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# **Nanocelluloses as Skin Biocompatible Materials for Skincare, Cosmetics, and Healthcare: Formulations, Regulations, and Emerging Applications**

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## **Abstract**

Skin biocompatible materials are amongst the fastest-growing markets for nanocelluloses, with a growing number of patents published over the past ten years. This review highlights the recent developments, market trends, safety assessment, safety regulations, and challenges for different nanocellulose types used in skincare, cosmetics, and healthcare. Firstly, different classes of nanocelluloses (nanoparticles, nanocrystals,

25 nanofibers, nanoyarns, hydrogels) and their synthesis methods were highlighted. Secondly,  
26 unique properties of nanocelluloses for applications onto the skin (i.e. high surface  
27 functionality, high dispersion stability, high water-holding capacity, and biocompatibility)  
28 were highlighted. Thirdly, recent uses of nanocellulose composite as carriers for bioactive  
29 compounds and UV-blockers as well as wound healing and skin sensors were also provided.  
30 Finally, a toxicological assessment for various nanocellulose types was discussed based on  
31 their sizes and morphologies. The challenges and perspectives for an industrial breakthrough  
32 are related to further optimization of production and processing conditions of nanocelluloses  
33 were also highlighted.

34 **Keywords:** Spherical Cellulose Nanoparticles; Cellulose Nanocrystals; Cellulose Nanofibers;  
35 Bacterial Cellulose; Cellulose Nanoyarn; Cellulose Hydrogels; Wearable Sensors; Skin  
36 Regeneration

37

## 38 **1. Introduction**

39 Over the past decades, nanocelluloses have dramatically evolved as highly functional and  
40 biocompatible materials for applications onto the skin e.g. skincare, cosmetics, healthcare and  
41 health monitoring (Mohiuddin, 2019). A new class of wearable sensors so called as lab-on-  
42 skin where smart, flexible and stretchable devices are integrated into the skin, provides direct  
43 monitoring and diagnostic interfaces to the body. Skincare formulations (makeup, creams,  
44 lotions, facemask) are generally created by combining chemical compounds from synthetic or  
45 natural sources (Banerjee, 1988). Thickening agents, film formers, ultraviolet absorbents,  
46 antioxidants, sequestering agents, coloring agents, vitamins, pharmaceutical agents are the  
47 main components in many cosmetics and skincare formulations (Herman et al., 2012). The  
48 oily materials (e.g., oils, fats, waxes, and ester oils, and surface-active agents, emulsifiers,  
49 solubilizing agents, higher alcohols, fatty acids, and silicones) further control the evaporation

50 of moisture from the skin and improve the sensitive feeling (Santos et al., 2019). Natural and  
51 synthetics polymers are key ingredients in products for hair care (shampoos, tip repair,  
52 conditioners, hair dyes, fixing gels, moisturizing masks), skincare (liquid soaps, body oils,  
53 moisturizing lotions, sunscreen), and appearance improvement (nail care, fragrance, make-  
54 up). Nowadays, industrial investments are growing in the development of “green-tech”  
55 solutions replacing synthetic ingredients with natural materials. New skincare, cosmetics,  
56 health monitoring products include natural biopolymers and bioactive compounds to meet the  
57 high demands for therapeutic and protective care products, which stimulate the skin functions  
58 such as healing, protection, immunity and thermoregulation (Aguilar-Toalá et al., 2019). The  
59 proteins (e.g., collagen and wheat proteins) and polysaccharides (e.g., cellulose, alginic acid,  
60 and hyaluronic acid) have been particularly added to enhance specific functionalities of the  
61 products applied onto the skin.

62 Nanocelluloses (nanoparticles, nanocrystals, nanofibers, nanoyarns, and bacterial  
63 cellulose) have been recently integrated into skincare, cosmetics, and health monitoring  
64 products as green alternative biopolymers to replace synthetic polymers such as polyethylene,  
65 polyacrylamides, and nylon (Almeida et al., 2021). The nanocelluloses are primarily  
66 produced from soft and hardwood species, phloem fibers (flax, hemp, jute, ramie), grasses  
67 (bagasse, bamboo); or non-pathogenic bacteria, fungi, algae, and marine animals (Sfiligoj et  
68 al., 2013). The nanocelluloses are promising sustainable nanomaterials for skincare  
69 formulations with enhanced performance, owing to their biocompatibility, high aspect ratio,  
70 high surface area, abundant surface charge, and mechanical strength. In addition, the surface  
71 chemistry of nanocelluloses can be easily modified for tuning affinity towards specific  
72 bioactive molecules and drugs (Thomas et al., 2018). At present, the global nanocelluloses  
73 market is forecasted to achieve USD 783 million by 2025, with an expected annual market  
74 growth rate of 21.4% from 2020 to 2026 (Trache et al., 2020). To date, nanocelluloses have

75 been used as anti-wrinkle agents, compatibilizers, moisturizers, and rheological agents or  
76 thickeners. They have been added in cleansing formulations to remove dirt, reduce sebum  
77 and exogenous contaminants, and control skin odor and microflora (Mishra et al., 2020).  
78 Especially nanocellulose hydrogels show great promise in a range of skincare and healthcare  
79 applications. They provide a thick but non-tacky feel and are especially applied as an additive  
80 in mask packs and basic cosmetics. Nanocellulose hydrogels retain high water content and  
81 this keeps the wound warm and moist, which is optimal for healing. They have been also  
82 used for in developing novel wearable biosensors that able to monitor biomarkers levels for  
83 disease diagnosis and health monitoring (Dervisevic et al., 2020).

84         This review discusses recent advances in nanocelluloses in the framework of skin  
85 biocompatible materials, as well as their formulations, composition and functionality as well  
86 as their emerging skincare applications. The roles of different nanocellulose types (spherical  
87 nanoparticles, nanowhiskers or nanocrystals, nanofibers, nanoyarns, hydrogels, bacterial  
88 cellulose) and their exceptional properties for application in cosmetics, skincare, skin  
89 regeneration, wound healing, and skin wearable sensors are presented. This multidisciplinary  
90 article also offers an updated and critical assessment of recent findings on uses of  
91 nanocelluloses as thickeners, anti-wrinkle agents, compatibilizers, moisturizers, film-forming  
92 materials, formulation modifiers, UV-blockers, and drug delivery vehicles. Both relevant  
93 scientific research topics and industrial patents on nanocelluloses in skincare and cosmetics  
94 are comprehensively summarized. A perspective on nanocelluloses used in skincare  
95 formulations is given concerning current safety regulations. The challenges for fast progress  
96 in commercial application and future perspectives of nanocelluloses for applications onto the  
97 skincare are finally covered.

98

## 99 **2. Origins and production of nanocelluloses**

100 Nanocellulose is obtained as an engineered product from cellulose, which occurs as the most  
 101 abundant material in plant cell walls with an intrinsic hierarchical nanostructure. The  
 102 chemical structure and number of repeating cellobiose units in the cellulose structure  
 103 determine the polymerization degree. The functional groups (hydroxyl groups) at the outer  
 104 sites give rise to strong intermolecular hydrogen bonds forming a network with parallel sheet-  
 105 like molecular stacking and supramolecular ordering. The morphologies and characteristics  
 106 of nanocellulose (size, morphology, aspect ratio, surface charge, functionality) can be  
 107 modulated by selecting specific raw materials, fabrication techniques, and processing  
 108 parameters. According to their length, diameter, aspect ratio, and composition, the  
 109 nanocelluloses can be classified as in Table 1 (Barhoum et al., 2020), with: (i) nanocellulose  
 110 spherical particles (NCSPs; amorphous and crystalline), (ii) cellulose nanocrystals (CNCs,  
 111 crystalline), (iii) cellulose nanofibrils (CNFs, semi-crystalline), or (iv) bacterial cellulose  
 112 (BNC, higher crystallinity), and (iv) cellulose nanoyarns (CNY, semi-crystalline). A  
 113 description of the different nanocellulose morphologies is best illustrated with microscopic  
 114 images in Figure 1.

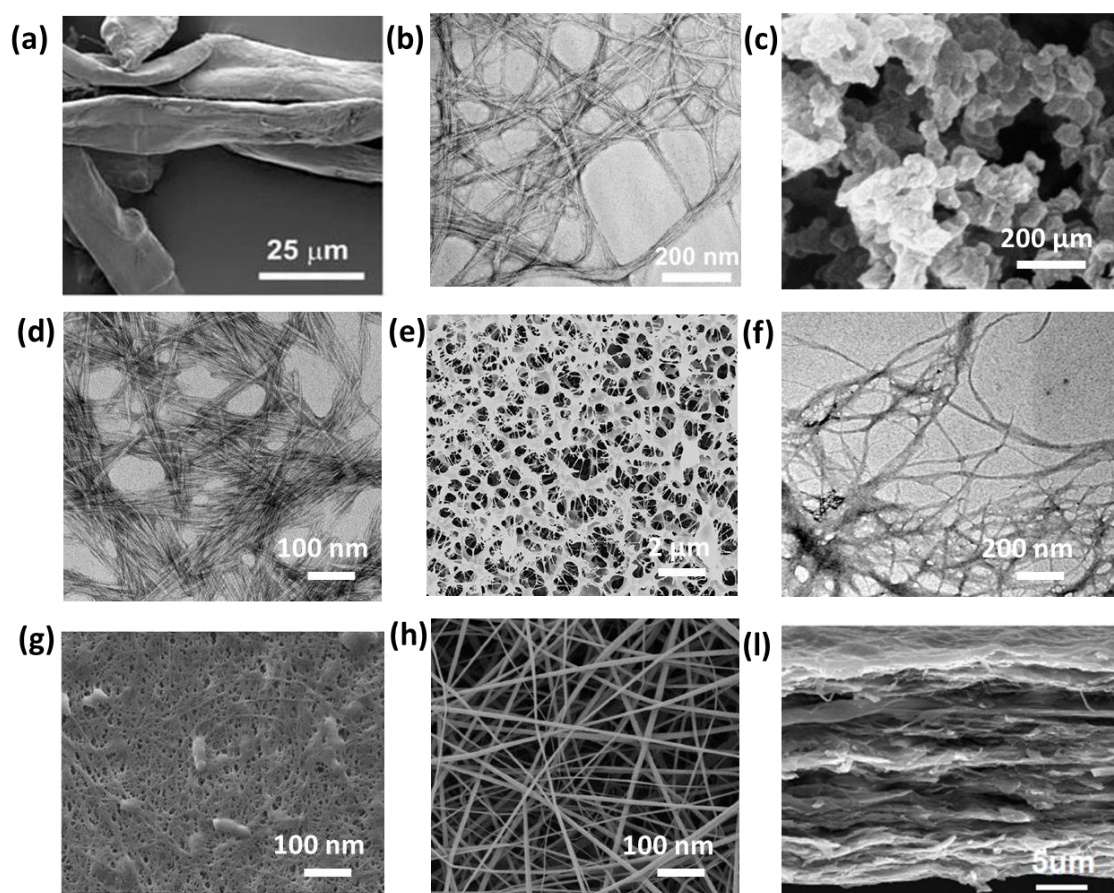
115 Table 1. Nomenclature, size, morphology, and preparation methods of cellulose  
 116 nanomaterials

| <b>Nanocellulose type</b>                | <b>Size range</b>                | <b>Morphology</b>              | <b>Crystallinity</b>          | <b>Sources and preparation</b>                 | <b>Ref</b>                 |
|--|----------------------------------|--------------------------------|-------------------------------|--|----------------------------|
| Nanocellulose spherical particles (NCSP) | Diameter: 50-100 nm              | Spherical                      | Amorphous or semi-crystalline | Waste cotton through mild enzymatic hydrolysis | (Meyabadi et al., 2014)    |
| Cellulose nanocrystal (CNC)              | Length: 100 nm–1 $\mu$ m         | Rod-like                       | Crystalline                   | Alkali treatment and acid hydrolysis of        | (Heath & Thielemans, 2010) |
| Cellulose nanofibril (CNF)               | Length: 1–3 $\mu$ m<br>Diameter: | Fibers with network structures | Semi-crystalline              | Mechanical treatment (refining) of wood or     | (Barhoum et al., 2020)     |

|                               |                                       |  |                    |   |                        |
|-------------------------------|---------------------------------------|--|--------------------|---|------------------------|
| Bacterial nanocellulose (BNC) | Length: 200 nm–3 $\mu$ m<br>Diameter: | Fibers with network structures                       | Highly crystalline | Biological treatment of cellulose-based materials | (Boisset et al., 2000) |
| Cellulose nanoyarn (CNY)      | Length: several microns<br>Diameter:  | Fibers with network structures or aligned structures | semi-crystalline   | Electrospinning of cellulose derivative with a    | (Gouda et al., 2014)   |

117

118



119

120 Figure 1. Different size and morphologies of cellulose-based materials observed by scanning  
 121 electron microscopy (SEM) or transmission electron microscopy (TEM): (a) cellulose  
 122 microfibrils (CMFs) from wood pulp (Gentile et al., 2018); (b) cellulose nanofibers (CNFs)  
 123 from wood pulp (Nissilä et al., 2021); (c) spherical cellulose nanoparticles (NCSPs) from  
 124 plant sources (Zhang et al., 2007); (d) cellulose nanocrystals (CNCs) from plant source ( J.  
 125 Dai et al., 2018); (e) hydrogel prepared from cellulose nanocrystals (Zhang et al., 2017); (f)

126 cellulose nanofibers (CNFs) from plant origin (Yassin et al., 2019); (g) bacterial  
127 nanocellulose (BNC) (Orlando et al., 2020); (h) cellulose nanoyarns (CNYs) by  
128 electrospinning from cellulose acetate (Rodríguez et al., 2014); (i) cross-section of cellulose  
129 film prepared from cellulose nanofibers (Qi et al., 2020).

