4^-$ as anion also has excellent catalytic performance. The yield of sugar used for hydrolysis of cellulose was dependent on the dosage of water, reaction conditions including reaction temperature and time and acidity of the ionic liquids. Further, they stated that these acidic ILs catalysts are expected to have a diverse application in the conversion of cellulose into valuable chemicals.

Zhang *et al.* [132] used 1-allyl-3-methylimidazolium chloride ([Amim][Cl]), for the dissolution and regeneration of cellulose. The cellulose (MCC), dissolved pulp, and cotton linters samples without any pretreatment were readily dissolved in [Amim][Cl]. The regenerated cellulose materials synthesized by coagulation in water displayed a good mechanical property. Due to its non-volatile nature and thermostability, IL was simply recycled. They, proposed a non-polluting and novel process for the manufacture of regenerated cellulose materials using IL. They found that IL was found to be a nonderivatized single-component, powerful solvent for cellulose and can be easily recycled and prepared.

Ramenskaya *et al.* [152] studied interactions of hydrated cellulose films doped with ionic liquids based on the 1-butyl-3-methylimidazolium cation with either trifluoroacetate or, bis(trifluoromethylsulfonyl)imide or chloride anions. Their experimental results depicted that 1-butyl-3-methylimidazolium cation was retained in the polymer matrix of cellulose, due to the formation of hydrogen bonds between the protons of the cellulose hydroxy groups and ILs anions. The hydrogen bonding strength, depending on the nature of the anion series is $[Cl]^- >$ $[CF_3CO_2]^- >> [N(Tf)_2]^-$. Facile preparation of chitin/cellulose composite films using two ionic liquids, 1-butyl-3-methylimidazolium chloride ($[C_4mim][Cl]$) and 1-allyl-3-methylimidazolium bromide ($[Amim][Br]$) was elucidated by Kadokawa *et al.* [153]. Thermal stabilities of the films, were depicted by the TGA measurement, were comparable to chitin and cellulose. The prepared film with the 1:7.6 chitin/cellulose unit ratio showed the highest fracture stress. They demonstrated that the mechanical properties of the films by tensile testing were the relatively better than those of the previously reported films.