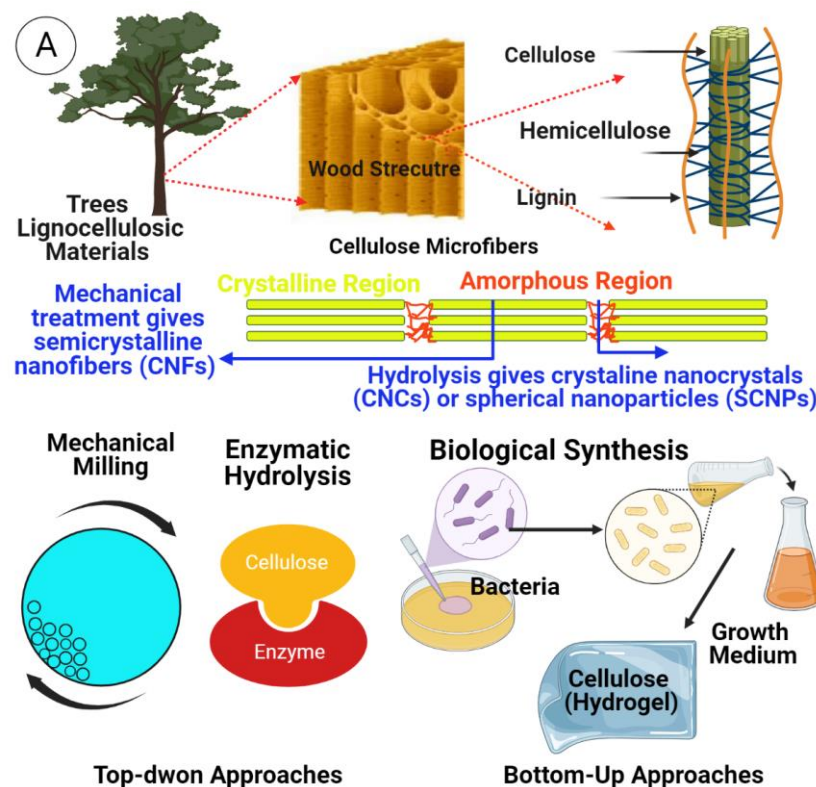
130

131 To date, the main raw materials to obtain nanocelluloses are plants, whereas bacteria  
132 and microalgae, tunicates are currently less used (Barhoum et al., 2020). The selected plant  
133 fibers for the production of cellulose can be distinguished according to six main clusters, i.e.  
134 bast, core, grass and reed, leaf, seed, or other fibers. Wood pulp fibers or residual paper fibers  
135 are common sources for conversion into nanocellulose due to the relatively high purity of  
136 cellulose after bleaching, their ductility, and excellent physical properties (Barhoum et al.,  
137 2020). Using the proper combination of mechanical, chemical, physicochemical, and/or  
138 biological processing steps, both length and diameter of native cellulose microfibrils can be  
139 progressively reduced to create cellulose substances with at least one dimension in the 10-100  
140 nm range. Researchers have currently developed several processing routes for nanocellulose  
141 fabrication (Zhang et al., 2019), as schematically illustrated in Figure 2: (i) mechanical  
142 routes, including milling, grinding, refining, homogenization, cryo-crushing normally require  
143 high-energy input and provide a high yield of low-crystalline nanocelluloses (CNF) at  
144 relatively low cost; (ii) physical routes, including ultrasonication, steam explosion, wet  
145 spinning, dry spinning, melt spinning, electrospinning, and 3D printing have been used to  
146 produce electrospun cellulose acetate nanofiber (Barhoum et al., 2019), (Long et al., 2019);  
147 (iii) chemical routes, including alkali treatment, followed by acid hydrolysis with appropriate  
148 chemicals and optimized reaction conditions generally provide highly crystalline  
149 nanocelluloses (CNCs) with specific functionalities and high purity (Barhoum et al., 2019);  
150 (iv) biological routes, including enzymatic hydrolysis are typically combined with



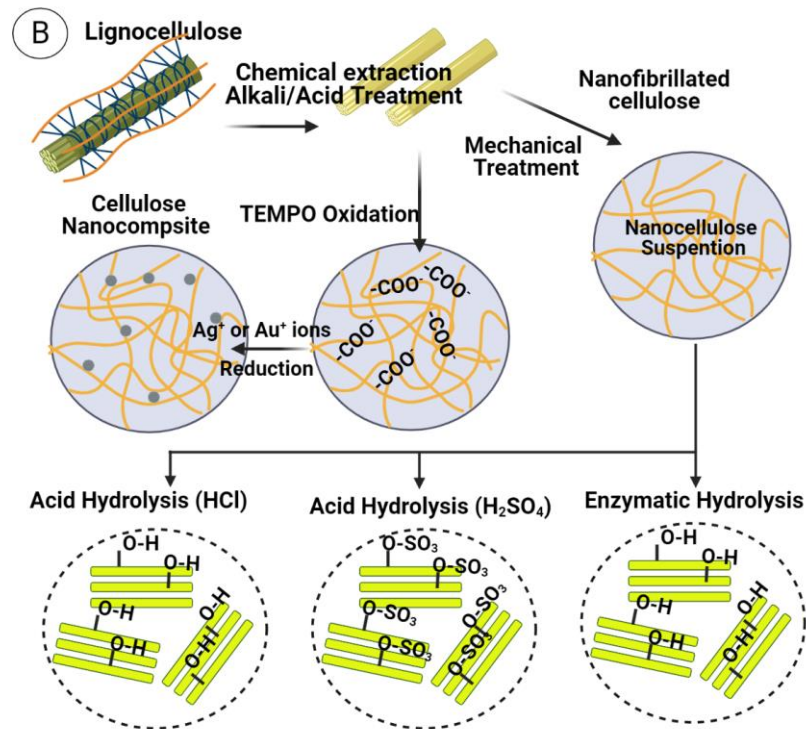
151 mechanical fragmentation or chemical hydrolysis to reduce chemical waste and energy  
 152 consumption. Bacterial nanocellulose (BNC) is naturally produced as an exopolysaccharide  
 153 by some bacteria (former *Gluconacetobacter*) cultivated in a medium with carbon and  
 154 nitrogen sources (Rasouli et al., 2019). Unlike nanocelluloses produced by former methods,  
 155 BNC is free of lignin, hemicelluloses, and pectin. Similarly, microalgae are a largely  
 156 unexplored source of new forms of nanocellulose. Microalgae can be grown in ocean-based  
 157 systems or on non-arable land using salt- or wastewater (Ross et al., 2021). Tunic tissue of  
 158 tunicates (marine invertebrate animals) is the only known animal source of crystalline  
 159 nanocelluloses (Zhang et al., 2019).

160

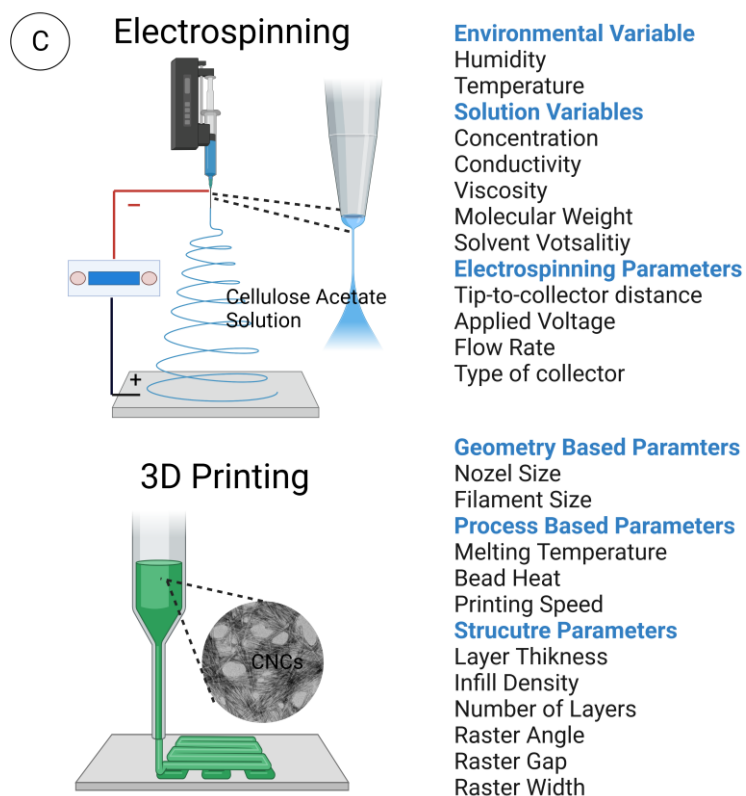


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165 Figure 2. A schematic presentation summarizes different routes for synthesis and surface

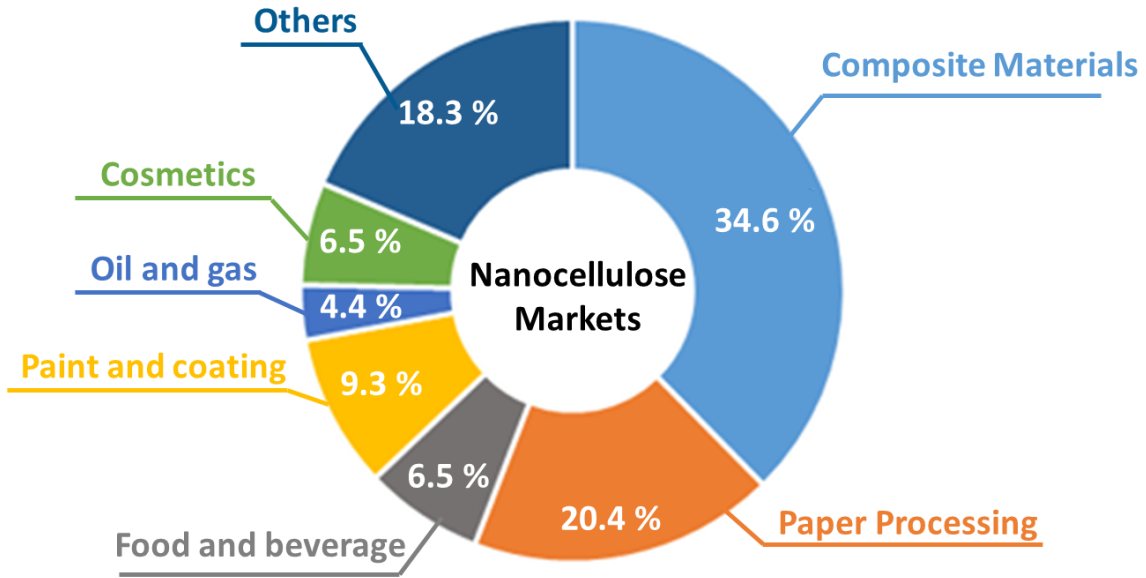
166 functionalization of nanocelluloses: (a) Mechanical (ball milling) and biological routes

167 (enzymatic hydrolysis and bacterial synthesis) for producing nanocelluloses; (b) chemical

168 routs for producing nanocelluloses from bacteria followed by chemical functionalization from  
169 plant sources; (c) physical routes for fabrication of nanocelluloses electrospinning and 3D  
170 printing process and their processing parameters.

171

172         Size, morphology, crystallinity, and surface chemistry among other properties of  
173 nanocelluloses, vary with their origin and processing protocols. Thus, it offers a toolbox set  
174 to adapt desired features towards a given application while it is challenging to produce  
175 nanocelluloses with predetermined and constant properties. After the discovery of  
176 nanocellulose in the early 1980s, the initial commercialization was limited by the high energy  
177 requirements ( $\cong$  30,000 kWh/ton) for fiber disintegration during mechanical production  
178 (Barhoum et al., 2019). However, recent progress in energy-saving pretreatments of cellulose  
179 fibers has reduced the energy requirements by more than 98% (Zhang et al., 2019).  
180 Consequently, the first industrial pilot-scale factories for CNCs and CNFs production were  
181 established from 2012 on with increasing capacities. The global market size of nanocelluloses  
182 turns close to USD 146.7 million in 2019 and is expected to grow at an annual rate of 21.4%  
183 from 2020 to 2026 (Katz et al., 2015). Figure 3 depicts the market distribution of  
184 nanocellulose and its use in specific niche segments (Kiral Puldini, 2020). Although the  
185 market share of nanocellulose in skincare, cosmetics, health monitoring products is relatively  
186 small, this is expected to be the most expanding domain in coming years particularly for  
187 sunscreen lotions, creams and novel cosmeceuticals (Kiran Pulidindi, 2020), (Blanco et al.,  
188 2018).



189

190 Figure 3. Market share of nanocellulose products with the contribution in different segments  
 191 with 6.5 % in cosmetics and personal care products.

192

193 **3. Unique properties of nanocellulose for application onto skin**

194 Some nanocelluloses properties are superior comparing to those of the native cellulose,  
 195 thanks to their high surface reactivity and ability for formation of a dense network structure  
 196 with high intrinsic strength and high stiffness along the single fibers (Blanco et al., 2018; De  
 197 Amorim et al., 2020). The high specific surface area occupied by hydroxyl side groups (-OH)  
 198 and large water holding capacity provide the nanocellulose materials with interesting features  
 199 for skincare, cosmetics, health monitoring products.

200

201 **3.1 High surface functionality**

202 Nanocelluloses, like many other polysaccharides, have a surface with plenty of hydroxyl  
 203 moieties that are available for chemical modification or become easily hydrated, thus  
 204 increasing the compatibility with biological tissue. The surface modification of

205 nanocelluloses can be classified into three groups: (i) native surface chemistry during the  
206 isolation/purification process or as a result of similar methods of surface treatment, (ii)  
207 physical adsorption at the surface through electrostatic charge interactions, and (iii) covalent  
208 bond formation or derivatization (Tortorella et al., 2020). The chemical modifications are  
209 mainly performed to introduce charged or hydrophobic moieties through amination,  
210 esterification, oxidation, silylation, carboxymethylation, epoxidation, sulfonation, thiol- and  
211 azido-functional reactions (Vecino et al., 2017). Recently, nanocelluloses have been produced  
212 by grafting side groups near the hydroxyl groups at positions C2, C3, or C6 of the  
213 glucopyranose monomer. The chemical stability, salt tolerance and acid resistance of  
214 modified nanocelluloses are thus improved compared with native nanocellulose. The aqueous  
215 media with modified nanocellulose display higher viscosity, pseudo-plasticity, and thixotropy  
216 when added at high concentrations to suspensions and emulsions, increasing the gel strength  
217 and thickening performance (Barhoum et al., 2019). The high surface area and  
218 functionalization capacity make nanocelluloses suitable as thickeners, emulsifying agents,  
219 wetting agents, foaming substances, and hydrating and/or moisturizing agents to enhance skin  
220 perception (Mellou et al., 2019).

221

### 222 **3.2 High viscosity and shear thinning behavior**

223 Nanocellulose has interesting rheological features resulting in good applicability and skin  
224 feel. As an additive in skincare and cosmetic formulations, it regulates the rheological  
225 features for viscosity, thickening, and film formation, allowing to adapt the performance and  
226 physical properties of personal care products (Mitura et al., 2020; Alves et al., 2020). The  
227 rheological properties are mainly governed by the morphology, concentration, and degree of  
228 substitution of the nanocellulose. The good applicability of nanocellulose in creams and  
229 lotions is explained by its intrinsic viscous-elastic properties. In particular, the high viscosity

230 at zero shears reduces the dripping effect and the intrinsic shear-thinning effect facilitates the  
231 spraying application (Tortorella et al., 2020). The gelling properties with high gel strength are  
232 attributed to the formation of chemical cross-links between carboxyl groups, forming a three-  
233 dimensional network structure. In parallel, the gel network retains water inside and can be  
234 exploited to improve the water retention of the final product. Unlike other rheological  
235 modifiers, the thickening and film-forming properties of nanocelluloses allow the formation  
236 of a thick layer by only one spray application. The thickening features make them suitable for  
237 sunscreen sprays. After application and drying, they provide a homogeneous layer with a  
238 non-oily skin appearance having a smooth haptic feeling on the body and face (Dufresne,  
239 2019). Nanocelluloses have been used as slipping agents to enhance the cream's smooth  
240 texture, as an anti-caking agent for skincare and cosmetic foundations, and as film former for  
241 thin-layer nail polishes. By tuning the rheological and iridescence features of the dispersions,  
242 a nanocellulose thickener is compatible with cosmetic products for eyelashes, hair, nails, and  
243 eyebrows, among pharmaceutical products (Dhali et al., 2021).