Phanthong *et al* [154] reported extraction of about 93.1% yield of nanocellulose from cellulose powder (CP) in a facile one-step way by planetary ball milling in the presence of $[C_4mim][Cl]$ at room temperature. Also, comparison of nanocellulose products by 1-ethyl-3-methyl imidazolium acetate $[C_2mim][Ac]$ where IL showed less crystal size, thermal stability, crystallinity, and product yield, due to its higher ability of interaction with hydroxyl groups of CP. Tan *et al.* [155] synthesized high crystallinity nanocellulose by using $[C_4mim][HSO_4]$. The prepared NCC offers an easy and environmentally friendly route, as IL can regenerate and reusable. Wang *et al.* [156] demonstrated the preparation of nano-cellulose by high-pressure homogenization. Cotton cellulose was dissolved in $[C_4mim][Cl]$, then isolated by high pressure a homogeneous media through homogenization. Zasadzinska *et al.* [157] applied 1-butyl-3-methylimidazolium hydrogen sulfate ($[C_4mim][HSO_4]$) treatment for the production of nanometric cellulose particles of two polymorphic forms, further they are used for preparation of chitosan-based composites.
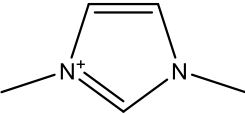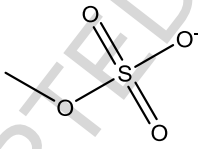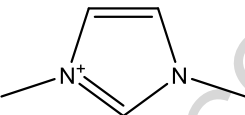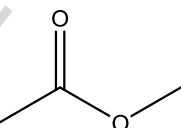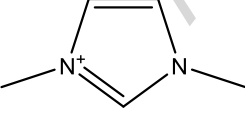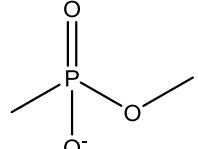
Well-defined rod-like Cellulose type I nanocrystals were extracted from cotton fibers by Lazko *et al.* [158]. via bronsted acid-type ILs through a two-step swelling/hydrolysis route, the switch between these two stages being induced by water addition. The total process was attained in a single reaction medium mainly based on 1-butyl-3-methylimidazolium chloride
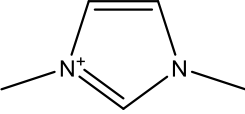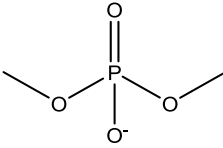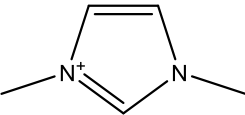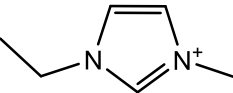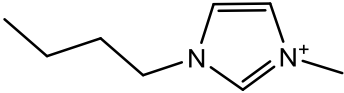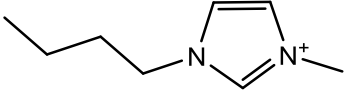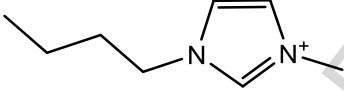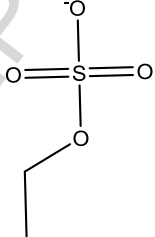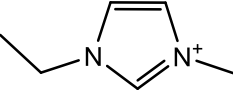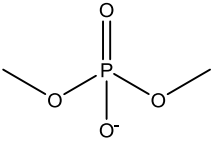
([C$_4$mim][C1]) and 1-(4-sulfobutyl)-3-methylimidazolium hydrogen sulfate ([SBmim][HSO$_4$]). Abushammala *et al* [159] accounted the direct extraction of cellulose nanocrystals (CNCs) from wood by means of 1-ethyl-3-methylimidazolium acetate ([C$_2$mim][Ac]) treatment. A native cellulosic product could be recovered in 44% yield with respect to wood cellulose content. Tan *et al.* [160] synthesized high crystallinity cellulose nanocrystals (CNCs) from microcrystalline nanocrystals (MNCs) using an environmentally friendly and green chemistry approach. For this, they used [C$_4$mim][HSO$_4$] both as the solvent and catalyst. Cellulose structure was conserved in CNCs during the catalytic conversion process and the degree of crystallinity (95.8%) was found to be higher compared to the MCC. Lazko *et al.* [161] prepared cellulose nanocrystals from cotton fibers by a two-stage method involving ionic liquid ([C$_4$mim][Cl]) swelling treatment followed by hydrolysis under mild acid conditions. Controlled swelling of cellulosic fibers was accomplished in [C$_4$mim][Cl] at 80 ^{0}C, Hydrolysis occurred even under mild conditions, due to the considerably enhancement and accessibility of the substrate. Using up to 60 times less sulfuric acid than the traditional extraction methods based on concentrated sulfuric acid. Obtained individual rodlike nanocrystals, observed under field emission gun scanning electron microscopy, exhibited a length ranging from 150 to 350 nm and average diameter of around 20 nm. Mao *et al.* [162] used Taguchi experimental strategies to optimize the production yield of cellulose nanocrystals with a two-stage mildly acidic [C$_4$mim][HSO$_4$]-mediated hydrolysis approach. In another study by the same research group [163] synthesized cellulose nanowhiskers with a relatively high yield (48 ± 2 %) by single-stage hydrolysis of microcrystalline cellulose with an aqueous solution of [C$_4$mim][HSO$_4$]. Iskak *et al.* [164] produced cellulose nanocrystals (CNCs) with particle size of 9 nm and 73% crystallinity index at 30 min reaction time from MCC as starting materials, by using [C$_4$mim][Cl]. Cellulose nanocrystals (CNCs) with desirable yield, crystallinity and particle size has been produced under catalytic hydrolysis process of [C$_4$mim][Cl]. In addition, 100 °C reaction temperature supervised to produce CNC with 76% crystallinity and 90% yield. Mao *et al.* [165] used IL [C$_4$mim][HSO$_4$] for extracting cellulose nanocrystals from pulp fibers and examined swelling and hydrolysis kinetics of bleached hardwood Kraft pulp in pure and aqueous IL solutions. They proposed that water content in [C$_4$mim][HSO$_4$] confirmed a significant effect on the rate constant of hydrolysis of weak links
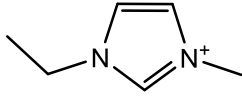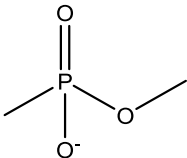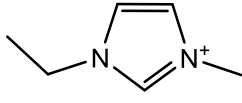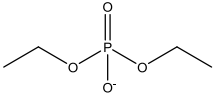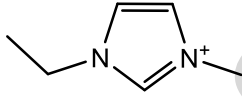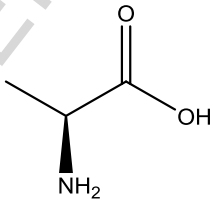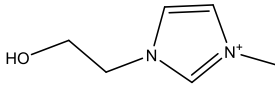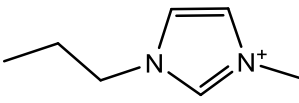
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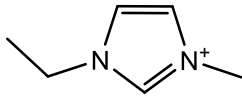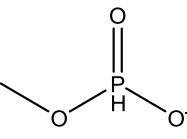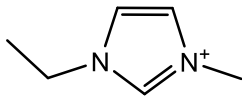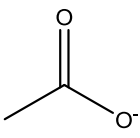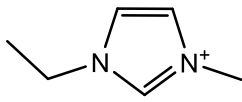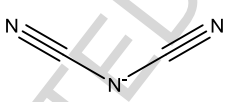
and on the accessibility to weak links. Abushammala et al. [159] reported direct extraction of cellulose nanocrystals (CNCs) from wood by means of [C₂mim][Ac].
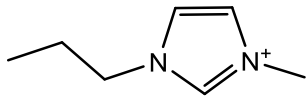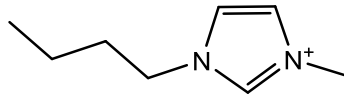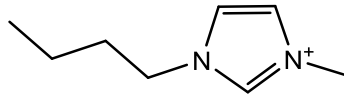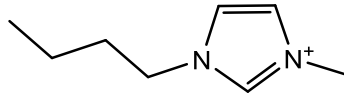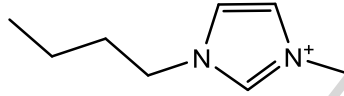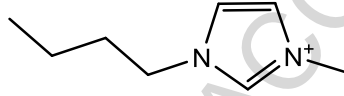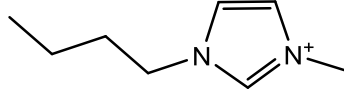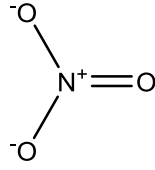