244

### 245 **3.3 High dispersion stability over a wide pH range**

246 Nanocelluloses possess long shelf life and provide aqueous dispersions with enhanced  
247 stability at a broad pH range and high temperatures. The formulations of skincare emulsions  
248 and suspension can benefit from better stability and homogeneous mixing of its components  
249 in aqueous media. Nanocelluloses are used in skincare formulations to stabilize oil-in-water  
250 emulsions without the need for additional surfactants. Unmodified pristine nanocelluloses  
251 with high surface charge density are not effective stabilizers for oil-in-water emulsions (Lin  
252 et al., 2019). The nanocelluloses with grafted hydrophobic polymers such as cinnamoyl  
253 chloride or butyryl chloride can enhance their affinity towards the oil phase, thus reducing the  
254 interfacial tension. The hydrophobic nanocelluloses are therefore increasingly used as a

255 natural stabilized for Pickering emulsions. Depending on the increase in the aspect ratio of  
256 different CNCs morphologies, the different stabilization mechanisms of nanocellulose in  
257 emulsions are illustrated in **Figure 4a** (Tang et al., 2019). The CNCs with increasing aspect  
258 ratio could be obtained through acid hydrolysis of various sources including cotton (low  
259 aspect ratio), BNC (intermediate aspect ratio), and Cladophora green algae (high aspect ratio)  
260 (Kalashnikova et al., 2013). The nanocellulose emulsions have better stability upon changes  
261 in pH, temperature, and salt concentrations compared with gum-based formulations (Ullah et  
262 al., 2016).

263

### 264 **3.4 High water-holding and retention capacity**

265 Nanocellulose has a high water-holding capacity with a water content of up to 80% and  
266 consequently has a gel-like appearance even at rather low concentrations. The high water  
267 holding capacity or water retention is particularly mentioned as a key property of a dense  
268 fibrillary nanocellulose network (CNF), where the free water is entrapped and not easily  
269 released (Tortorella et al., 2020). Although nanocelluloses display excellent water-holding  
270 capacity, they are not water absorbents and not soluble in water (Lin et al., 2019). Therefore,  
271 nanocellulose can preserve the moisturizing effect on the skin and enhance wet compatibility  
272 with skin and hair. The nanocellulose can be dispersed in strong polar solvents (especially  
273 water) due to the strong interaction between the surface hydroxyls or carboxyl group and  
274 their gelation mechanism can be tuned by changing the nanocellulose concentration, varying  
275 pH of the medium, adding salt, or crosslinking (**Figure 4b**) (Mendoza et al., 2018). As drying  
276 of nanocellulose is an irreversible process, it cannot be easily redispersed and does not re-  
277 absorb the same amount of water. The drying process introduces agglomeration that reduces  
278 the surface area and changes the surface character permanently. Relying on the water-holding  
279 properties, nanocellulose was industrially introduced in diapers and deodorant sheets,

280 allowing the production of less fluffy material and thinner pads with high mechanical  
281 strength. Using the recently developed nanohydration technology, the nanocellulose is also  
282 contained in moisturizing masks with anti-aging features for the eye, face, or neck.

### 283 **3.5 Purity and biocompatibility**

284 Nanocellulose can be obtained with high purity and biocompatibility, which makes it reliable  
285 to use, while not affecting the smell and appearance of the final formulations. The source and  
286 processing route define the nanocellulose composition and possible impurities. When  
287 produced from plant (lignocellulosic) sources, the nanocelluloses contain different grades of  
288 hemicelluloses and lignin. However, these impurities can be removed using additional  
289 pretreatment steps such as chemical bleaching. Alternatively, the BNC is preferred as it is  
290 directly produced with extremely high purity and 100% cellulose content (Lin et al., 2019).  
291 Highly pure nanocelluloses for cosmetics are typically whitish and have a neutral appearance,  
292 thus avoiding the need to adjust the final formulations to obtain a constant color and  
293 appearance (Lin et al., 2019). Impurities might lead to incompatibilities or decrease the  
294 formulation performance due to interactions with other formulation ingredients. Impurities  
295 might also interact with the hydroxyl groups of nanocellulose, making them less available for  
296 proper interaction with the formulation ingredients. Impurities might also lead to allergies,  
297 unwanted effects or unexpected reactions (Blanco et al., 2018). High water  
298 retention capability, flexibility, biocompatibility, high purity, and high drug loading capacity  
299 make BC a potential material for wound healing applications.

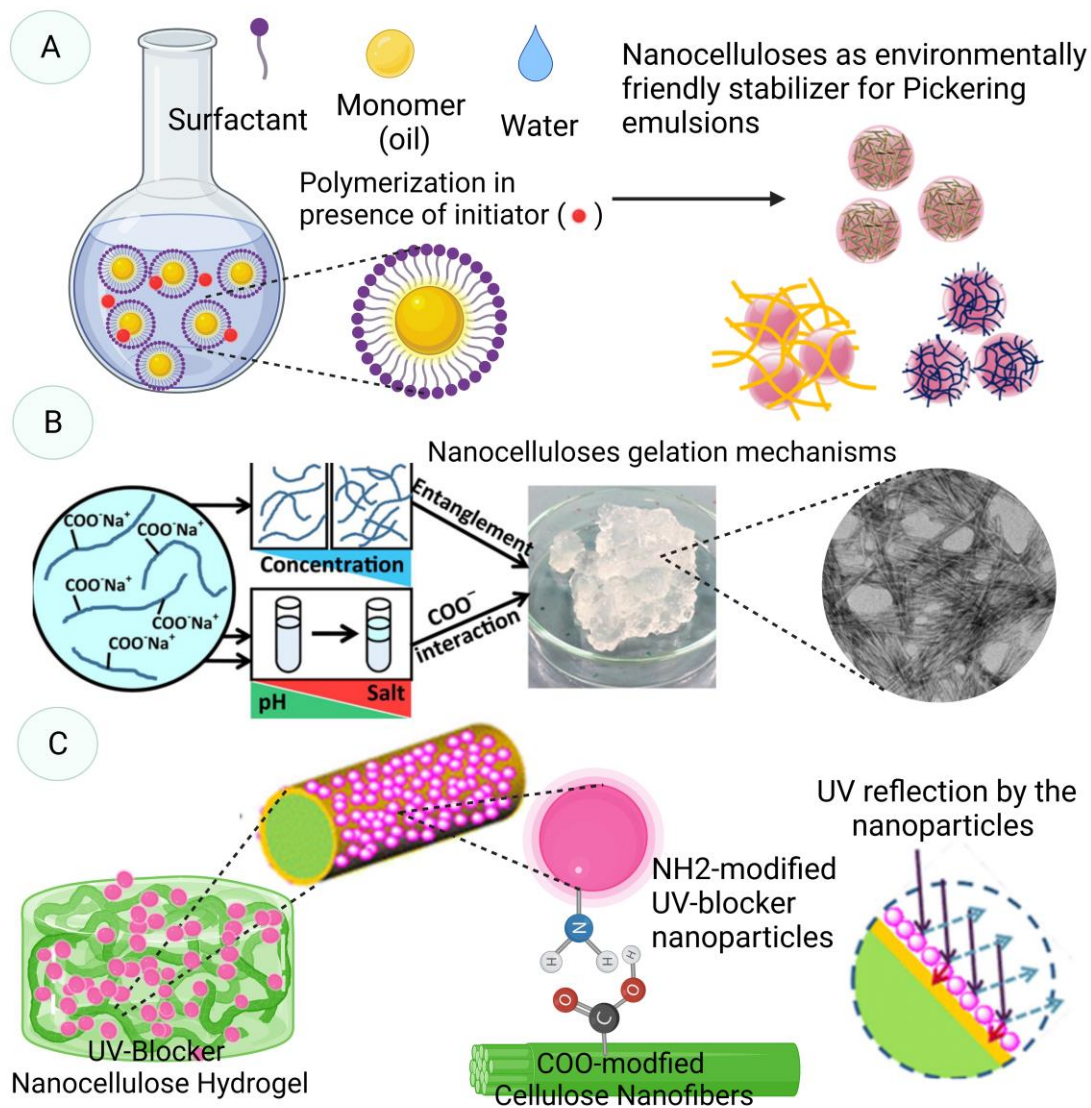
300

### 301 **3.6 Multifunctional nanocarriers**

302 Nanocellulose hydrogels with nanoscale porosity offers the capacity to load bioactive  
303 ingredients and UV-blockers. The nanocellulose matrix protects the encapsulated ingredients  
304 as they will not react or decompose upon direct exposure to the environment or sunshine. The



305 nanocelluloses themselves have no antimicrobial properties, but they can be added through  
306 loading with an antimicrobial agent (Kupnik et al., 2020). Recently, CNFs decorated with  
307 TiO<sub>2</sub> and ZnO nanoparticles having high refractive index and UV absorbance are used to  
308 produce transparent nanocellulose films (**Figure 4c**). The deposition of TiO<sub>2</sub> nanoparticles  
309 through physical interaction adds good UV resistance to nanocellulose fibers (Souto et al.,  
310 2020). The TiO<sub>2</sub> can be further modified with hydrophobic ( $\gamma$ -aminopropyl) triethoxysilane to  
311 obtain –NH<sub>2</sub> groups that can interact with the –OH groups of the CNF (Zhao et al., 2018).  
312 The high transparency of such hybrid films results in materials with excellent optical and  
313 mechanical features. Therefore, nanocellulose-based composites have a high potential for  
314 protective skincare formulations. As nanocellulose is odorless, it does not interfere with the  
315 selected fragrance added to a skincare product or it can serve as a carrier for the fragrance  
316 itself. Due to its intrinsic properties (biocompatibility, biodegradability, high surface area,  
317 unique rheological properties, and geometrical dimensions), nanocellulose is widely studied  
318 for drug delivery systems to the skin and oral routes. Its potential multifunctionality through  
319 chemical modification can be exploited to bind and release therapeutic agents and/or  
320 antibacterial compounds (Kupnik et al., 2020).



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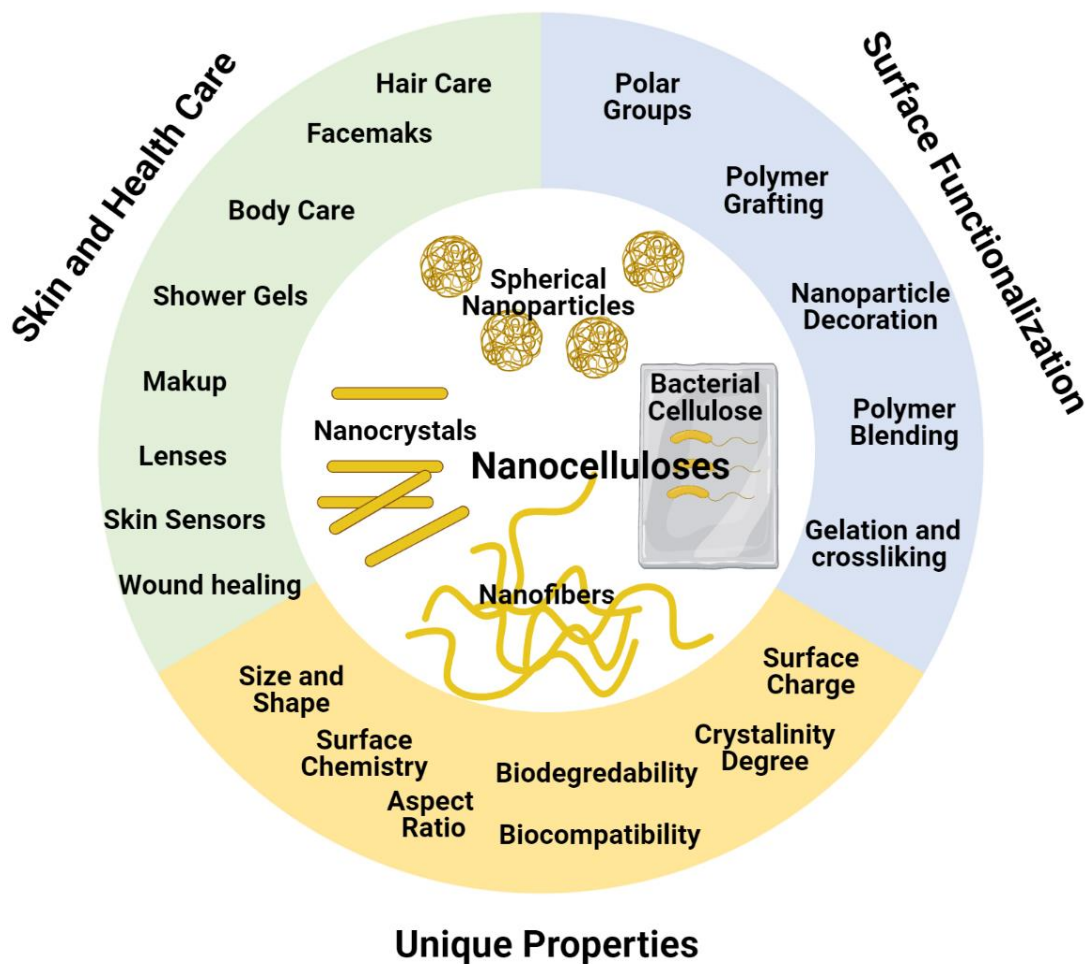
322 Figure 4. Unique characteristics of nanocelluloses for skincare formulations: (a)  
 323 Nanocellulose satisfies the increasing demands for a sustainable and environmentally friendly  
 324 stabilizer for Pickering emulsions with different aspect ratio to stabilize oil droplets. (b)  
 325 Nanocelluloses have high ability for dispersion in some strong polar solvents (water) and gel  
 326 formation mechanism can be controlled by changing the reaction parameters such as  
 327 nanocellulose concentration, pH of the medium, or adding salt or cross-linker, Figure adapted  
 328 from (Mendoza et al., 2018); and (c) Nanocellulose can be used as in production of a UV-  
 329 resistant composite by adding inorganic UV-blocker nanoparticles with appropriate surface  
 330 modification.