Based on the above discussion and present literature on cellulose -IL dissolution competence of ILs follows the sequence order of imidazolium > pyridinium > ammonium > carboxylate > alkylphosphate > halide-based ILs [131, 136, 139, 143]. Also, hydrogen bond accepting ability of the anions is closely linked to the solubility of cellulose in case [C₄mim] based ILs increased almost linearly with increasing hydrogen bond accepting ability of the anions as [Ac] > [HSCH₂COO] > [HCOO] > [(C₆H₅)COO] > [H₂NCH₂COO] > [HOCH₂COO] > [CH₃CHOHCOO] > [N(CN)₂] [126]. The role of the cations in the dissolution of cellulose was non-negligible. The mystery of dissolution mechanism of cellulose in IL is still not completely understood and still more studies are required to standardize the mechanism. Extraction/preparation techniques of various types of cellulose and their advantages /disadvantages has given in Table 3.
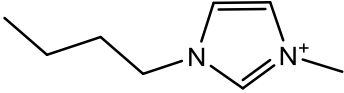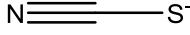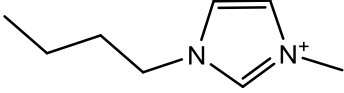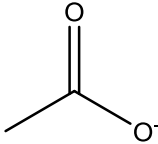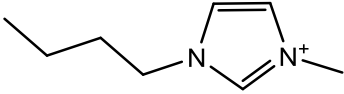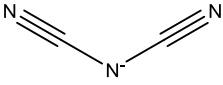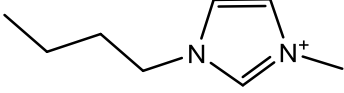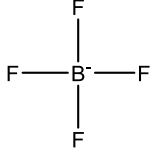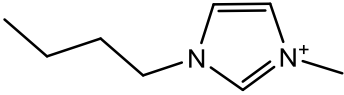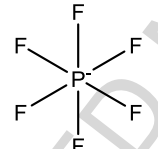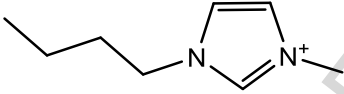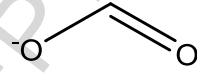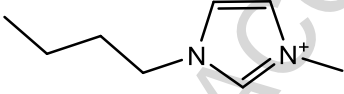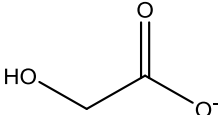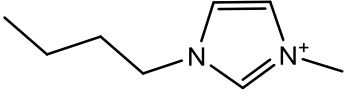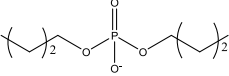
Table 2. Cellulose-dissolving capacity of different ionic liquids.
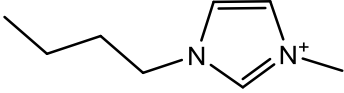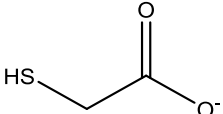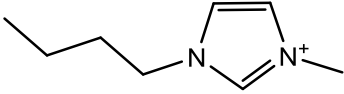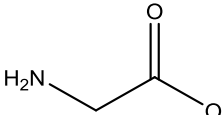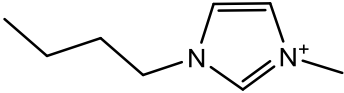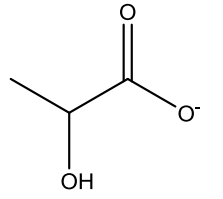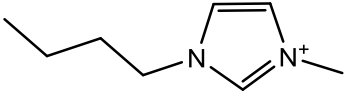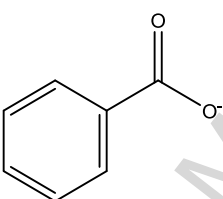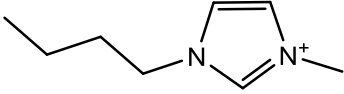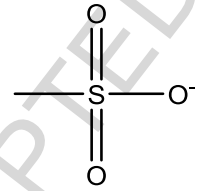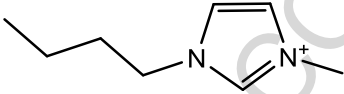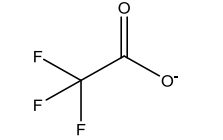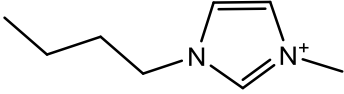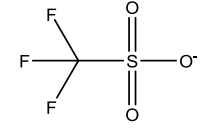
Structure of Ionic Liquids		Full name	Cellulose	Nano-cellulose	Nano-crystal
Cation	Anion				
[C₁mim]	[MeSO₄]	1,3-dimethylimidazolium methyl sulfate	[144]		
[C₁mim]	[MeAc]	1,3-dimethylimidazolium methl acetate	[144]		
[C₁mim]	[(MeO)(Me)PO₂]	1,3-dimethylimidazolium methyl methylphosphonate	[144]		
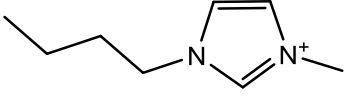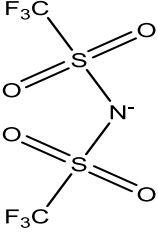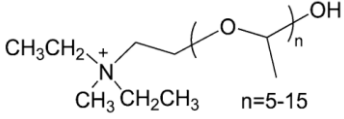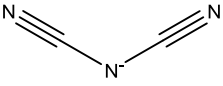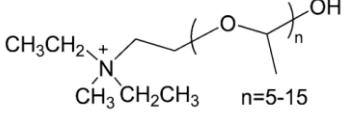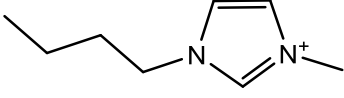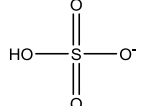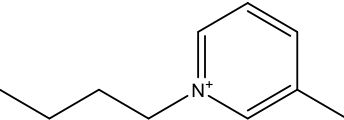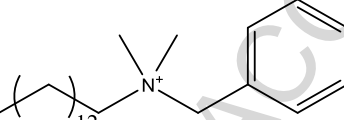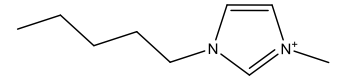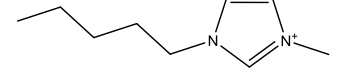
[C₁mim]	[Me₂PO₂]	1,3-dimethylimidazolium dimethyl phosphate	[143]
[C₁mim]	I⁻ [I]	1,3-dimethylimidazolium dimethyl iodide	[143]
[C₂mim]	Cl⁻ [Cl]	1-ethyl-3-methylimidazolium chloride	[119, 129, 143, 148, 166-168]
[C₂mim]	F⁻ [F]	1-ethyl-3-methylimidazolium fluoride	[143]
[C₂mim]	Br⁻ [Br]	1-ethyl-3-methylimidazolium bromide	[143]
[C₂mim]	[EtSO₄]	1-ethyl-3-methylimidazolium ethylsulphate	[143]
[C₂mim]	[(MeO)₂PO₂]	1-ethyl-3-methylimidazolium dimethyl phosphate	[130]
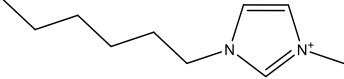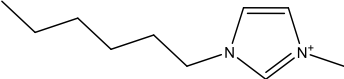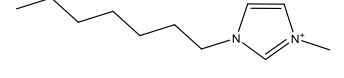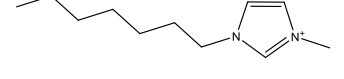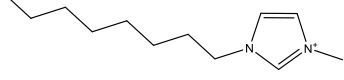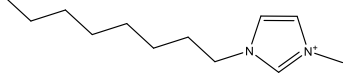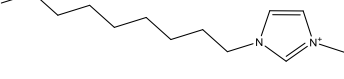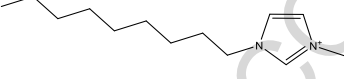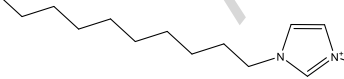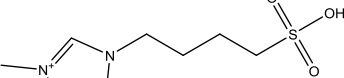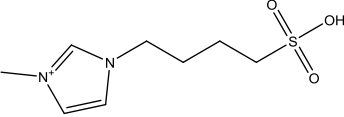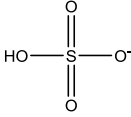
[C₂mim]	[(MeO)MePO₂]	1-ethyl-3-methylimidazolium methyl methylphosphonate	[130]		
[C₂mim]	[(Et)₂PO₄]	1-butyl-3-methylimidazolium diethyl phosphate	[143]		
[C₂mim]	[(MeO)HPO₂]	1-ethyl-3-methylimidazolium methyl phosphonate	[130]		
[C₂mim]	[Ac]	1-ethyl-3-methylimidazolium acetate	[129, 143, 148, 150, 169]	[154]	[159]
[C₂mim]	[N(CN)₂]	1-ethyl-3-methylimidazolium dicynaamide	[143]		
[C₂mim]	[Ala]	1-ethyl-3-methylimidazolium methyl alanine	[170]		
[C₂OHmim]	Cl⁻ [C1]	1-octyl-3-methylimidazolium chloride	[171]		
	Cl⁻	1-propyl-3-methylimidazolium	[143, 167]		
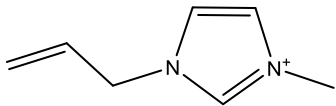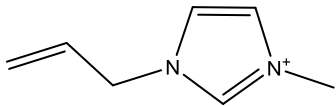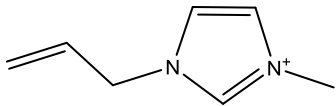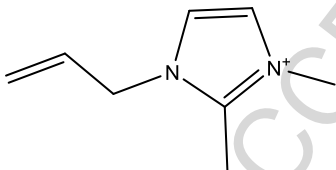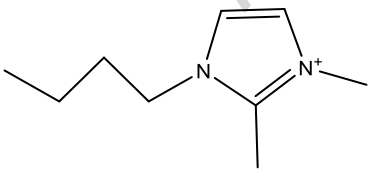
Cation	Anion	Name	Ref	Ref	Ref
[C3mim]	[C1]	m chloride			
[C3mim]	Br⁻ [Br]	1-propyl-3-methylimidazolium bromide	[143, 172]		
[C4mim]	Cl⁻ [C1]	1-butyl-3-methylimidazolium chloride	[118, 129, 131, 149, 151-153, 166, 168, 172-176]	[154]	[158, 161, 164]
[C4mim]	Br⁻ [Br]	1-butyl-3-methylimidazolium bromide	[118, 143, 148]		
[C4mim]	F⁻ [F]	1-butyl-3-methylimidazolium fluoride	[143]		
[C4mim]	I⁻ [I]	1-butyl-3-methylimidazolium Iodide	[143]		
[C4mim]	OH⁻ [OH]	1-butyl-3-methylimidazolium hydroxide	[143]		
[C4mim]	[NO₃]	1-butyl-3-methylimidazolium nitrate	[143]		
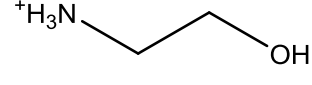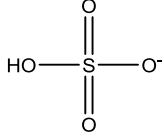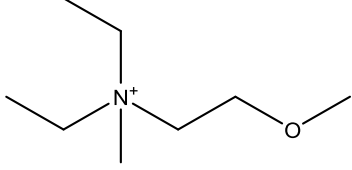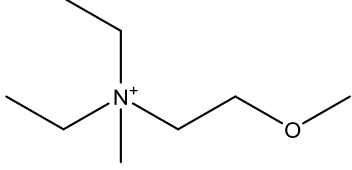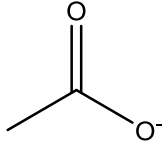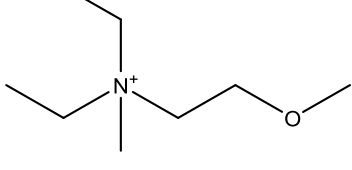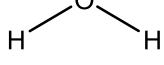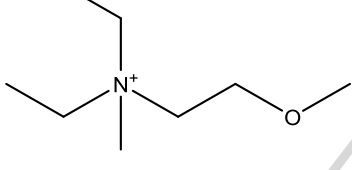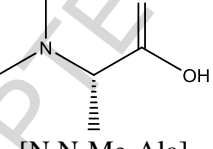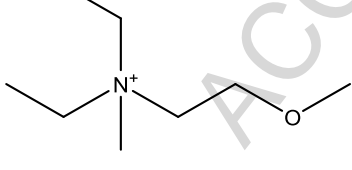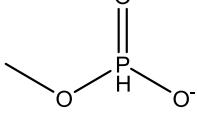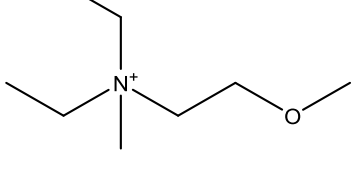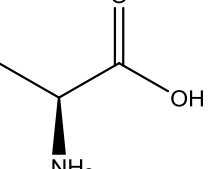
Cation	Anion	Name	Ref.
[C₄mim]	N≡C—S⁻ [SCN]	1-butyl-3-methylimidazolium thoicyanate	[118]
[C₄mim]	[Ac]	1-butyl-3-methylimidazolium acetate	[126, 143, 149]
[C₄mim]	[N(CN)₂]	1-butyl-3-methylimidazolium dicynaamide	[126, 174]
[C₄mim]	[BF₄]	1-butyl-3-methylimidazolium tetrafluoro borate	
[C₄mim]	[PF₆]	1-butyl-3-methylimidazolium hexafluorophosphate	[118]
[C₄mim]	[HCOO]	1-butyl-3-methylimidazolium formate	[126]
[C₄mim]	[HOCH₂COO]	1-butyl-3-methylimidazolium glycollate	[126]
[C₄mim]	[(Bu)₂PO₄]	1-butyl-3-methylimidazolium dibutyl phosphate	[143]