#### 331 **4. Application of nanocelluloses for cosmetics and skincare products**

332 Emerging applications of nanocelluloses in cosmetics and skincare formulations are  
333 increasing because of their superior functionality, stability and long-lasting effects  
334 (Mihrianyan et al., 2012). An overview of application domains of nanocelluloses in cosmetics  
335 and skincare formulations together with unique properties and surface functionalization  
336 during production is summarized in **Figure 5**. Initially, nanocelluloses were incorporated in  
337 cosmetics and skincare formulations as film-forming material to create a protective shield for  
338 the skin against harmful sunlight radiation (Kushwaha et al., 2020). New skincare products  
339 based on nano-emulsion systems use nanocellulose thickeners and stabilizers (Hameed et al.,  
340 2019; S. Singh et al., 2020), and they were also used as nanocarriers and delivery agents for  
341 active pharmaceutical ingredients (Hameed et al., 2019). To date, the personal care industry  
342 is expected to become the second-fast growing sector for the nanocellulose market. Among  
343 the leading companies commercializing medical-grade nanocelluloses, different grades were  
344 marketed as CNF hydrogels, wound dressing products or CNF/alginate bio-inks. The bio-inks  
345 have been used to fabricate human cartilage by co-culturing stem cells with chondrocytes in a  
346 hydrogel (X. Wang et al., 2020).

347 The nanocelluloses display many interesting features for the skincare and cosmetics  
348 industry, such as thickening, film-forming, bonding, dispersing, suspending, homogenization,  
349 emulsifying, gelling controlling, and stabilizing properties (Trache et al., 2020).  
350 Nanocelluloses also have a plasticizing effect and promote the formation of soft and elastic  
351 films with strong adhesion to protect the skin, therefore providing a lubricating function  
352 (Kukrety et al., 2018). Besides, chemical modification of nanocelluloses has been produced  
353 through modification of the hydroxyl groups to improve their solubility and compatibility.  
354 The robust humectant properties of nanocelluloses enhance the moisture quantity on the skin.  
355 Hence, nanocelluloses were added to moisturizing products, such as lotions, masks, and

356 creams (Amnuaikit, 2011). For example, nanocelluloses such as CNFs and CNCs masks  
 357 possess superior mechanical features compared with hydrogel masks, that facilitate their  
 358 applications and handling (Sharma et al., 2018). Some recent applications of nanocellulose  
 359 based materials and their advantages in different skincare and cosmetic products are  
 360 summarized in **Table 2**. **Table 3** gives an overview of a patent summary and emerging  
 361 industrial applications for different types of nanocelluloses in skincare and cosmetic  
 362 applications. The specific utilization of the nanocellulose types in skincare and cosmetic  
 363 applications is further detailed in next paragraphs.



364  
 365 Figure 5. Different applications domains of nanocelluloses as ingredients for topical use in  
 366 skincare, cosmetics, and healthcare products concerning their unique properties and  
 367 functionalization.

368 Table 2. Potential use of nanocellulose as active ingredients and application domains in  
 369 skincare and cosmetic products.

| <b>Products</b>                                     | <b>Nanocellulose ingredient</b>   | <b>Attributes</b>   | <b>Function</b>  | <b>Ref.</b>                                  |
|---|---|---|--|--|
| Sunscreen cream with UV filters function            | Nanocellulose decorated with inorganic metal oxide nanoparticles (TiO <sub>2</sub> and ZnO) | <ul style="list-style-type: none"> <li>- TiO<sub>2</sub> are UV-B filters</li> <li>- ZnO have a broad spectrum of activity (against UV-A and UV-B)</li> <li>- ZnO and TiO<sub>2</sub> provide optimal transparency</li> </ul>   | <ul style="list-style-type: none"> <li>- Homogeneous distribution of UV filters</li> <li>- Increased layer thickness</li> <li>- Non-dripping</li> <li>- Film formation</li> <li>- Water protection</li> <li>- Anti-wrinkling effect</li> <li>- Soft skin feeling effect</li> <li>- Cleansing effect</li> </ul> | (Hameed et al., 2019; Kushwaha et al., 2020) |
| Body cream with antibacterial and antifungal agents | Nanocellulose decorated with Ag and Au nanoparticles  | <ul style="list-style-type: none"> <li>- Broad-spectrum activity</li> <li>- Superior antimicrobial activity comparing to Ag<sup>+</sup> ions</li> <li>- Able to interfere with biofilm formation</li> <li>- Provide high dispersion stability for the NPs</li> <li>- Broad-spectrum activity</li> <li>- Au NPs are safer and more colloidal stable than Ag NPs</li> </ul> | <ul style="list-style-type: none"> <li>- Body cream with antibacterial and antifungal agents</li> <li>- Film formation</li> <li>- Non-dripping</li> </ul>  | (Fratoddi, 2018; Oun et al., 2019)           |
| Anti-aging cream                                    | Nanocellulose   | <ul style="list-style-type: none"> <li>- Nanocelluloses act as immediate anti-wrinkle agents by combining the soft-focus effect due to their morphology, the moisturizing effect due to their high water holding capacity, and the filler effect that reduces the skin roughness.</li> </ul>  | <ul style="list-style-type: none"> <li>- Anti-wrinkling effect</li> <li>- Water protection</li> </ul>  | (Rizzi et al., 2021)                         |

|   |  |  |   |                            |
|---|--|--|---|----------------------------|
|   | Nanocellulose decorated with Au and Au nanopartilces as an elucidated anti-aging agent | <ul style="list-style-type: none"> <li>- Multiple and not fully elucidated anti-aging action (e.g., antioxidant effect and prevention of ECM protein modifications).</li> <li>- Physiologically involved in dermal regeneration</li> <li>- Mainly used in beauty devices</li> </ul>  | - Anti-wrinkling effect   | (Souto et al., 2020)       |
| Cleansing agents                            | Face mask composed of nanocellulose  | <ul style="list-style-type: none"> <li>- A cleansing product for over accumulated oil on the skin.</li> <li>- Efficient removal of skin soil while preserving barrier integrity</li> </ul>   | - Cleansing effect  | (N. Sharma et al., 2018)   |
| Skin regenerative membranes                 | Cellulose nanofiber based wound dressing in skin graft donor site treatment            | <ul style="list-style-type: none"> <li>- Wood based cellulose nanofibers wound dressing tested in split-thickness skin graft donor site treatment for nine burn patients in clinical trials</li> </ul>   | <ul style="list-style-type: none"> <li>- Cellulose nanofiber dressing seems promising for skin graft donor site treatment</li> <li>- Biocompatible, attaches easily to wound bed,</li> <li>- remain in place until donor site has renewed.</li> </ul> | (Hakkarainen et al., 2016) |
| Sensor platform for wearable Skin Biosensor | Skin-adherent biosensors based on pure nanocellulose fibers substrate                  | <ul style="list-style-type: none"> <li>- Sensor platform based on pure nanocellulose fibers substrate</li> <li>- enables the detection of uric acid, 17<math>\beta</math>-estradiol, Pb<sup>2+</sup> and Cd<sup>2+</sup> in sweat.</li> <li>- Screen printing on cellulose based membranes allow optimal skin integration in wearable technologies.</li> </ul> | - Biocompatible adherent to human skin used in electrochemical sensors  | (Silva et al., 2020b)      |

371 Table 3. Patents related to the use of nanocelluloses for skincare and cosmetic products

| <b>Nanocellulose type</b>                 | <b>Publication Date</b> | <b>Patent number</b> | <b>Patent description</b>   |
|---|-------------------------|----------------------|---|
| Microcrystalline cellulose (MCC)          | April 01, 2004          | WO2004026263A2       | Cosmetic composition containing microcrystalline cellulose  |
|   | August 12, 2004         | US20040156811A1      | Decorative skin and hair cosmetics containing microcrystalline cellulose as an enhancing agent                                |
|   | August 26, 2004         | WO 2004071322        | Colloidal microcrystalline cellulose toothpaste of reduced stringiness and improved flavor release                            |
|   | June 14, 2007           | WO2007066222A1       | Cellulose gel formulations  |
|   | January 18, 2011        | US20090130287A1      | Microcrystalline cellulose compositions   |
|   | December 06, 2011       | CA 2488158C          | Stable oral compositions comprising microcrystalline cellulose and a surface-active agent                                     |
|   | April, 11, 2013         | WO2013052114A1       | Stabilizer composition of microcrystalline cellulose and carboxymethylcellulose, a method for making, and uses                |
| Nanocellulose spherical particles (NCSPs) | October 21, 1997        | FR2769836B1          | Use of essentially amorphous cellulose nanofibrils associated with organic polyhydroxy compounds in cosmetic formulations     |
|   | February 02, 2017       | WO2017018554         | Nanocellulose utilizing non-lignocellulosic biomass, and cosmetic composition and superabsorbent material containing the same |
|   | August 25, 2015         | US9114077B2          | Nanocrystals for use in topical cosmetic formulations and method of production thereof  |
|   | February 2, 2016        | CA2956661A1          | Method for producing functionalized nanocrystalline cellulose and functionalized nanocrystalline cellulose                    |
|   | June 7, 2018            | CA3044721A1          | Sunscreen composition comprising  |

|   |                   |   |   |
|---|-------------------|---|---|
|   |                   |   | nanocrystalline cellulose   |
|   | June 7, 2018      | CA3044727A1   | Cosmetic composition comprising nanocrystalline cellulose, method, and use thereof                                |
|   | October 11, 2018  | WO2018185768A1  | Haircare compositions   |
|   | October 9, 2019   | EP3548144A1   | Powdery cosmetic composition comprising nanocrystalline cellulose   |
|   | February 13, 2020 | WO2020031186  | Cellulose-based topical formulations  |
| Cellulose nanofibers (CNFs) and nanocrystals (CNCs) | June 29, 2001     | FR2794466B1   | Composition in the form of an oil-in-water emulsion containing cellulose fibrils and its particular cosmetic uses |
|   | September 7, 2007 | JP2009062332A   | Cosmetic composition containing fine fibrous cellulose and/or its composite material                              |
|   | April 13, 2011    | EP 2 307 100 A2   | Liquid cleansing compositions comprising microfibrinous cellulose suspending polymers                             |
|   | October 11, 2012  | JP2012193139A   | Cosmetics having an excellent moisturizing property, less skin irritation and non-stickiness                      |
|   | June 12, 2018     | CN108143680B  | Plant cellulose nanofibril antibacterial moisturizing mask and preparation method thereof                         |
|   | July 3, 2018      | US10010490B2  | Cosmetic composition comprising cellulose fibers with small fiber diameter and comparatively small aspect ratio   |
|   | January 3, 2020   | KR20200000579A  | Composition for skin care enhancement including denaturalized cellulose   |
|   | April 1, 2020     | KR102095715B1   | Mask pack composition comprising a cellulose nanofiber  |
|   | October 22, 2020  | US 16/854944  | Topical delivery system containing cellulose nanofibers   |
|   | November 25, 2020 | EP3741354A1   | Sunscreen agent comprising cellulose nanofibers   |
| May 4,  | WO2017075402A1    | Sweat sensing devices based nanocellulose platform with |   |



|                               |                   |                 |  |
|-------------------------------|-------------------|-----------------|--|
|                               | 2017              |                 | electromagnetically shielded sensors, interconnects, and electronics   |
|                               | July 20, 2017     | WO2017122224A1  | Cellulose nanocrystals based composite formulation for wound healing and a process for the preparation thereof                             |
| Bacterial nanocellulose (BNC) | November 29, 1998 | US4788146A      | Liquid-loaded pad for medical applications   |
|                               | October 11, 2006  | EP1473047B1     | Microbial cellulose wound dressing sheet, containing polyhexamethylene biguanide, for treating chronic wounds                              |
|                               | October 26, 2006  | US20060240084A1 | Microbial cellulose materials for use in transdermal drug delivery systems, method of manufacture and use                                  |
|                               | August 16, 2007   | WO2007091801A1  | A sheet device comprising bio-cellulose for alleviating skin damage and relieving skin problem   |
|                               | December 04, 2007 | BRPI0601330A    | Topical composition of biocellulose in gel form, spray aerosol, cream and/or aqueous suspension for treatment of epithelial lesions        |
|                               | February 12, 2009 | US20090041815A1 | Assembly comprising a substrate comprising biocellulose, and a powdered cosmetic composition to be brought into contact with the substrate |
|                               | Mai 05, 2009      | FR2924342       | Make-up and/or skincare product  |
|                               | June 05, 2009     | FR 2924340A1    | Procedure for nail make-up   |
|                               | December 12, 2009 | FR2916971A1     | Slimming assembly  |
|                               | November 30, 2011 | EP 2 390 344 A1 | Bacterial cellulose film and uses thereof  |
|                               | January 17, 2012  | US20110039744A1 | Personal cleansing compositions comprising a bacterial cellulose network and cationic polymer  |
|                               | May 03, 2012      | WO2012057486A2  | Cosmetic bio-cellulose mask pack sheet and method for manufacturing the same   |
|                               | June 27, 2013     | WO2013094077A1  | Cosmetic bio-cellulose sheet for lips  |

|                            |                   |                 |   |
|----------------------------|-------------------|-----------------|---|
|                            | February 10, 2015 | US8951551B2     | Multi-ribbon nanocellulose as a matrix for wound healing  |
|                            | March 26, 2015    | WO2015040106A1  | Method for the production of structured cellulose patches or elements and devices made using such a method      |
|                            | August 6, 2015    | US20150216784A1 | Cosmetic composition containing fragments of bacterial cellulose film and method for manufacturing thereof      |
|                            | June 21, 2017     | EP3181153A1     | Wound care product comprising extracellular matrix-functionalized nanocellulose                                 |
|                            | March 12, 2020    | KR102088350B1   | Cosmetic mask pack sheet of biocellulose and the method for preparing thereof                                   |
|                            | April 19, 2001    | WO2001026610A1  | Electrospun skin masks and uses thereof   |
|                            | February 2, 2015  | US8951551B2     | Bacterial nanocellulose as a matrix for wound healing   |
|                            | November 3, 2016  | WO2016174104A1  | Modified bacterial nanocellulose and its uses in chip cards and medicine  |
| Cellulose nanoyarns (CNYs) | October 14, 2010  | WO2010115426 A1 | Skincare compositions for the delivery of Agents  |
|                            | October 01, 2015  | US20150272855A1 | Cosmetic sheet formed from nanofibers with controlled dissolution velocity and method of manufacturing the same |
|                            | February 04, 2016 | WO2016016704A2  | Cellulose acetate-based non-woven nanofiber matrix with high absorbency properties for female hygiene products  |
|                            | November 12, 2019 | US 10,470,983   | Cosmetic pack and manufacturing method  |
|                            | November 16, 2019 | JP2019001071A   | Laminate and sheet for skin adhesion  |
|                            | July 29, 2020     | EP3231320B1     | Beauty care pack and method for manufacturing the same  |

372 **5. Nanocellulose Spherical Particles (NCSP)**

373 Amorphous NCSPs have spherical to elliptical shapes (average aspect ratios of 0.91 to 1.10)  
374 with relatively uniform particle sizes (diameter of 50 to 200 nm) (Zhang et al., 2007). The  
375 particles are highly amorphous (75 to 80%), which explains their extremely high wettability  
376 and water holding capacity together with complete decomposition in the presence of cellulose  
377 enzymes. With their small particle size, low aspect ratio along with their strong swelling  
378 properties, the NCSPs are not suitable as abrasive peeling or scrubbing media (Bouillon et al.,  
379 1998). However, they can be used for advanced skin treatment and healing (Uddin et al.,  
380 2019). Some specific features and attributes of NCSPs for utilization in skincare and cosmetic  
381 applications are below.