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Cation	Anion	Name	Ref
[C₄mim]	[HSCH₂COO]	1-butyl-3-methylimidazolium thioglycolate	[126]
[C₄mim]	[NH₂CH₂COO]	1-butyl-3-methylimidazolium glycinate	[126]
[C₄mim]	[CH₃CHOHCOO]	1-butyl-3-methylimidazolium lactate	[126]
[C₄mim]	[(C₆H₅)COO]	1-butyl-3-methylimidazolium benzoate	[126]
[C₄mim]	[CH₃SO₃]	1-butyl-3-methylimidazolium methanesulfonate	[148]
[C₄mim]	[CF₃CO₂]	1-butyl-3-methylimidazolium trifluoroacetate	[152]
[C₄mim]	[CF₃SO₃]	1-butyl-3-methylimidazolium trifluoromethanesulfonate	[143]

[C₄mim]	[NTf₂]	1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide	[143, 152, 174]	
[Amm110]	[N(CN)₂]	Ammoeng110 dicyanamide	[174]	
[Amm110]	Cl⁻ [C1]	Ammoeng110 chloride	[174]	
[C₄mim]	[HSO₄]	1-butyl-3-methylimidazolium hydrogen sulfate	[155, 157]	[163, 165]
[C₄mpy]	Cl⁻ [C1]	1-butyl-3-methylpyridinium chloride	[131, 166, 168, 170]	
[BDTAC]	Cl⁻ [C1]	benzyldimethyl(tetradecyl)ammonium chloride	[131, 166]	
[C₅mim]	Cl⁻ [C1]	1-pentyl-3-methylimidazolium chloride	[143, 167]	
	Br⁻	1-pentyl-3-methylimidazoliu	[143]	

[C₅mim]	[Br]	m bromide	
[C₆mim]	Cl⁻ [Cl]	1-hexyl-3-methylimidazolium chloride	[118, 143, 167]
[C₆mim]	Br⁻ [Br]	1-hexyl-3-methylimidazolium bromide	[143]
[C₇mim]	Cl⁻ [Cl]	1-heptyl-3-methylimidazolium chloride	[143, 167]
[C₇mim]	Br⁻ [Br]	1-heptyl-3-methylimidazolium bromide	[143]
[C₈mim]	Cl⁻ [Cl]	1-octyl-3-methylimidazolium chloride	[118, 143, 167]
[C₈mim]	Br⁻ [Br]	1-octyl-3-methylimidazolium bromide	[143]
[C₉mim]	Cl⁻ [Cl]	1-nonyl-3-methylimidazolium chloride	[118, 143, 167]
[C₉mim]	Br⁻ [Br]	1-nonyl-3-methylimidazolium bromide	[143]
[C₁₀mim]	Cl⁻ [Cl]	1-decyl-3-methylimidazolium chloride	[167]
		1-(4-sulfobutyl)-3-methyl imidazolium	[158]

[SBmim]	[HSO$_4$]	hydrogen sulfate	
[Amim]	Cl$^-$ [Cl]	1-allyl-3-methylimidazoliu chloride	[119, 131, 132, 143, 145, 148, 153, 166-168, 175, 177-179] [129, 173] [153]
[Amim]	Br$^-$ [Br]	1-allyl-3-methylimidazolium bromide	
[Amim]	$^-$O—CHO [HCOO]	1-allyl-3-methylimidazolium formate	[179]
[Admim]	Br$^-$ [Br]	1-allyl-2,3-dimethylimidazolium bromide	[173]
[Cdmim]	Cl$^-$ [Cl]	1-butyl-2,3-dimethylimidazolium chloride	[129, 166, 173]

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[2-HEA]	[HSO4]	2-hydroxyethyl amonium hydrogensulphate	[180]
[N221ME]	[AA] where AA=amino acids	N,N-diethyl-N-methyl-N-(2-methoxy)ethylammonium amino acids	[170]
[N221ME]	[Ac]	N,N-diethyl-N-methyl-N-(2-methoxy)ethylammonium acetate	[170]
[N221ME]	[OH]	N,N-diethyl-N-methyl-N-(2-methoxy)ethylammonium hydrogen oxide	[170]
[N221ME]	[N,N-Me2Ala]	N,N-diethyl-N-methyl-N-(2-methoxy)ethylammonium N,N-dimethylalanine	[170]
[N221ME]	[(MeO)HPO2]	N,N-diethyl-N-methyl-N-(2-methoxy)ethylammonium phosphonate	[170]
[N221ME]		N-butyl-N,N-diethyl-N-methylammonium alanine	[170]

[N₄₂₂₁ME] structure [P₁ME]	[Ala] AlH_4^- [Ala]	N-methyl-N-(2-methoxyethyl)pyrolidin-1-ium alanate	[181]
[P₁ME]	[Lys]	N-methyl-N-(2-methoxyethyl)pyrolidin-1-ium lysine	[181]
[P₁ME]	[Ac]	N-methyl-N-(2-methoxyethyl)pyrolidin-1-ium Acetate	[181]
[P₄₄₄ME]	[Ala]	2-methoxyethyl(tributyl)phosphonium alanine	[170]
[Py_ME]	[Ala]	1-methylpyridinium alanine	[170]
[P₆₆₆₁₄]	[N(CN)₂]	Trihexyltetradecyl phosphonium dicynaamide	[174]
[Cyanomim]	[Br]	1-(2-cyanoethyl)-3-methylimidazoliu	[172]
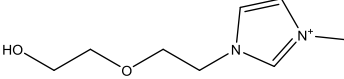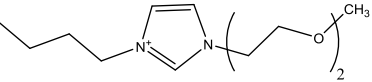
| | Cl⁻ | 1-(3,6-dioxahexyl)-3-methylimidazolium chloride | [174] |

[[H(OEt)₂-Memim]]   [Cl]

| | Cl⁻ | 1-(3,6,9-trioxadecyl)-3-butylimidazolium chloride | [174] |

[Me(OEt)₂-Et-Im]   [Cl]

m bromide

Table 3. The Extraction/preparation techniques of various types of cellulose and their advantages /disadvantages

Techniques	Advantages	Disadvantages	Reference
High-Pressure Homogenization	Extensively used method for large-scale production of CNF.	Insufficient disintegration. More energy consumption. Extreme mechanical damage to the CNF crystalline structure	[14, 45, 182-186]
Microfluidization	Operates at constant pressure and constant shear rate.	Required to repeat the process many times and to use various sized chambers in order to increase the degree of fibrillation	[14] [187, 188]
Grinding	Extra mechanical pretreatments are not necessary	Necessity for disk stone maintenance and replacement, as wood pulp fibers can erode the grooves and grit.	[14] [189, 190]
Cryocrushing	Mechanical fibrillation technique for cellulose in a frozen state. This technique produces fibrils with comparatively large diameters. Prepared nanofibers displayed superior dispersion ability in acrylic emulsion compared to water.	Low productivity, expensive technique, High-energy consumption.	[14, 189, 190]
High-Intensity Ultrasonication	General laboratory method. Produces effective cavitations that contain the expansion, formation, and implosion of	All ultrasound treatments contain high-energy consumption and can cause a dramatic decrease in the NFC	[14, 191]

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	microscopic gas bubbles, when the water molecules absorb ultrasonic energy. Gives aggregated fibrils with a broad width distribution.	yield and fibril length.	
Ionic liquid	Ability for making functional CNCs. Ionic liquids are reusable.	Expensive	[162, 192]
Deep eutectic solvent	Environmentally friendly, biodegradable and recoverable.	However, the reaction degree is low, so it needs follow-up mechanical treatment to get the CNCs products.	[192, 193]
Subcritical water	Environmentally friendly	Costly to prepare CNCs. CNCs have bad suspension stability.	[192, 194, 195]
Mineral acid hydrolysis	CNCs have exceptional suspension stability.	It is problematic to treat waste acid.	[192, 196-199]
Enzymatic hydrolysis	environment-friendly method	Cost is expensive	[192, 200-204]
Oxidation degradation	Carboxylation CNCs can be formed.	Huge quantity of oxidants were expended in the process.	[192, 205-208]