### 382 **5.1 NCSP as delivery bioactive ingredient**

383 NCSPs can serve as nanocarriers of bioactive ingredients due to their intrinsic properties  
384 (fine particle size, high porosity, high abundance of hydroxyl groups, good stability in  
385 different solvent systems with no decomposition in the medium) that offer protection of the  
386 encapsulated ingredients. The NCSP chemical surface modification by selective oxidation  
387 (with nitrogen tetroxide) results in the introduction of carboxylic groups that provide  
388 additional hemostatic properties (Barhoum et al., 2019). Active substances for therapeutic  
389 skincare (e.g., enzymes) can be adsorbed into the NCSPs and they can chemically bind to the  
390 functional groups. Similarly, the sulfate functional groups allow the binding of ions with the  
391 enzyme basic functional groups (e.g. histidine, lysine, or arginine). The acidic functional  
392 groups (-COO or -SO<sub>3</sub>) on NCSPs may bind with antibacterial agents (e.g., Ag or ZnO  
393 particles) by irreversible sorption (Tortorella et al., 2020), while other functional groups such  
394 as aldehydes also covalently bind to proteolytic enzymes. The encapsulated enzymes are then  
395 protected against degradation in the liquid formulation due to protein self-denaturation or  
396 autolysis at specific pH ranges and high temperatures (Tortorella et al., 2020). This ensures  
397 the long-term stability of the encapsulated enzymes and allows tuning the pH as a function of

398 optimized enzymatic activity. NCSPs can be also used as surfactants and slow-release agents  
399 in skincare and cosmetic formulations and wound healing (e.g., creams and lotions) because  
400 they improve the application and penetration of cosmetic or drugs into the skin (Tortorella et  
401 al., 2020).

### 402 **5.2 NCSP as a gelling agent**

403 The aqueous dispersion of amorphous NCSPs at moderate concentrations in presence of  
404 enzymes (e.g., trypsin, lysozymes, amidases) leads to a network of cellulosic material  
405 forming a gel structure upon cooling of the solution (Abushammala et al., 2010). The  
406 formation of a paste with high NCSPs concentrations exhibits good thickening properties and  
407 can be used as an additive to prevent phase separation of dispersions (Chirayil et al., 2014).

### 408 **5.3 NCSP as a moisturizer**

409 The amorphous nature of NCSPs favors the absorption of fluids and provides a higher ability  
410 for water uptake compared with CNCs and CNFs, while the surface modification through  
411 TEMPO oxidation further enhances the hydrophilicity and superabsorbent properties  
412 (Tortorella et al., 2020). Therefore, the NCSPs produced from residual woody or non-woody  
413 biomasses (e.g. palm tree leaves, palm trunk, corn stanchion, corn stover, sunflower reeds)  
414 has been incorporated in skincare preservatives for moisturizing and alleviating skin wrinkles  
415 (patent WO 2017018554),

## 416 **6. Cellulose Nanofibers (CNFs)**

417 CNFs are thin fibers with a diameter below 100 nm and length in the micrometer range.  
418 CNFs can be created using various mechanical procedures, such as high-pressure  
419 homogenization, refining, micro-fluidization, ultrasonication, cryo-crushing and grinding  
420 (Zhang et al., 2007), in combination with an enzymatic or chemical pretreatment step. Such  
421 fibrils contain amorphous and crystalline domains and are characterized by the formation of a  
422 dense fibrillary network structure. As the morphology of CNF is similar to that of BNC with

423 higher purity (see later), they have been relatively less exploited for skincare and cosmetics  
424 products. However, a cytotoxicity study on CNFs indicated no harmful effect on skin and/or  
425 eye irritation when used at appropriate concentrations (Kim et al., 2019). Toxicological  
426 effects are explained by the nanocellulose morphology (size, aspect ratio) and  
427 physicochemical properties (surface charges) (Lopes et al., 2017). The specific concerns and  
428 benefits of CNF for utilization in skincare and cosmetic applications are given in next  
429 paragraphs.

### 430 **6.1 CNFs as formulation modifier**

431 CNFs are generally used as a stabilizer and thickener for liquid systems. It is particularly  
432 suited for controlling the viscosity of dispersions and/or emulsions, and thus the applicability  
433 and feeling of use. Traditional aqueous thickening and gelling agents for skincare  
434 formulations are based on water-soluble natural polymers (e.g. sodium hyaluronate, sodium  
435 alginate, xanthan gum), semi-synthetic polymers (e.g. hydroxyethyl cellulose, carboxymethyl  
436 cellulose), or synthetic polymers (e.g. carboxy vinyl polymer, polyvinyl alcohol, sodium  
437 polyacrylate) (Alves et al., 2020). However, the gelling mechanism for these polymers is  
438 based on ionic interactions that are strongly influenced by the pH and significantly alter in the  
439 presence of electrolytes. Therefore, sweat can dramatically decrease the viscosity of the  
440 applied cosmetic that will consequently slide off the skin. Conversely, CNFs are considered  
441 to be a suspending aid or gel-forming agent in the fabrication of cosmetic sheets with better  
442 compatibility and salt-resistance (Alves et al., 2020). Moreover, the sensitive feeling of a  
443 CNFs-containing gel is enhanced by the reduction of adherence, stickiness and clumping in  
444 parallel with a reduced viscosity of the cosmetic formulation during application. The control  
445 of the gelling properties with CNFs allows homogeneous drying and formation of a sol after  
446 application. The gel formulations with CNFs display thixotropy and can thus be sprayed as a  
447 mist without dripping after application. For skincare applications, the mixing of CNFs in an

448 oil-in-water emulsion with at least one fatty phase and one aqueous phase provides good  
449 stability to the formulation. During the preparation of formulations with high solid content,  
450 the stabilizing effect of the non-soluble 3D fibrillar network of CNFS also prevents the  
451 settling and sedimentation of ingredients. Therefore, CNFs is mixed with creams, lotions,  
452 pastes, gels, foundations, sera, and ointments (Bacakova et al., 2019).

## 453 **6.2 CNFs as a functional additive**

454 The high water holding capacity of CNFs (up to 75-100%) is superior to that of other  
455 nanocellulose types due to their hydrophilicity and specific morphology with a dense  
456 nanofibrillar network. Moreover, the high affinity of CNFs for water can further be increased  
457 by surface carboxylation after TEMPO oxidation. The CNFs are therefore preferentially used  
458 as a moisturizing component with better performance than traditional polymers, such as  
459 collagen or hyaluronic acid (Bacakova et al., 2019). The crystallinity degree of CNFs is an  
460 important parameter determining the water absorption capacity and should be between 40 and  
461 50% to make the amorphous cellulose regions accessible for water uptake. Conversely, other  
462 nanocellulose types (CNCs and BNC) have a degree of crystallinity above 80% (Sharma et  
463 al., 2014).

464 The dense fiber network also provides improved mechanical reinforcement with high  
465 strength, ductility, and excellent elasticity. Due to their high flexibility, the CNFs sheets  
466 favorably serve as face masks providing a good fitting and comfortable feeling on the skin  
467 and lips (Perugini et al., 2018). Moreover, peeling films can be formed as a separate free-  
468 standing layer with a good affinity to the skin (Tang et al., 2021). The formation of a coherent  
469 film with CNFs is enhanced by avoiding cracking and the film remains transparent due to the  
470 thin fibril diameters. The interaction between fibril bundles has a matting effect on the skin  
471 due to the filling of pores and flaws, with an anti-wrinkling and whitening effect. When  
472 combined with other polymers such as chitosan, the CNFs can be used to fabricate face

473 masks with antibacterial activity (Ribeiro et al., 2021). The CNFs provide the bulk, whereas  
474 the electropositive chitin nanofiber reactive surface amino groups can form strong covalent  
475 and hydrogen bonds into a dense cross-linked fiber network with CNFs. The incorporated  
476 chitin/chitosan presents intrinsic antimicrobial properties against Gram-negative bacteria,  
477 Gram-positive bacteria, and fungi, which can vary in function of the molecular weight and  
478 degree of acetylation of chitosan (Ribeiro et al., 2021).

### 479 **6.3 CNFs as drug delivery**

480 The CNFs are used as topical encapsulating and delivery agents of active skincare products,  
481 providing better regulation of the ingredient penetration into the skin through controlled  
482 release. The drying of a cellulose network structure in presence of active compounds may  
483 involve entrapment (Kupnik et al., 2020) and controlled release (Abushammala et al., 2012),  
484 depending on the fiber morphology and concentration. The skin delivery systems with CNFs  
485 form a three-dimensional matrix that can be further stabilized in combination with external  
486 cross-linkers such as alginate (Morais et al., 2020). The encapsulation of essential oils and  
487 microalgae is an interesting alternative to increase the exposure time of an active component  
488 during dermic and cosmetic applications. Other products may include, e.g., essential oils,  
489 plant extracts, repair enzymes, sunscreen active components, humectants, botanical extracts,  
490 peptides, vitamins, antioxidants, or preservatives. Such cosmetic treatments may offer long-  
491 term improvement of the skin texture, smoothness, and healing of photochemically damaged  
492 and red or sensitive skin (Morais et al., 2020).

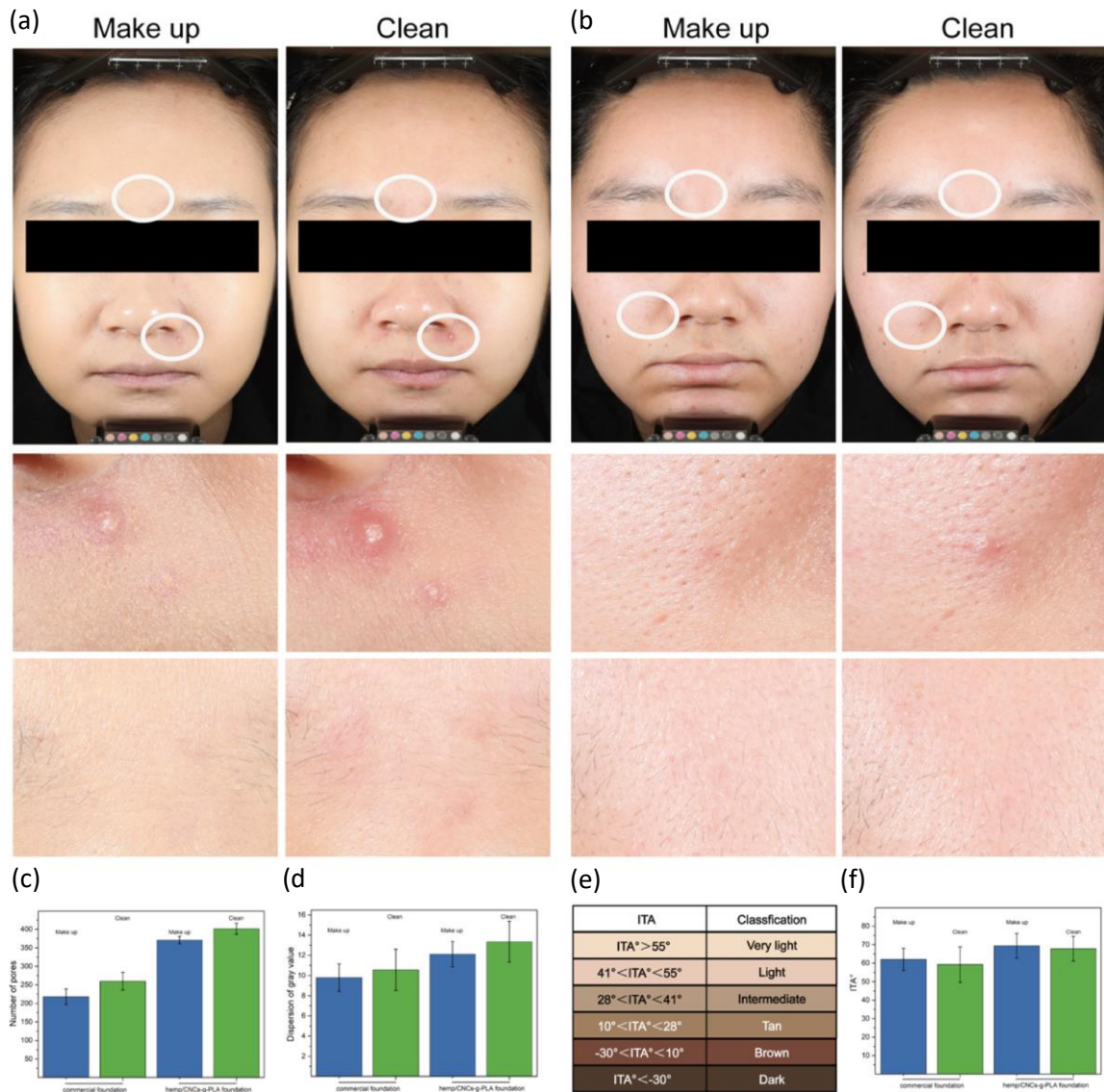
### 493 **7. Cellulose nanocrystals (CNCs)**

494 CNCs are short rod-like fibers with a diameter of 5 to 10 nm and a length below 100 nm. The  
495 crystallites are fabricated by chemically removing the amorphous domains using ultrasound  
496 treatment and strong acid hydrolysis with a selection of concentrated sulfuric acid,  
497 hydrochloric acid, hydrobromic acid, or phosphorous acid depending of the required

498 properties. The dispersibility and rheological features of CNCs vary as a function of the  
499 chosen acid (Blanco et al., 2018). Specifically, CNCs obtained by phosphoric or sulfuric acid  
500 hydrolysis disperse readily in water because of the abundance of highly polar phosphate or  
501 sulfate groups at their surface. Conversely, CNCs fabricated by hydrobromic or hydrochloric  
502 acid hydrolysis cannot be easily dispersed as their aqueous suspensions tend to flocculate  
503 (Wulandari et al., 2016). Alternative green methods were recently developed using  
504 enzymatic-assisted hydrolysis and recyclable ionic liquids to reduce environmental  
505 contamination from acidic wastewater (Meyabadi et al., 2014). The structures of CNCs  
506 produced from enzymatic-assisted hydrolysis have extremely high crystallinity and better  
507 mechanical strength and stiffness than acid hydrolysis CNCs (Wulandari et al., 2016).

508 CNCs display various features suitable for skincare applications, such as a better  
509 penetration in the skin membrane, high adhesion, and better permeation via the  
510 gastrointestinal wall. Due to their nanosize dimensions, CNCs can enter and open the  
511 individual skin pores for penetration through the lipid layer and epidermis towards the other  
512 skin strata (Barhoum, Jeevanandam, et al., 2020). Therefore, CNCs are mainly used for  
513 personal care products that are topically applied because they reduce the administered dose,  
514 offer a sustained release, and increase customer compliance. Aqueous CNCs suspensions are  
515 compatible with skincare products and are added at a typical dilution factor of 50. Inspired by  
516 the protective effect of a fiber-rich diet on the intestinal mucosal mechanical barrier, a novel  
517 hemp/CNCs-based foundation liquid has been recently formulated (Figure 6), which  
518 effectively solves the post-makeup skin cleaning problems (Tang et al., 2021). The basic  
519 features provide easy removal of the foundation through simple wiping, which avoids skin  
520 damage caused by excessive cleansing. The CNCs foundation liquid has an excellent  
521 performance in terms of biological compatibility, water resistance, and controlled skin  
522 penetration. Some main functionalities of CNCs for use in cosmetics are discussed below.





523

524 Figure 6. Cellulose nanocrystals (CNCs) for skin barrier protection by preparing a versatile  
 525 foundation liquid: (a) Images obtained under a standard flashlight after using commercial  
 526 make-up and wiping off; (b) Images after using foundation liquid based on hemp/CNCs and  
 527 wiping off; (c) Number of pores on both sides of the nose was counted; (d) Variations in gray  
 528 value of facial skin was measured; (e) Schematic diagram of the individual typology angle  
 529 (ITA°) and its colour classification; (f) ITA° values of commercial and hemp/CNCs  
 530 foundation liquid after making up and wiping off (Tang et al., 2021).

531

532 **7.1 CNCs as formulation modifier**

533 The CNCs particularly play an important role as stabilizing agents for Pickering emulsions, in  
534 which solid particles organize at the liquid/liquid interface to prevent coalescence of the  
535 liquid droplets (Figure 3a) (Tang et al., 2019). Oil-in-water and water-in-oil emulsions  
536 contain two or more immiscible phases and one is dispersed as droplets in the other. The  
537 system is thermodynamically unstable and usually stabilized by surfactants or amphiphilic  
538 molecules to prevent phase separation by reducing the interfacial energy (Kralchevsky et al.,  
539 2005; De et al., 2015). Alternatively, the stabilization of emulsions with solid particles is  
540 governed by the formation of a physical boundary through a particulate network (Chevalier et  
541 al., 2013; Wu et al., 2016). Although several particle morphologies can be used, emulsions  
542 are more efficiently stabilized with a smaller number of rod-like particles than spherical  
543 particles (Kontturi et al., 2018). The CNCs display better-stabilizing features than native  
544 cellulose fibers (Costa et al., 2018); however, unmodified CNCs with many surface hydroxyl  
545 groups are often too hydrophilic for oil-in-water emulsion stabilization (Lu et al., 2018). The  
546 CNCs that are chemically modified with carboxylic groups, succinic anhydride or fatty acids  
547 display more balanced hydrophilic/hydrophobic surface properties and consequently higher  
548 emulsifying capacity. As such, the surfactant-free emulsions for skin drug delivery system  
549 and pharmaceutical uses can be formulated using natural nanomaterials as stabilizing agents  
550 (Tang et al., 2018).

## 551 **7.2 CNCs as functional filler and additives**

552 CNCs represent an alternative to traditional fillers such as graphene, carbonate, silica,  
553 calcium, or organic polymer particles (polyphenols) and polysaccharides (chitin, starch)  
554 (Fujisawa et al., 2017). Due to their high degree of crystallinity, CNCs are physically and  
555 chemically inert and only interact weakly with other active ingredients in the formulation.  
556 However, the presence of residual sulphuric acid charges after hydrolysis may interfere with  
557 the dispersion stability of other ingredients. Therefore, the sulfuric acid concentration can be

558 reduced through a naturalization procedure by dilution of the CNCs suspension and  
559 separation of the hydrolysed cellulose through centrifugation (Barhoum et al., 2019). The  
560 increase in pH of the CNCs acid environment towards neutral pH in presence of calcium  
561 carbonate or barium carbonate allows the conversion of the sulphuric residues into white  
562 inorganic pigment. The *in-situ* formation of this white pigment is a cheap alternative to TiO<sub>2</sub>  
563 and ZnO and is less abrasive than pure inorganic nanomaterials (Samyn et al., 2018).

564         The high crystallinity of CNCs as compared to CNFs, endows them with extremely  
565 high mechanical stiffness, strength and hardness. Therefore, CNCs can compete with the  
566 intrinsic abrasive properties of inorganic pigments, such as silica carbide, silica dioxide, or  
567 aluminum oxide for scrubbing. The CNCs are suited as an additive for gentle skin cleansing,  
568 dentifrices or peeling, as they enhance the effects of mechanical scrubbing and removal of  
569 dead skin tissue. Inorganic materials are harder than CNCs, but they may be too abrasive and  
570 cause skin damage. Conversely, CNCs have better-balanced properties for abrasive cleaning  
571 as their nanoscale size does not hurt the skin and provides a gentle feeling without scratching  
572 (Panchal et al., 2019). Other nanocellulose types with higher amorphous content are less  
573 efficient as peeling additives as they are too soft and become even softer after swelling in a  
574 water environment. CNCs can also improve the appearance of photo-aged skin and stimulate  
575 wound healing by reducing scar formation (Singh et al., 2016).

### 576 **7.3 CNCs as hair-straightening agent**

577 In combination with good film-forming properties, CNCs may provide a functional protective  
578 layer onto hair, thus enhancing and restoring the straightening effect of the hair. The  
579 negatively charged CNC surfaces with sulfate groups provide the binding to cationic  
580 compounds and/or hair (Kontturi et al., 2018). This demonstrates that cationic surfactants can  
581 facilitate the CNC binding to the hair through electrostatic interactions (coulomb forces)  
582 and/or additional hydrophobic interactions. Indeed, the hair surface is naturally hydrophobic

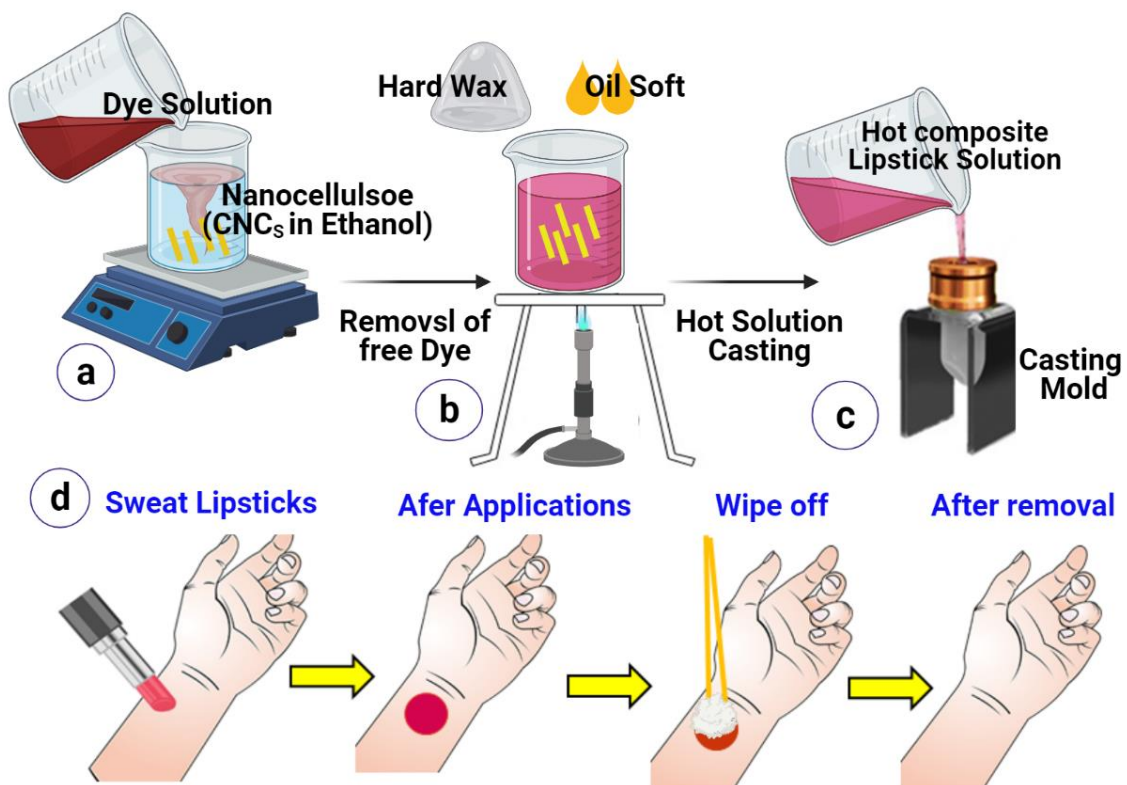
583 in presence of lipids. Moreover, CNCs contribute to the reconfiguration of keratin structure in  
584 hair, offering mechanical support to the fresh keratin structure upon straightening and/or  
585 shielding from ambient humidity and pollution (Soodeh et al., 2020).

#### 586 **7.4 CNCs as nanocarrier for UV-blockers**

587 The optical properties of CNCs suspensions are suitable for utilization as nanocarriers for  
588 UV-blockers and protection of other cosmetics ingredients from photodegradation (Panchal  
589 & Mekonnen, 2019). The CNCs suspensions have a maximum UV absorbance peak at  
590 around 278 nm, and their absorption intensity is influenced by the acid hydrolysis duration  
591 (Bongao et al., 2020). The UV-blocking performance of CNCs is compatible with  
592 conventional UV-blockers (TiO<sub>2</sub> or ZnO nanoparticles) that display an absorption peak at 356  
593 to 428 nm (Awan et al., 2018). Therefore, CNCs might be a potential alternative to mineral-  
594 based nanoparticles in cosmetics with UV protection features, remediating facial aging by  
595 sun exposure. The CNCs regulate interaction with light through absorption, scattering,  
596 transmission and reflection, and they can highlight the natural appearance with matt or soft-  
597 focus effects of the skin while hiding imperfections. The refractive index of particles for a  
598 soft-focus should differ from the value of the medium in which the particles are present, but it  
599 cannot be too high as it would give an unnatural look to the skin with high opacity. The *in-*  
600 *situ* growth of UV-blockers such as ZnO nanoparticles onto the CNC surface (melamine  
601 formaldehyde-covered CNCs) was tested for smart skincare applications (Awan et al., 2018).  
602 The CNCs/ZnO hybrid nanomaterials present attractive photocatalytic activity and UV  
603 absorption under solar radiation, providing an intelligent skincare formulation with high  
604 photocatalytic efficiency. The use of CNCs offers various benefits, such as, e.g., a better-  
605 controlled growth and dispersion of ZnO in the medium, a higher specific ZnO surface area,  
606 and preventing the recombination of active photocatalytic sites.

#### 607 **7.5 CNCs as nanocarrier for bioactive ingredients**

608 CNCs have been tested as nanocarriers of topical or bioactive substances for transdermal  
609 delivery and advanced skincare products including therapeutic lotions, liposomal dispersions  
610 and creams. In relation with their size and high specific surface area, CNCs are reactive for  
611 binding to substances and allow better transdermal penetration and delivery through the skin.  
612 The CNCs reactivity facilitates the chemical binding of active health components, such as,  
613 e.g., (i) proteolytic enzymes and amino acids that provide gentle skincare in combination with  
614 peeling, and (ii) lipases for selective skin degreasing (Chirayil et al., 2014). CNCs have also  
615 been used as a carrier for the topical delivery of hydroquinone to improve its therapeutic  
616 efficacy and decrease the cosmetic skin effects (Sunasee et al., 2016). Hyperpigmentation is a  
617 frequent skin disorder where hydroquinone limits melanin production and skin discoloration.  
618 The preparation of hydroquinone-CNCs complexes was done by simply incubating  
619 hydroquinone with CNCs suspensions. CNCs containing rutin (flavonoid) as an active  
620 ingredient are used for toothpaste applications to replace hydroxyapatite, the main component  
621 of tooth enamel (Hameed et al., 2019). For lipsticks, colored ingredients (dye molecules) are  
622 typically in contact with the skin, whereas the lipstick made with dyed-CNCs (CNCs-lipstick)  
623 would reduce the contact. The use of dyed-CNCs declines the rate of dye molecules diffusion  
624 so the migration of color from the lipstick is reduced and complete removal of the color after  
625 application can be achieved (Figure 7) (Kang et al., 2019). In addition, CNCs with anti-  
626 oxidant properties provide protection as a scavenger of free radicals and prevent skin  
627 degradation (Kang et al., 2019).



628 Figure 7. Schematic presentation showing the use of CNCs as dye carriers and protective  
 629 materials in a lipstick matrix for inhibiting color migration: (a) loading of the dye and  
 630 removal of excess dye; (b) preparation of the lipstick from oil, wax, solvent and dye-CNCs;  
 631 (c) casting of the prepared solution; (d) application and removal of lipstick with reduced  
 632 diffusion rate of dye molecules. Figure adapted from the abstract of (Kang et al., 2019) using  
 633 Biorender.

634

### 635 8. Bacterial nanocellulose (BNC)

636 BNC forms a dense network of cellulose fibrils produced by aerobic micro-organisms such as  
 637 Gram-negative bacteria, e.g. *Gluconacetobacter xylinus* (formerly known as *Acetobacter*  
 638 *xylinum*). Unlike native cellulose fibers that are scaled down to nanoscale units, BNC is  
 639 directly produced as nanoscale fibril units in the culture medium through fermentation (Jacek  
 640 et al., 2019), and complex biochemical conversion (Meftahi et al., 2018). Its production  
 641 mainly involves the assimilation of carbon sources (i.e. polymerization of fructose, mannitol,

642 sorbitol, glucose, cellobiose, glycerol, galactose, lactose, sucrose, maltose, monomers) and  
643 secretion of cellulose in weak acidic conditions (pH 4.5 to 6.5). During fermentation, micro-  
644 organisms travel freely in the medium or are connected to cellulose fibers and produce a  
645 swollen gel structure. After synthesis, dead micro-organisms and cell waste is removed  
646 during purification by repeated alkaline washing in a hot sodium hydroxide solution or a  
647 strong oxidizing agent until neutral pH is reached (Abouelkheir et al., 2020). More recently,  
648 this cleaning step with aggressive chemicals could be replaced by autoclave and gamma  
649 irradiation treatment. Although the culture techniques are complex, the lower energy that is  
650 required for production and purification makes BNC a more environmentally friendly  
651 material. The quality of the synthesized ribbon-like BNC fibers highly depends on the  
652 washing efficiency (Abouelkheir et al., 2020).