5. Processing of nanocomposites

The cellulose based nanocomposites are developed by dispersing the stable aqueous suspensions of cellulose nanoparticles mostly in hydrosoluble or hydrodispersible or latex-form polymers. The dispersion state of the cellulose nanoparticles has a specific advantage to remain in an aqueous medium for the processing. The following resins are generally being utilized as the matrices for the cellulose based nanocomposites as shown in the figure below (**Fig. 8.**).
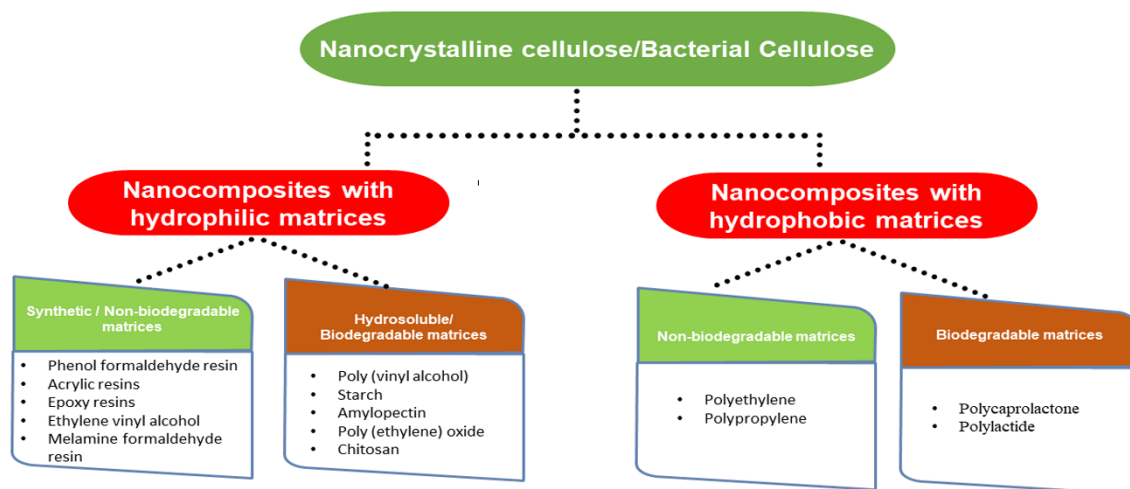
Fig. 8. Schematic diagram of various types of matrices for cellulose based nanocomposites.

Generally, water soluble or water dispersible polymers after forming a solution, are first made to mix aqueous suspension of cellulosic nanoparticles. The obtained combination of matrix and a reinforcing cellulosic nanoparticles is generally cast and evaporated to form a solid nanocomposite film. Freeze-dried and hot-pressed processing techniques have also applied on the same mixture. There are numerous reports in the literature wherein different composites were prepared which includes cellulose nanofiber reinforced starch [209-211], silk fibroin [212], poly(oxyethylene) (POE) [18, 19, 57, 213], polyvinyl alcohol (PVA) [214-217], hydroxypropyl cellulose (HPC) [214, 215], carboxymethyl cellulose (CMC) [218], or soy protein isolate (SPI) [219].

Latex which was synthesized by the copolymerization of styrene and butyl acrylate (poly(S-co-BuA)) and tunicin (the cellulose extracted from tunicate) whiskers was the first publication reported for the development of cellulose nanocrystals-reinforced latex nanocomposites [220]. The wheat straw [221, 222] or sugar beet [18, 19] cellulose nanocrystals have been used as a reinforcement for the same copolymer. The other latexes which have been also used as matrix material with cellulose nanocrystals include poly (β-hydroxyoctanoate) (PHO) [223-225], polyvinylchloride (PVC) [226-229], waterborne epoxy [230], natural rubber (NR) [231, 232] and polyvinyl acetate (PVAc) [63]. Lately, mini-emulsion polymerization technique has been used to prepare a stable aqueous nanocomposite dispersions-constituting

cellulose whiskers and a poly(styrene-co-hexyl-acrylate) matrix [53]. For the stability of the dispersion, reactive silane was used. Mixing and casting solid nanocomposite films followed by water evaporation can be produced.

On the other hand, dispersion of cellulosic nanofibers in non-aqueous solvents has been made possible by the utilization of surfactants or chemical grafting and by doing so various other avenues of nanocomposites processing were made possible. It has also been reported that typically cellulose nanoparticles contain a functional surface covered with hydroxyl groups, hence extensive chemical modification is very much a possibility. The chemical modification normally had an adverse effect on the mechanical performance of the nanocomposite materials by reducing the surface energy and polarity of the nanoparticles and thereby ameliorating the adhesion with the nonpolar polymeric matrix. The forces of hydrogen bonding have been considered to be responsible for this unusual behavior which basically helps the reinforcing phenomenon of polysaccharide nanocrystals resulting from the formation of a percolating network. Hence, researcher prefers to carry grafting of long chains rather than small molecules in order to maintain the mechanical properties of the composite material.

The extrusion technique has been reported at a very few places concerning the processing of cellulose nanofibers-reinforced nanocomposites. The major cause of concern of cellulose is its hydrophilic nature which creates irreversible agglomeration during drying and flocculation in nonpolar matrices on account of the formation of further hydrogen bonds between amorphous parts of the nanoparticles. Therefore, the the extrusion method was used for the preparation of cellulose whiskers-reinforced poly (lactic acid) nanocomposites by melt extrusion was carried out by forcing the suspension of nanocrystals into the polymer melt [22]. Poly vinyl alcohol has been tried-at being used as a compatibilizer to accelerate the dispersion of cellulose whiskers within the poly (lactic acid) matrix [233]. It has also been reported that Low-density poly(ethylene) were extruded with organic acid chlorides grafted cellulose whiskers [234]. The nanocomposite so obtained has been to be homogeneous and was further observed that the homogeneity of the nanocomposite increases with the grafted chains length. The ring-opening polymerization (ROP) of the corresponding monomeric lactone units leading to the polycaprolactone-grafted cellulose nanocrystals were also used as "masterbatches" by melt blending with a polycaprolactone matrix [235]. It has recently been reported that an attempt was

made to disperse carbon nanotubes in polymeric matrices using the DOPE technique (Dispersed nanoobjects protective encapsulation). The cross-linked alginate capsules have been successfully produced in the presence of either cellulose whiskers or microfibrillated cellulose [236]. These as-synthesized alginate capsules have been extruded with a thermoplastic polymer.

5.1. Interactions at the interface

The reinforcing properties have been reported in one of the studies where it was observed that strength of the interactions plays an important role between the cellulose nanofibers isolated from cottonseed linters and the filler and the glycerol-plasticized starch matrix [237]. In freeze-dried cellulose nanocrystals case which forms a nonpercolating systems, the strong interaction between matrix and a filler increases the reinforcing effect of the filler [238]. The surfactant has also been reported to improve the matrix/filler interactions by coating cellulose whiskers with a surfactant which was found to have a great impact on the nonlinear mechanical properties, specifically on the elongation at break [239]. The reinforcing effect has been observed by Grunert and Winter [62] to be higher in case of unmodified cellulose whiskers than trimethylsilylated whiskers.

5.2 Manufacturing methods of nanocomposites

There are numerous methods of manufacturing of biofiber based composites which include:

i) Compression molding,

ii) Injection molding,

iii) Resin transfer molding (RTM) and

 iv) Vacuum bagging.

The Preforms and Prepregs are widely used for composite preparation wherein preform are mostly fibers, fabrics or nonwovens and prepregs which is mostly an impregnated resin system [240]. The important parameters for the manufacturing of the composites are being optimized in relation to temperature, pressure and molding time. Commonly, it is important to dehydrate the natural fibers by preheating in order to reduce the moisture content before being processed for the composite production. There are chances of degradation of the cellulose at high temperatures; hence, reducing the mechanical properties of the composites. The tensile strength

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of the composite material is affected by the non-uniform dispersion of the fiber in the matrix which causes fiber agglomeration [240]. The majority of the previous study has been carried on natural fiber composites mainly focused on reinforcements such as flax, hemp, sisal and jute, and thermoplastic and thermoset matrices. In certain cases, the composites have been manufactured by using matrices made of derivatives from cellulose, starch and lactic acid to produce fully biodegradable composites or biocomposites [241].

The sandwich structures based on natural fiber composite skins have also been an emerging diversity of applications of composite materials. The paper honeycomb and natural fiber-reinforced thermoplastic or thermoset skins are one of the special cases of sandwich composites. Some of the important criteria for choosing the apt process technology for the manufacturing of natural-fiber composites are; the desired product geometry, the performance needed, the cost and the ease of manufacture. The manufacturing methods for natural fiber composites are similar to those of glass fibers. The following are the commonly used manufacturing processes:

5.2.1 Manufacturing by hand laminating

This manufacturing process involves the placement of the fibers in a mold with the resin being applied later by rollers. The curing is being carried out by the use of a vacuum bag, as then the pressure is exerted by the atmospheric pressure to compact the composite material. The major advantages of this manufacturing process lies in its simplicity, low cost of tooling and flexibility of design while the disadvantages include the long production time, intensive labor and low automation potential.

5.2.2 Manufacturing by resin transfer molding (RTM)

This technique is also regarded as close mold technique wherein the fibers are placed inside a mould consisting of two solid parts. The fibers within the mold are impregnated with liquid resin by virtue of a tube which connects the mold with a supply of resin and this liquid resin is injected at low pressure through the mold. The composite material inside the mold is cured at room temperature or above until the completion of the curing reaction and then the mold is opened and the fabricated product is taken out.

The major parameters which are very important specifically for thin cavities include; injection pressure, fiber content or mold temperature which have a great influence on the development of the temperature profiles and the thermal boundary layers of these products. This processing method has the advantage of manufacturing of large, complex and high-performance parts rapidly. Many resins are generally being used for resin transfer molding technique like epoxy, polyester, phenolic and acrylic as long as these resins have low enough viscosity to ensure a proper wetting of the fibers. For high-quality parts, it is mandatory to have a thorough knowledge of all the operating steps [242].

Similar to RTM is the vacuum assisted resin transfer molding (VARTM), wherein a polymeric film and a single solid mold are being used. This processing technique is quite a clean and cost effective fabrication method wherein the resin is processed into a dry reinforcement on a vacuum bagged tool, utilizing only the partial vacuum to drive the resin. The compressibility of the fiber–resin composite before curing and the vacuum negative pressure are the two important parameters which determine the molded laminate thickness.

5.2.3 Manufacturing by compression molding

Another important manufacturing technique for the fabrication of fiber reinforced polymers is compression molding which involves a semi-finished composite sheet typically known as sheet molding compound (SMC) that is later molded into the final parts by compression. For the sheet molding compound, the fibers are added on a rolling film resin. This is followed by the second film of resin which is then added, in order for the later to be compressed in a composite sheet that may be kept for few days. At the end the final product which is a reinforced sheet is then placed into a press to get its desired shape.

The major features of the compression molding include its ability to produce very high volume, the excellent reproducibility, the short cycle times and the low level of crap formation. Reports of meagre processing times of < 2 min have been achieved during the compression molding of three-dimensional components with a high forming degree. To achieve a good mechanical properties of natural fiber composites, the interaction of natural fibers and matrix resin is important and further the amelioration of the mechanical properties were found to be dependent on the molding condition, the molding pressure and temperature. The major issue

which needs to be taken care of during compression molding is the high pressure which can spoil the fibers and the structure as well.

5.2.4 Manufacturing by injection molding

This method of processing produces composites with good surface finish and dimensional accuracy with high production rate and low manufacturing cost, so is quite suitable to form complex shapes and materials with fine details. The injection molding process involves mixing of resin granules and short fibers into a heated barrel and transported to the mould cavity by a spindle. This technique of manufacturing is an important process for the production of plastics/composites, and can manufacture from very tiny products such as bottle tops to very large car body parts.

5.2.5 Manufacturing by pultrusion

This method of composite manufacturing produces composite profiles at any length. The die plays an important role in this method wherein the impregnated fibers are forced through a die, which gives a desired cross-sectional shape to the product. The final profile is shaped until the drying of the resin. The following are the advantages of this method of manufacturing composites which includes capability to build thin wall structures, the numerous variety of cross-sectional shapes and the possibility for high degree of automation.

6. Cellulose fiber reinforced biocomposites

6.1 Biomedical applications of Polyurethane based composites

For the development of vascular Prostheses, pine apple leaf derived nanocellulose embedded Polyurethane has been reported to be an attractive and easily available range of materials. Nanocellulose polyurethane vascular grafts development has been put under extensive research efforts due to its characteristics which includes the elastic properties of the material, conjugated with low thrombogenicity and exceptional physical and mechanical properties (**Fig. 9.**). These vascular grafts possessing a wall thickness of 0.7–1.0 mm revealed elongation at break of 800–1200%, and resisted hydraulic pressures up to 300 kPa.
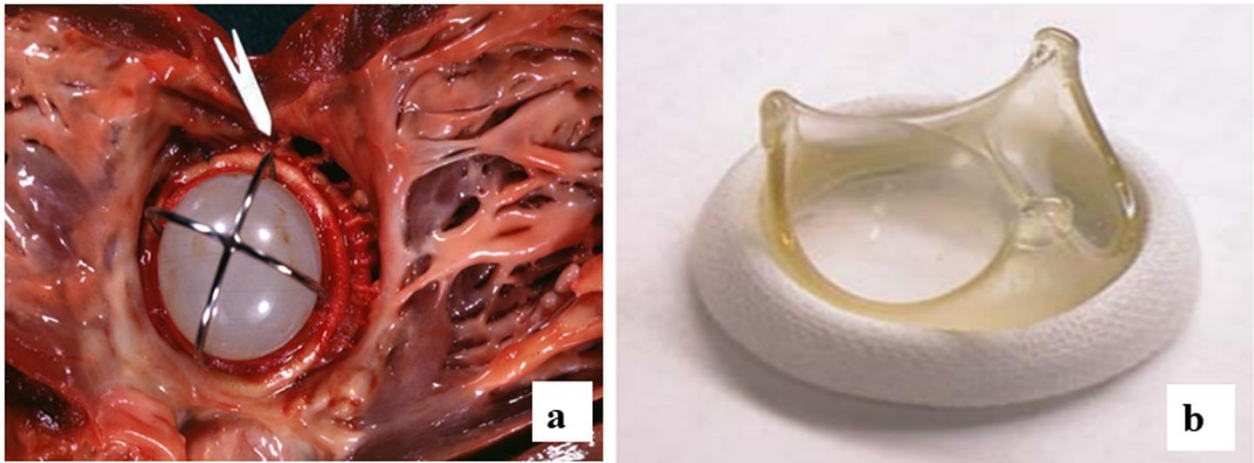
Fig. 9. Heart valve from Nanocellulose–Polyurethane: (a) Bioprosthetic valve implant (b) Heart valve

Nanocomposites from nanocellulose and polyurethane were found to have high tensile strength and high strain-to-failure with strongly ameliorated modulus. The technique used for the development these cellulose nanocomposites was by solvent casting, wherein dry crystalline cellulose was incorporated into the hydrophilic polyurethane. Cellulose nanofibrils present in dry nanoscale cellulose particles were allowed to disperse successfully. The dispersion of cellulose nanofibrils in the developed nanocomposites was characterized by ESEM. The crystalline structure of cellulose I in its originality in the developed nanocomposites were analyzed by XRD analysis. The optimum reinforcement concentration of 5 wt% cellulose was observed to have the highest strain-to-failure. The developed nanocellulose based composites proved to be a versatile material having the wide range of applications in the medical field which includes repair of articular cartilage, vascular grafts cardiovascular implants, scaffolds for tissue engineering, penile prostheses, adhesion barriers, urethral catheters, mammary prostheses, and artificial skin. The best thing about these implants was that these were fabricated from biodegradable materials which will eventually lead to the progressive decomposition of the implant material and then be accompanied by the production of the new tissues. The same nanocomposite material can also find its applications in the production of non-latex condoms, medical bags, organ retrieval bags surgical gloves, surgical gowns or drapes, breathable wound dressing and medical disposables. The new generation of biostable polyurethanes and pineapple leaf fibers derived nanocellulose–polyurethane valve design **(Fig. 9.)** applied on 6-month, strained, rat implant model was found to

have good biological durability, fatigue resistance and haemodynamics, and which has proven themselves of superior biostability. Hence it is being foreseen that early improvement of a polyurethane valve with good haemodynamic function which can be maintained during long-term implant, and which is expected never to fail from biological decomposition nor from fatigue-induced material failure, while maintaining a low thrombogenic surface. It has been found that out that during an accelerated fatigue tests, five out of five successively developed valves crosses the equivalent of 12 years cycling without any failure. The only failure happened after the equivalent of almost 13 years cycling, and three valves have reached 608 million cycles (almost 15 years equivalent) to date.