653 BNC is characterized by a left-hand twist and long aspect ratio, with very high  
654 crystallinity (up to 86%), ultra-high purity (absence of non-cellulosic substances), and  
655 consequently superior mechanical properties compared with CNFs from plant sources (de  
656 Amorim et al., 2020). The incorporation of functional additives or cellulose derivatives in the  
657 bacterial culture medium together with dextrose during BNC secretion allows to the  
658 production of *in-situ* functionalized nanofibers. The development of a nanofibrillar network is  
659 controlled by the motion of the bacteria during synthesis (Pacheco et al., 2018), and provides  
660 ideal porosity to be used as medical membranes with excellent mechanical features, purity,  
661 malleability, biodegradability, tensile strength, porosity, and easy handling (Meftahi et al.,  
662 2018; Ullah et al., 2016). In cosmetics, BNC is mainly used in facial scrubs, facial masks,  
663 personal cleansing formulations, and contact lenses (Ullah et al., 2016). The extensive use of  
664 BNC as wound dressing materials is outside the scope of this review as it has been widely  
665 discussed in other reviews (Bielecki et al., 2012).

## 666 **8.1 BNC as formulation modifier or additive**

667 The BNC can be added in skincare and cosmetic formulations as a rheological modifier or  
668 stabilizing agent for oil-in-water emulsions. In parallel with previous descriptions of CNFs,  
669 the emulsions with BNC do not require additional surfactants that may be harmful or induce  
670 skin irritation (Paximada et al., 2016). The BNC permits reducing the percentage of  
671 surfactants used in a liquid matrix without changing its rheological features (Paximada et al.,  
672 2016). The BNC is compatible and provides stabilization with other ingredients present in a  
673 scrub, such as olive oil, aloe vera extract, ascorbic acid, vitamin C, or powdered glutinous  
674 rice. The inclusion and topical delivery of drugs in cosmeceuticals and medical skincare  
675 (wound healing and burn repair) including BNC can be also tuned for a controlled stimulus-  
676 responsive release.

677 The rheological properties of BCN are essential for the application in the facial  
678 scrubs, providing homogeneous spread and optimized drying time. The decrease in viscosity  
679 as a function of shear rate (i.e., shear-thinning) of BNC is enhanced through conformational  
680 changes and alignment of the BNC fibrils under shear. Therefore, an enhanced scrubbing  
681 effect is obtained with formulations that include BNC (Hasan et al., 2012). Facial scrubs with  
682 BNC have a relatively higher viscosity than commercial scrubs at low shear rates, but  
683 viscosities under higher shear are comparable.

684

## 685 **8.2 BNC as membranes and facial masks**

686 Facial masks are predominantly proposed for skin restitution, sebum control, deep and fast  
687 hydration, and moisturizing. The BNC membranes attracted the most interest as natural  
688 skincare facial masks because of their low toxicity, biodegradability, optimized mechanical  
689 properties versus porosity, together with skin moistening and hydrating potential (Kolesovs &  
690 Semjonovs, 2020). The BNC is a preferred substrate facial mask due to its nanoporous  
691 membrane shape with high mechanical stability. In contrast, conventional hydrogel masks are



692 often difficult to handle because they lack high mechanical strength. Also, the CNFs from  
693 plant sources have weaker mechanical strength in wet conditions than BNC. The comfort of  
694 BNC masks and their satisfactory feeling is mainly related to the high moisture level, water  
695 retention (water content up to 98%), and good adherence to the skin (Pacheco et al., 2018). A  
696 single application of the BNC highly improves moisture uptake by the skin (Mohite & Patil,  
697 2014). After mask removal, improvements in skin moisture, sebum, elasticity, texture,  
698 dullness, and desquamation levels were reported (Press, 2011). As a result, the skin hydration  
699 performance of BNC mask is 7 to 28% higher than common creams. The BNC masks  
700 additionally help to reduce the sebum concentrations and saturation, resulting in a brightening  
701 effect, smooth feeling, translucence and firm look.

702         Protocols were developed to monitor the BNC mask quality and stability. The  
703 changes in water content and nutrient additives at different locations of the mask have been  
704 investigated by NIR spectroscopy. A study on the organoleptic properties, viscosity and pH  
705 stability of BNC masks from different manufacturers estimated their stability and shelf life at  
706 6 months (Perugini et al., 2018).

707

## 708 **9. Electrospun Cellulose Nanoyarns (CNY)**

709 Different systems for electrospinning cellulose derivatives (e.g. cellulose acetate,  
710 hydroxypropyl cellulose, hydroxypropyl methylcellulose, ethyl-cyanoethyl cellulose) with  
711 suitable solvents are available to produce a regular non-woven fiber mat with nanoscale  
712 fibers (Taylor et al., 2008). The properties and morphology of CNYs depend on their  
713 processing parameters, such as spinning conditions, solvent system, degree of cellulose  
714 polymerization, and final coagulation in a water bath. The CNYs are mostly amorphous,  
715 however, the degree of crystallinity of fibers can be controlled by modulating various process

716 conditions, including spinning temperature, flow rate, and nozzle-collector distance (Kim et  
717 al., 2006; Miguel et al., 2018).

718 Although electrospinning is easy to use at a low cost, there is a large number of  
719 processing parameters that highly influences fiber generation and nanostructures (Gugulothu  
720 et al., 2018). Increasing solution conductivity increases the stretching of the solution jet  
721 resulting in CNYs with smaller diameters (Barhoum et al., 2019). Solvent volatility must be  
722 in a certain range as the more volatile solvents result in ribbon/flat fibers and fibers with  
723 surface pores. The higher viscosity of the cellulose solution will induce a larger CNY  
724 diameter, while the higher temperatures will result in lower viscosity and thinner CNY  
725 diameter (Bubakir et al., 2019).

### 726 **9.1 CNY as membranes and masks**

727 The CNY membranes are frequently used in skincare formulation as wound dressings, skin  
728 covers, protective sheets, healing agents, or masks (Fathilah et al., 2019). The electrospun  
729 mat can directly be applied onto the skin without the need for an intermediate fabrication  
730 step, for instance using a transient, charged receiver to first collect the fibers into a mat before  
731 application on the skin. The mask may function as a hydration medium or as a medium to  
732 absorb excess moisture or oil from the skin. The superabsorbent capacities due to the large  
733 pore volume, surface area, and porosity, together with high mechanical strength of the porous  
734 membranes can be adapted by modulating the concentration of a spinning solution from  
735 cellulose acetate in N, N-dimethylacetamide (Yadav et al., 2016). Recently, the  
736 functionalized CNY membranes were fabricated by blending silver sulfadiazine within the  
737 cellulose acetate spinning solution, resulting in wound dressing membranes with embedded  
738 antibacterial properties (Khan et al., 2019).

739

### 740 **9.2 CNY as a topical delivery medium**

741 The bioactive agents or nutrients (e.g. peptides, vitamins) can be incorporated into  
742 electrospun CNY single fibers or membranes to enhance skin healing and cleansing, or to  
743 provide specific functions for a medical purpose (e.g., whitening, anti-wrinkle, moisturizing,  
744 skin irritation relief, skin elasticity enhancement, antibacterial activity). An advantage of  
745 CNYs is that skincare ingredients can be directly incorporated in liquid form (as a solution or  
746 dispersion) in the mixture used to electrospun the fibers. Because of their high surface area  
747 and small interstices, the penetration of active ingredients into the skin is enhanced with a  
748 strong increase in drug efficacy (Nafisi et al., 2017). The CNYs of hydroxypropyl cellulose  
749 and polyurethane have been used for transdermal drug delivery, with reduced skin irritation  
750 and diffusion-controlled release of the encapsulated drug (Gencturk et al., 2016). However,  
751 when cellulose acetate is combined with cream of rubber extracts, fewer influences on the  
752 efficiency and/or degradation of the incorporated bio-active components were noticed when  
753 used as facial masks (Suwannateep et al., 2015).

754 The adhesion of electrospun CNY membranes to the skin is critical and can be resolved  
755 by the fabrication of a double layer and/or the addition of proper additives. The polymer  
756 fibers incorporated in the mat can vary and/or can be combined by co-electrospinning in a  
757 laminated mat to tune the density, mechanical strength, chemical composition and physical  
758 properties in order to provide intimate skin contact and absorption. Therefore, the electrospun  
759 CNY is sometimes used as outer layer in a multilayer dressing in combination with a second  
760 layer of polymer nanofibers that contain the active cosmetic component for migration into the  
761 skin. The additional layer also mechanically supports the shape of a weak and moisturized  
762 cellulose layer in beauty care packs. In particular, the release and easy peeling after use can  
763 be adapted and/or the masks made from water-soluble cellulose derivatives can be easily  
764 washed from the skin with water.

765

766 **10. Emerging nanocelluloses applications in wearable skin sensors and skin**  
767 **regeneration**

768 Use of nanocelluloses in skin regeneration, wound healing, and wearable skin sensors  
769 have attracted widespread attention over the past decades. Interestingly, nanocelluloses have  
770 been applied to daily life in health monitoring sectors, motion monitoring, human-computer  
771 interaction, and artificial intelligence (Herrmann et al., 2021; Z. Wang et al., 2021; Zhao et  
772 al., 2021). Nanocellulose as skin biocompatible materials have also shown a vital role in the  
773 development of wearable skin sensors, for in-situ mentoring of biomarker diseases release  
774 from the skin (Figure 8a). In relation to skin biosensors, nanocellulose membranes have been  
775 successfully investigated as sensing platform for bioreceptors (e.g. enzymes, antibodies,  
776 aptamers) immobilization, due to its high surface area, characteristic particle size, and pore  
777 structure. Surface functionalization (-OH, -COOH, -SO<sub>3</sub>H) of nanocelluloses allows to  
778 accommodate binding sites for bioreceptors, and then selective binding with the targeted  
779 biomarkers released from the skin. Nanocelluloses effectively address the skin sensors  
780 problems not only to fabricate flexible and skin biocompatible wearable sensors, but also  
781 lightweight property, cost-effectiveness, disposability, and robustness (L. Dai et al., 2020),  
782 (H. Xu et al., 2020). Recently, nanocellulose hydrogels can also be used as a reducing and  
783 stabilizing agent, which provides plasmonic NPs (Ag and Au NPs) with strong stabilization  
784 and allows them to monodisperse in solutions without aggregation (Divya et al., 2021). BNC  
785 have been used as sensor platforms to host optically active species to detect E. coli  
786 (Cheeveewattanagul et al., 2017). Recently, Silva et al. developed wearable sensing platforms  
787 made of screen-printed carbon electrodes on the bacterial cellulose-based platform. This  
788 sensor can detect 17 $\beta$ -estradiol, uric acid and toxic metals (Pb<sup>2+</sup>, Cd<sup>2+</sup>) in sweat with limits of  
789 detection of 0.58, 1.8, 0.43 and 1.01  $\mu$ M, respectively (Silva et al., 2020a). In another study,  
790 Xu et al. developed a flexible piezoresistive electronic skin (E-skin) by TEMPO-oxidized  
791 CNFs and sulfonated-CNTs. The flexible sensor exhibited an extremely high sensitivity of

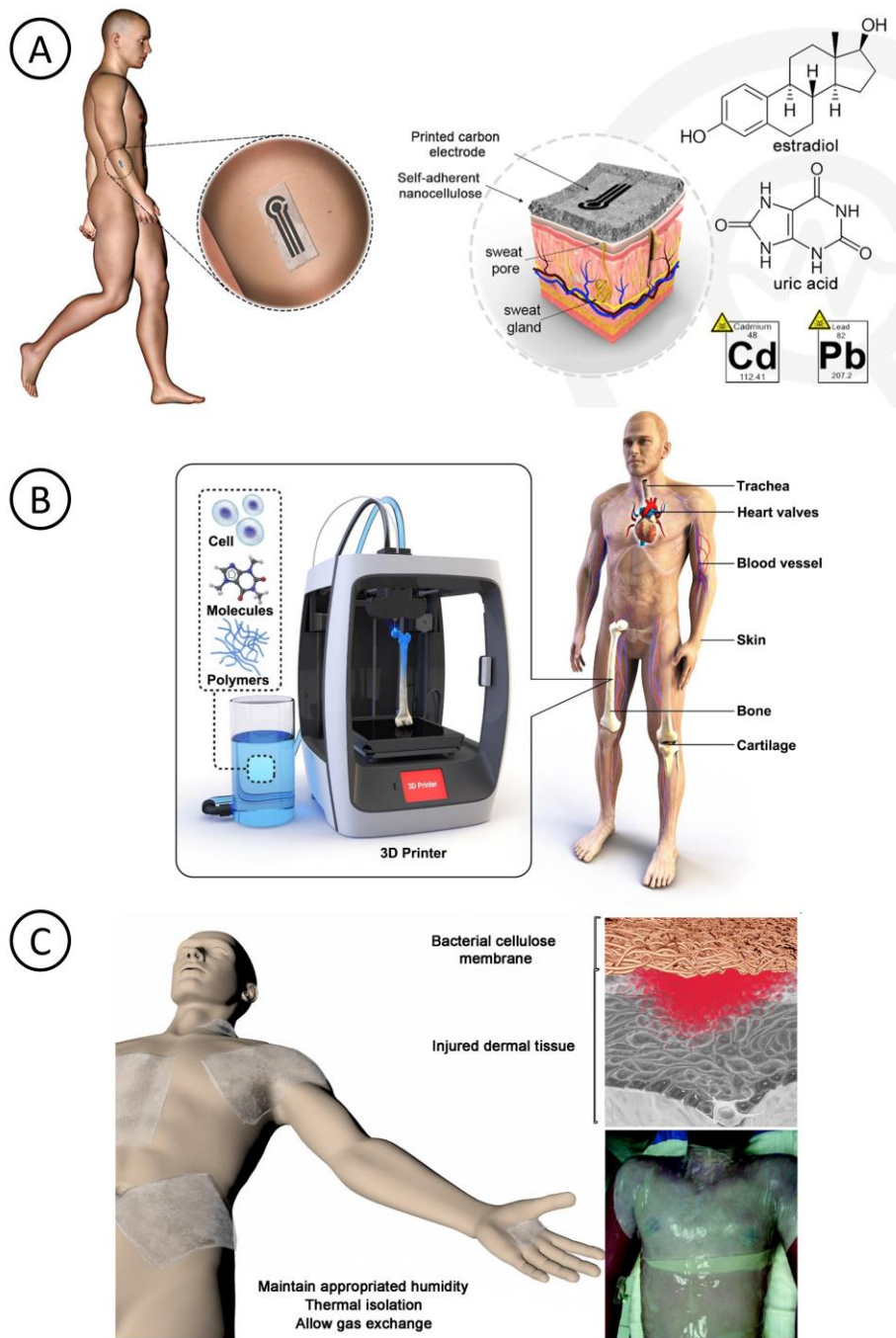
792 about 4.4 kPa<sup>-1</sup>, ultrafast response time below 10 ms, ultralow detection limit of 0.5 Pa, good  
793 stability (>11000 cycles) and mechanical strength of up to 184 MPa (H. Xu et al., 2020).