6.2 Biomedical applications of polvinyl alcohol based composites

One of the best hydrophilic biocompatible polymer with many important properties vital for biomedical applications is polyvinyl alcohol (PVA). The solid hydrogel can be developed from PVA using freeze-thaw cycles with reasonable mechanical properties by physical crosslinking. PVA reinforced with hydrophilic nanocellulose fibers of an average diameter of 50 nm are utilized to form biocompatible nanocomposites. As per Millon and Wan [243], the produced PVA nanocomposites exhibit a broad range of mechanical properties and can manipulate the mechanical properties equivalent to that of cardiovascular tissues, like aorta and heart valve leaflets. Further, it was concluded by the same researcher that the stress–strain properties for porcine aorta matches to one variety of PVA–nanocellulose nanocomposite in both the circumferential and the axial tissue directions. A PVA–Nanocellulose nanocomposite with equivalent characteristics as heart valve tissue has also been developed. All the samples were found to relax at a faster rate and to a lower residual stress than the replaceable tissues upon studying their relaxation properties, which are essential for cardiovascular applications. Therefore, PVA– Nanocellulose based composites can be considered as a novel and a promising material for cardiovascular soft tissue replacement applications.

7. Other biomedical field applications

7.1 Application in pharmaceuticals

Pharmaceutical stake holders have been using cellulose since long. The cellulose is considered to be having extraordinary compaction properties when mixed with other pharmaceutical excipients by virtue of which drug-loaded tablets form dense matrices applicable for the oral administration of drugs. The hydrophilic matrices reinforced by polysaccharides, natural polymers stay popular biomaterials for controlled-release dosage forms and the selection of a hydrophilic polymer matrix is considered as one of the most popular ways in formulating an extended release dosage forms [26]. These formulations due to the fact of being comparatively flexible and a well-designed system typically provide reproducible release profiles. Drug release is the procedure by which a medication leaves a drug item and is subjected to retention, conveyance, digestion, and excretion (ADME), inevitably getting to be accessible for pharmacologic activity. As a drug delivery excipient, crystalline nanocellulose is considered to have many promising advantages. Advanced pelleting systems which comprise of nanocrystalline cellulose and other varieties of cellulose is a cutting-edge system whereby the rate of tablet disintegration and drug release may be controlled by excipient layering, microparticle inclusion or tablet coating [244]. The advantage of nanocrystalline cellulose being having a very large surface area and negative charge helps large amounts of drugs that can be attached to the surface of this cellulosic material with the prospect for high payloads and optimal control of dosing.

Some other alternative nanocrystalline materials, like nanocrystalline clays have been found to bind and subsequently release drugs in a controlled manner via ion exchange mechanisms and are being explored for their utilization in pharmaceutical formulations [245]. The nanocellulose in pharmaceutical formulations has been established to be used on account of biocompatibility of cellulose. The presence of a large number of surface hydroxyl functional groups on nanocrystalline cellulose equips a site for the surface modification of the cellulosic material with a large variety of chemical groups by different methods. The hydrophobic drugs can be made to attach with the nanocellulose surface by virtue of surface modification of nanocellulose which may help it to regulate the loading and release of drugs. Poly(caprolactone) chains can be attached onto the nanocrystalline cellulose surface for the same purpose of surface modification as studied by Lonnberg et al. [80]. Moreover, renewability and sustainability are the two important virtues of nanocrystalline cellulose which makes it a low-cost option, ubiquitous

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material and thus provides a substantial environmental advantage as compared to other nanomaterials.

7.2 Application in the medical field

Lately, nanocellulose has been regarded as an important biomaterial with many applications in the biomedical industry. These applications include blood vessel growth; nerves, skins replacements for burnings and wounds; drugs releasing system; gum and dura-mater reconstruction, covering, scaffolds for tissue engineering and bone reconstruction [246-248]. **Fig. 10.** shows some applications for nanocellulose in the biomedical field.
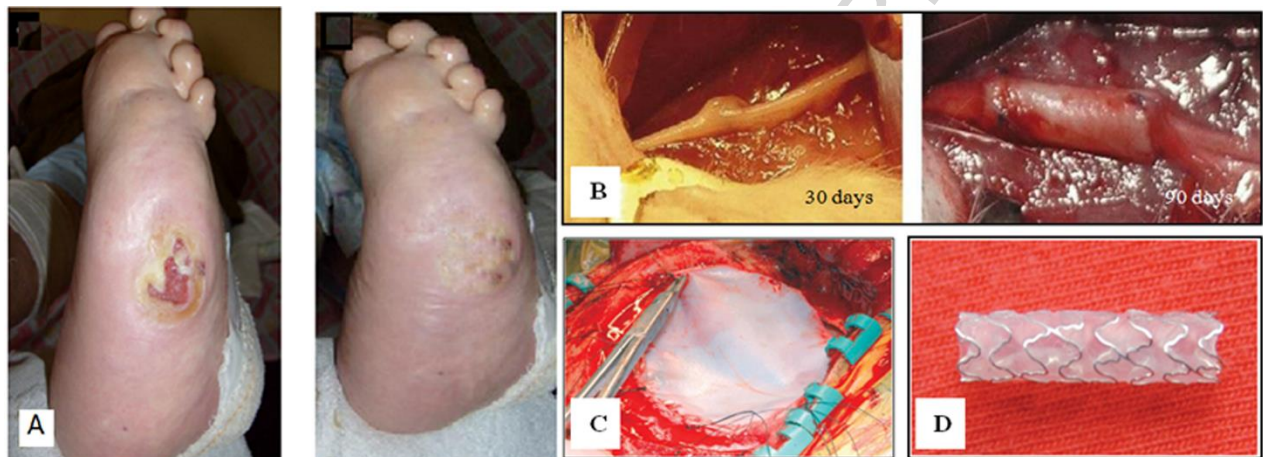
Fig. 10. Nanocellulose for Biomedical applications of (**A**) Nanoskin treatment for diabetic ulcer varicose patient which shows complete healing after 3 months [249]; (**B**) Bacterial cellulose tube overgrown with newly formed blood vessels after 90 days of implantation [250]; (**C**) Duramater reconstruction [251] (**D**) 16 mm-long stainless steel ballon-expandable slotted tube stent covered with biosynthetic cellulose after drying process [Bueno et al., 2009].

Tissue engineering is all about figuring out for new material and devices which has the capability of interacting positively with biological tissues [252], either in vitro for cell growth or reorganizing and developing tissue about to be implanted. This type of engineering also target at advanced classes biopolymers that are biocompatible and has the property of controllable activities and distinct [253], more feasible to be employed as cell scaffolds [254], or in vitro tissue reconstruction.

Recently, a number of biomaterials have been produced as mentioned above. These biomaterials having many characteristics which include physical/chemical and mechanical which eventually decide the final application whether it is tissue regeneration, tissue grafting,

medication holding and releasing, or scaffolding [255]. The biopolymer's chemical surface can dictate cellular response by interfering in proliferation, migration, cellular adhesion, and functioning and accordingly It can be concluded that the scaffold's success is greatly dependent on the cellular adhesion and growth onto the surface. Also, the scaffold surface interaction is highly important in implant effectiveness, including its rejection. As the interaction is well understood at a cell level, the development of new biomaterials and products can be easily thought out. [256]. However, the problems arise on account of the analysis and appropriate modelling, cell seeds and sources and extracellular matrix producing [257].

For the regeneration of tissue three important specifications are generally being taken into consideration: Cells, Support and Growth factors. These specifications play their role in the regeneration process wherein cells synthesize the matrix for the new tissues, support holds the new tissues and keeps the environment proper for the growth, while the growth factors helpsin the promotion of the cell regeneration [257, 258]. The implants endurance is very much dependent on the support cell interactions. The cell's capability to reject and accept the support cell interactions are closely being studied whether to adhere or not to its surface [259]. This factor is very important as it will engage in further responses as cell proliferation, migration and viability.

The advantage of the obtained cellulose in the nanosize provides a huge superficial surface area that gives high water absorption capacity and elasticity. The ideal healing bandage has all these properties of high adsorption capacity and elasticity. While it does not carry any microbial activity. For a good wound healing, nanocellulose mats are considered to be quite competent in promoting autolytic debridement, pain reduction, and accelerating granulation. These membranes can be manipulated in their shape and size, so that it sufficiently useful for the treatment of large and complex areas of the body. Bacterial cellulose has been used to develop a biological membrane along with the extract of propolis as studied by Barud [260]. The anti-microbial and anti-inflammatory activities are a few biological characteristics of propolis. These characteristics of the biological membrane help in the treatment of burns and chronic wounds (**Fig. 10.**). The field of dentistry is confronting the huge task of finding some ideal materials in order to replace the bones in several procedures, as bones malformation, maxillary and facial deformities. The alveolar bone replacement is a great challenge for the material researchers to be

dealt with. The mat comprising of nanocellulose with sufficient porosity provides an infection barrier, painkiller effect, loss of fluids, permits medicines to be applied easily. Besides, the cellulosic mat also absorbs the purulent fluids in the course of all inflammatory stages, drives it out later-on in a controlled and painless manner [255].

7.3 Application in the veterinary field

It has been reported that *A. xylinum* which produces biocellulose finds various applications in veterinary medicine which includes : conduit for separation and reconstruction of peripheral nerves; healing of experimental tegument wounds in equine and swine; healing of wounds of bovine mammary teats; prophylaxis of the formation of membrane post laminectomy in dogs; and healing of incisional experimental lesions of the cornea in dogs [261]. It has been observed that the membrane biologically synthesized from nanocellulose has greater advantages to be used in experimental trochleoplasty in dogs as compared to the conventional treatment [262]. Further, it has reported that these bio-cellulosic membranes help in the tissue formation of fibrocartilage ripe achieving good integration of the freshly formed tissue and the adjoining cartilage, thereby being utilized for the clinical use in dogs. The knee joint related medical issues were also treated by the cellulosic membranes by lateral para-patellar skin incision of 5–7 cm, which was followed by a cut of the retinaculum and articular capsule [262].

The deepening of the trochlear groove with the help of gouge forceps was carried out by Iamaguti et al. [262]. Iamaguti et al. [262] inserted the bionanocellulosic membrane inside the limb of the dogs, the base of cellulose was kept at 5 mm thickness, after making deep groove incision and attaching it at 4–5 simple points isolating the edge normal cartilage, by using synthetic absorbable suture thread [262]. The inclusion of the cellulosic membrane helps in the formation of a link between the subcutaneous tissue in simple continuous pattern and skin. Well defined repaired tissue is being generated which covers the area of trochleoplasty with higher thickness than the previous period.

The deformity of the abdominal wall has been reported to take care off by the nanocellulose membranes in humans or animals. It was Falcao et al. [263] who managed to incorporate host tissue with bio-cellulosic composite membranes obtained from the bacteria and polytetrafluoroethylene (PTFE) in order to treat the abdominal wall defects of rats. Prolene® and continuous suturing were carried at the level of the muscle aponeurotic defect by anchoring the

cellulose membrane at the four angles of the rectangle. Subsequently, Mononylon® thread was used to close the skin by an interrupted suture.

7.4 Application in the dental field

The regeneration of dental tissue is being carried with the aid of nanocellulose. For the regeneration of dental tissues in humans, microbial cellulose synthesized from Glucanacetobacter xylinus strain, has been reported to be used. **(Fig. 11.)**. Gengiflex® and Gore-Tex® are the two important stakeholders producing nanocellulose product which has a target application within the dental industry. It was developed to aid periodontal tissue recovery [264]. Gengiflex® therapy provides a full-fledged restoration of an osseous defect around an IMZ implant. This treatment has an advantage of the restoration of aesthetics and function of the mouth and that too with minimization of surgical steps.
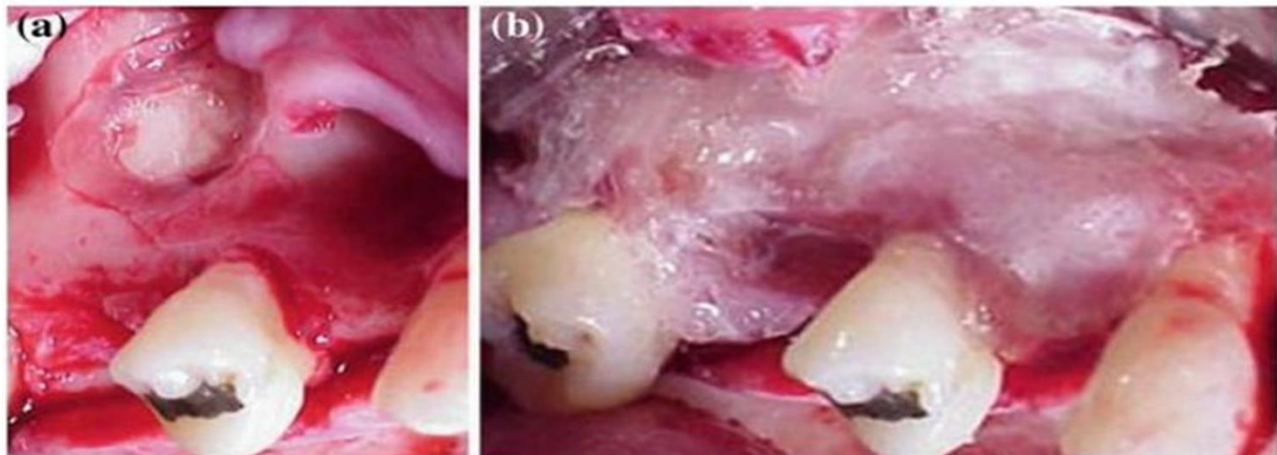
Fig. 11. Dental tissue regeneration by bacterial cellulose used in 38-years old male patient [265].

Gengiflex® which is simply a bandage comprised of two layers with the inner layer being composed of microbial cellulose, provides rigidity to the membrane and the outer alkali-cellulose layer is chemically modified [266]. Dahlin et al. [267] reported *in-vivo* non-healing bone-defect model was used by Salata et al. [268] to compare the biological performance of Gengiflex® and Gore-Tex® membranes.

Gore-Tex® membranes which are basically a composite with urethane, polytetrafluoroethylene, and nylon has proved that these membranes were coherent with substantially meagre inflammation and both membranes bolster the same amount of ossification

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(bone formation) during the same amount of time. It was reported that a greater amount of ossification was found in bone defects covered by either microbial cellulose membrane or Gore-Tex®, as compared to the control sites. It has been observed that Gore-Tex® is better endured by the tissues as compared to the Gengiflex®.

Lately, Macedo et al. (2004) [269] similarly also compared polytetrafluoroethylene (PTFE) and bacterial cellulose as physical barriers employed to treat bone defects in guided tissue regeneration. Macedo et al. [269] also studied two osseous defects (8 mm in diameter) that were executed in each hind-foot of four adult rabbits, using surgical burs with constant sterile saline solution soaking. PTFE barriers were used to cover right hind-feet in order to know its effects while the left hindfeet wounds were protected with Gengiflex® membranes. It was finally reported that after a span of 3 months, the histological evaluation of the treatments showed that the defects protected with PTFE barriers were comprehensively repaired with bone tissue, whereas defects treated with Gengiflex® membranes were found to have incomplete lamellar bone formation, thereby emanating in voids and lack of continuity of bone deposition.

8. Conclusions and future perspectives

The sustainability, renewability, nanosized fiber distribution, mechanical properties, compatibility and flexibility in its utilization are some of the major characteristics of nanocellulose which makes it a unique and indispensable biomaterial in the health sector. The nanocellulose composite scaffolds are biocompatible with less rejection with cellular contact and blood cells and thereby is considered as a promissory biomaterial which is also suitable for cell adhesion/attachment suggesting that these scaffolds can be used for wound dressing or tissue-engineering scaffolds.

The cellulose-based biocomposites and nanocomposites have a wide range of potential applicability. Some of the major fields of applications of nanocellulose-based materials on account of its varied and excellent characteristics include medical, pharmacy, cosmetics, dental and veterinary applications. The high tensile strength and stiffness, the surface functionality (having many hydroxyl groups), the specific arrangement as well as the nano-dimensions of nanocellulose ingrains very beneficial and excellent properties to reinforced nanocomposite materials.

The major focus and aim of this review were to highlight the current state of research and development in the field of nanocellulose which is simply a bio-polymeric sustainable material. This excellent supramolecular nanofiber network structure and the resulting valuable characteristics have led to real opportunities and extensive activity in the field of biomedical applications. The gist of this review is to widen the knowledge in this discipline of studies and to simulate the practical application of nanocellulose. In summary, the future of the cellulose-based biocomposites and nanocomposites will go through a combination of the different approaches and provides wide range of potential applications in medical and biomedical filed.

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