794 Nanocellulose with an exceptional skin-substitute natural polymer routinely used for  
795 wound dressing and offers unprecedented potential as a scaffolds for wound healing. In  
796 contract to nanocellulose produced from plant sources, BNC may have more advantageous  
797 for application of the skin as they are highly biocompatible with human tissues (J et al.,  
798 2020). BNC morphology and high purity mimics the nanoscale architecture of the native  
799 extracellular matrix, they have been investigated as temporary substrate for the adhesion and  
800 growth of skin cells for extensive burns and skin damaged by mechanical traumas or chronic  
801 ulcers (J et al., 2020). Dried BNC membranes display high permeability for liquids and gases  
802 and low skin irritation alongside adhesive-free adherence to skin moisture (Fontana et al.,  
803 1990; Portela et al., 2019). Nanocelluloses have been used in reconstructing the structural and  
804 functional components of skin, reducing scar formation, and improving the quality of wound  
805 healing. Every year, millions (Chung et al., 2020) of patients are waiting organ donors and  
806 suffer from long transplant waiting lists. For cell attachment and proliferation, the scaffolds  
807 must be coated with bioactive substances, or surface modification, or encapsulate cells in  
808 hydrogels to allow the self-assembly of cell aggregation and 3D print cells directly in the  
809 form of a scaffold (Figure 8b). An ideal biocompatible scaffold has to possess a surface that  
810 is suitable for cell attachment and 3D interconnected porous structures for extracellular  
811 matrix formation and vascularization. Nanocellulose provides biocompatible and mechanical  
812 properties, and cell adhesion for cellular attachment.

813 Nanocellulose hydrogels are characterized by a nanofiber network structure that  
814 confers mechanical stability and flexibility and high biocompatibility with skin tissue (Figure  
815 8c). Nanocellulose hydrogels has a water content of up to 95% and this creates a moist  
816 environment and prevents excessive fluid loss through the wound healing process.

817 Nanocellulose hydrogels can significantly reduce intradermal temperature and have a cooling  
818 effect, which is based on evaporation. Electrospinning and 3D printing of nanocelluloses  
819 (hydrogels) allows fabricating scaffolds with more controlled and precise structures  
820 compared to salt-leaching, freeze-drying, and foaming techniques (Chung et al., 2020).  
821 Compared with synthetic polymers, nanocelluloses also stand out in the field of 3D printing  
822 (bioinks formulation) serving as platform biomaterial owing to their high mechanical strength  
823 as well as the structural similarity mimicking natural extracellular matrix. However, the big  
824 challenge is to develop printable formulations and to keep the printed scaffolds stable. Recent  
825 cell tests have shown that the 3D-printed of cross-linked nanocellulose hydrogel scaffolds  
826 supported fibroblast cells' proliferation, which was improving with increasing rigidity. These  
827 3D-printed scaffolds render nanocellulose a new member of the family of promising support  
828 structures for crucial cellular processes during wound healing, regeneration, and tissue repair  
829 (C. Xu et al., 2018).

830



831

832 Figure 8. Emerging applications of nanocelluloses in healthcare: (a) Screen-printed carbon

833 electrode deposited on a bacterial nanocellulose substrate for non-invasive detection of

834 biomolecules in biological fluids released from the skin (Silva et al., 2020a). Copyright

835 Elsevier. (b) 3D printing of nanocellulose hydrogel with cells and bioactive molecules for

836 skin tissues and organs repair (Chung et al., 2020). Copyright Frontiers, (c) use of bacterial

837 cellulose membrane as skin regenerative materials for skin burns and wound healing.  
838 Copyright Elsevier (de Oliveira Barud et al., 2016).

839

## 840 **11. Safety and regulatory aspects of nanocelluloses in cosmetics**

841 Skin biocompatible products are in contact with the human body after application by  
842 pouring, sprinkling, rubbing, or spraying. As skincare products are often accompanied by  
843 drugs, bioactive components, or coloring materials also have additional therapeutic effects, a  
844 regulatory framework for labeling and usage is needed. As demonstrated in this review,  
845 nanotechnology has high potential in the skincare industry due to easy penetration through  
846 the skin towards the targeted tissue. In parallel, the World Health Organization (WHO)  
847 expressed concerns about the effect of nanomaterials on human health and administrative  
848 directives have been introduced (Pastrana et al., 2018). However, the regulation of cosmetics  
849 remarkably vary in US, Canada, Europe and Japan (Bilal et al., 2020).

850 According to the Food and Drug Administration (FDA), the physicochemical  
851 characteristics, agglomeration and size distribution of nanomaterials are some of the key  
852 points in their assessment, depending on the properties such as morphology, solubility,  
853 density, porosity, stability and impurities (Tan et al., 2018). Therefore, FDA published  
854 separate information on the health and safety guidance for the use of nanomaterials and  
855 nanotechnological approaches in skincare formulations and identified potential safety risks  
856 and their evaluation criteria (Bilal et al. 2020). Pre-market approval by FDA is essential for  
857 skincare products and drugs (both finished products and ingredients), and the manufacturer  
858 must ensure their safety before entering the marketing (Katz, 2007, Fytianos et al., 2020). It  
859 emphasizes that skin biocompatible products and their constituents must not be misbranded  
860 or adulterated (Effiong et al., 2020).

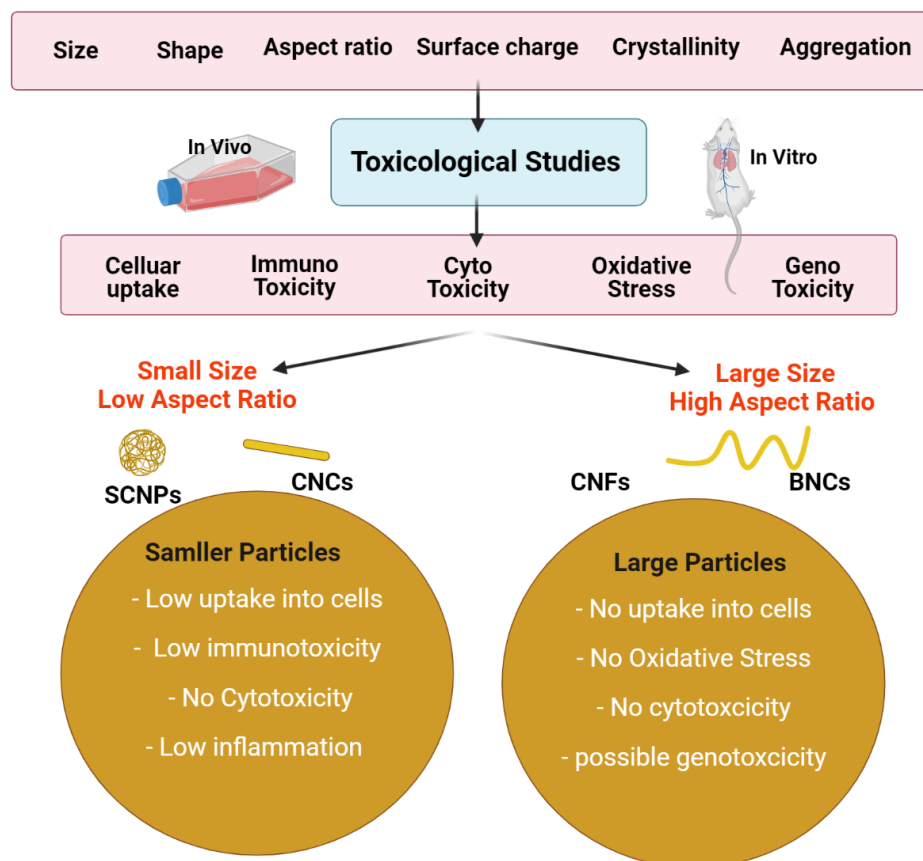


861 According to the European Commission (EC), the safety of nanomaterials in skincare  
862 and cosmetic products should focus on their intrinsic physicochemical characteristics and  
863 additional toxicological data. The EC Regulation (2007) provides a list including all skincare  
864 products and their ingredients, type, quantity, manufacturing, marketing, and the  
865 manufacturer's responsibilities. In Europe, all ingredients and nanomaterials used in skincare  
866 products must undergo a safety assessment and be notified six months before the marketing  
867 (Jeevanandam et al., 2018). Moreover, animal testing is strictly prohibited for the collection  
868 of toxicological information and hazard determination. Therefore, safety assessment of  
869 nanomaterials and nanocarriers is based on *ex-vivo* and *in-vivo* immunotoxicity tests  
870 (Bernauer et al., 2019).

871 The toxicological tests for various types of nanocelluloses with different  
872 physicochemical features, such as rigidity or surface properties, evoke variable results  
873 (Roman, 2015). The main parameters and physicochemical properties of nanocelluloses that  
874 affect toxicological studies and main outcomes are summarized in Figure 9 (Ventura et al.,  
875 2020). Nanocelluloses in powder or gel form may cause immunological reactions related to  
876 their agglomeration propensity when dispensed *in-vivo* or *in-vitro* (Ventura et al., 2020). The  
877 bioavailability, cellular uptake and interaction with sub-cellular constituents is largely  
878 influenced by the agglomeration of the nanocellulose. Therefore, the nanocellulose uptake  
879 and the interaction of its functional groups with the cell membrane – and hence downstream  
880 biological responses – will either be enhanced or retarded by surface functionalization  
881 depending on their surface charge, hydrophobicity and surface chemistry (Ventura et al.,  
882 2020).

883 In general, the nanocellulose absorption into cells is low and there was observed no  
884 direct induction of oxidative stress or no significant genotoxic and cytotoxic impact (Ventura  
885 et al., 2020). Nevertheless, macrophages caused moderate to severe inflammatory reactions

886 owing to their phagocytic function mostly for NCSPs and CNCs. In comparison, CNFs and  
 887 BNC were not phagocytized but represented notable genotoxicity for both *in-*  
 888 *vitro* (chromosomal destruction) and *in-vivo* (DNA destruction) testing. To date, various  
 889 studies revealed adverse effects such as interstitial fibrosis, pulmonary inflammation,  
 890 bronchioloalveolar hyperplasia, granuloma and even cancer (Ventura et al., 2020). In  
 891 comparison, the *in-vitro* effects such as cytotoxicity, genotoxicity and immunotoxicity  
 892 evidenced for nanocelluloses were inferior to those of other nanomaterials (e.g., carbon  
 893 nanotubes). Considering the various physicochemical properties of nanocelluloses, however,  
 894 the design of safe nanomaterials is essential for sustainable innovative applications in order to  
 895 impede adverse health effects by oral, dermal or respiratory human exposure (Ventura et al.,  
 896 2020).



897  
 898 Figure 9. Schematic representation of the main physicochemical properties of nanocelluloses  
 899 affecting toxicological studies and their main outcomes.

900

## 901 **12. Limitations and challenge of nanocelluloses in skincare formulation**

902 Nanocellulose has been commercialized for applications in the field of skincare, cosmetics,  
903 wound healing, and wearable skin biosensors. At present, it is particularly used as a  
904 functional additive in face masks and cosmetics. However, certain drawbacks currently  
905 hinder the further expansion of nanocellulose utilization, which are mainly related to its  
906 processing conditions:

907 1) High dispersion stability of nanocelluloses makes their separation from industrial  
908 wastewater system difficult and necessitates pH alterations or additions of salt to  
909 recover them after water treatment processes (Trache et al., 2020).

910 2) Due to high polarity and hydrophilic nature of nanocelluloses, the dispersion  
911 of nanocellulose in combination with hydrophobic polymers remains a critical issue.  
912 However, surface grafting of nanocelluloses with low molecular weight polymers can  
913 solve this problem and control the interaction with other skincare ingredients  
914 (Buffiere, 2020).

915 3) Production of nanocellulose from plant sources generally involves acid hydrolysis,  
916 alkali treatment, enzymatic hydrolysis, chemical modification. The high water and  
917 energy consumption together with limited yield are the main challenges in the  
918 preparation process, along with by-product toxicity (Espíndola et al., 2021; Trache et  
919 al., 2020).

920 4) Nanoscale dimension and morphology of nanocelluloses cause some considerations  
921 on their potential to affect the environment, humans and nature. The preparation  
922 methods, finishing treatments, the degree of aggregation, and chemical modification  
923 of nanocelluloses all have significant effects on toxicity (Roman, 2015).

- 924 5) Fundamental properties such as rheological behavior, thermal stability, viscoelastic  
925 properties and surface functionality impact the industrial application of  
926 nanocelluloses and require thorough characterization of the material quality (Li et al.,  
927 2015).
- 928 6) Standards, test methods and related tools for nanocelluloses are currently being  
929 developed and need fast implementation to enhance industrial applications and  
930 increase the market introduction of nanocellulose into skincare and healthcare  
931 products (Pyrgiotakis et al., 2018).
- 932 7) Application of nanocelluloses in skincare, cosmetic, skin tissue regeneration, and  
933 wearable skin sensors applications still has many open research questions. Some  
934 nanocelluloses (NCSPs and CNCs) have shown oxidative stress in cells and the  
935 dosage and concentration of these materials are relevant for human health.

### 936 **13. Conclusion and outlook**

937 Nowadays, the application of nanocelluloses developing skin biocompatible materials  
938 is one of the hottest topics in healthcare and biomedical applications and forms a fast growing  
939 economic sector worldwide. Among different types of nanomaterials, nanocelluloses are  
940 rapidly emerging for use in personal care, cosmetics, skin tissue regeneration, and wearable  
941 skin sensors, owing to their biocompatibility, high aspect ratio, high surface area, abundant  
942 surface charge, water holding capacity, biodegradability and mechanical strength. Different  
943 nanocellulose types have been recently integrated into a number of cosmetics and personal  
944 skin care formulations (e.g. creams, lotions, gels, face masks, make-up powders, hygienic  
945 powders, hair care) as well as hydrogels and membranes for wound healing, skin burns, and  
946 wearable skin sensors. The nanocelluloses are used in as anti-wrinkle agents, carriers for UV-  
947 blocking products, drug delivery systems, compatibilizers, moisturizers and thickeners, with  
948 aim of application onto the skin. The nanocelluloses are promising biomaterials for producing

949 green and ecofriendly cosmetics and skincare formulations with higher performance and  
950 additional features compared to traditional polymeric materials. However, the specific  
951 features of nanocelluloses with different morphologies and resulting physicochemical  
952 properties need to be fully understood in order to exploit their full potential. While initially  
953 the bacterial nanocellulose was a preferred material for biomedical applications, statistics also  
954 show a growth of nanocelluloses produced from wood for skincare applications. In particular,  
955 the control of surface functionalities and introduction of nanocomposite particles with  
956 multifunctional properties offer high potential for the creation of unique formulations.  
957 However, the main challenges facing the spread use of this wonderful nanomaterial in  
958 cosmetics and skin care applications are: (i) minimizing the cost of production; (ii)  
959 developing new techniques for large-scale production of nanocelluloses with minimum  
960 energy consumption and contamination of the water system; and (iii) determination of the  
961 efficient dosage, size/aspect ratio, and concentration of nanocelluloses in the formulations  
962 applied onto the skin without affecting human health.

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