

# Nanocellulose as a Functional Ingredient in the Management of Metabolic Syndrome: A Review

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## ABSTRACT

Alternative treatments in the management of metabolic syndrome are required because multiple drugs for individual components was found to have negative side effects on other components. Functional ingredients, particularly fiber, has shown great benefits in improving metabolic syndrome. Nanocellulose is a novel type of fiber, derived from cellulose through various processes that result in a nanoscale fiber with the dimension below 100 nm. Its smaller size brought improvements to the physicochemical properties of cellulose and consequently its biological activities. Nanocellulose appear to exhibit distinct functional activities that affect various processes in the gastrointestinal tract, including interference in lipid and carbohydrate digestion and reinforcement of gut microflora. These properties may ameliorate abdominal obesity, dyslipidemia, hyperglycemia, and high blood pressure through similar mechanisms of both soluble and insoluble fibers. In this review, we first introduce nanocellulose and its particular characteristics that makes it separate from cellulose. With the limited studies available, we try to go in depth into its activity in the gastrointestinal tract followed by the possible implications of those functional properties on health, especially on the components of metabolic syndrome. Lastly, we discuss the potential applications and advantages of incorporating nanocellulose in functional food for the management of metabolic syndrome.

**Keywords :** nanocellulose; fiber; metabolic syndrome; functional food

## BACKGROUND

As the numbers of noncommunicable disease cases such as cardiovascular disease and diabetes continue to increase, it brings about the rise of a discernible condition now commonly known as metabolic syndrome. Metabolic syndrome is generally characterized by at least three of the following signs, i.e. high blood glucose or insulin levels, high blood pressure, abdominal obesity, and abnormal lipid profile, specifically elevated triglycerides and low high-density lipoprotein (HDL) concentration.<sup>1</sup> The prevalence of metabolic syndrome is estimated to be about a quarter of the world's population, although the reported data might vary based on the criteria used and the characteristics of the studied population.<sup>2</sup> Approximately 12-49% of the Asian population were estimated to have metabolic syndrome, with women and urban residents having the higher proportion of cases.<sup>3</sup> In Indonesia, it was reported that about 28% of men and 46% of women have metabolic syndrome.<sup>4</sup> These numbers may continue to rise in the upcoming years especially with the growingly common dietary pattern of consuming high calorie food with low fiber intake.<sup>5,6</sup>

The general guidelines in the management of metabolic syndrome consist of medication and lifestyle changes, specifically regular physical activity and diet interventions. Medications given typically consist of multiple drugs that treats each component separately with common side effects that may adversely impact the other components.<sup>7-10</sup> The use of statin to reduce high cholesterol levels, for example, increased the risk for diabetes by 46% due to impaired insulin sensitivity and secretion.<sup>9</sup> Therefore, there is a need for alternative treatments that can improve various attributes of metabolic syndrome without causing much side effects. Functional food and nutraceuticals are viewed as promising options as they possess favorable effects on metabolic homeostasis.<sup>11,12</sup> Fiber, in particular, is a great functional ingredient as it has been proven to significantly decrease the risks for metabolic syndrome<sup>13</sup> through improving glucose homeostasis<sup>14,15</sup>, reducing the absorption of triglycerides<sup>16,17</sup>, and lowering body fat<sup>18,19</sup>. Traditionally, fiber can be obtained by eating vegetables and fruits, but the development of food technology has broadened our options and even enabled us to modify the content of functional ingredient in food to produce food with more health-

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promoting benefits.<sup>20-22</sup> The emergence of nanotechnology further aided the growth of functional food by introducing various nanomaterials including nanoscale fibers such as nanocellulose.

Nanocellulose is a nanomaterial derived from cellulosic materials with at least one dimension less than 100 nm. There is a growing interest for the application of nanocellulose as it has exhibited many attractive qualities, such as minimal toxicity, low density, biodegradability, and compatibility with biological tissue.<sup>23-26</sup> Aside from the general characteristics of cellulose, nanocellulose possesses larger surface area, higher viscosity, better dispersion, and most interestingly, gelling properties that resemble soluble fiber.<sup>26,27</sup> These characteristics may affect its behavior in the gastrointestinal tract and how it interacts with other nutrients and intestinal bacteria. Simulated digestion of starch along with nanocellulose revealed that 1% of nano-fibrillated cellulose impaired 26.6% of glucose release.<sup>28</sup> Other studies reported that nanocellulose significantly reduced the absorption of triglycerides, free fatty acids, and saturated fat.<sup>29,30</sup> Furthermore, nanocellulose significantly improved the production of short chain fatty acids during intestinal fermentation, increasing it by over 200%.<sup>31,32</sup> These findings imply hypoglycemic and hypolipidemic effects as well as other potential health benefits of nanocellulose that may become beneficial in the management of diseases including metabolic syndrome.

So far, only a few studies have investigated the application of nanocellulose in terms of its functional activities for health. DeLoid et al reported lipid-lowering benefits with reduced serum triglycerides up to 36% in rats given nanofibrillated cellulose, whereas Lu et al discovered significant decrease in plasma cholesterol from nanocrystal cellulose gavage in mice.<sup>29,33</sup> Previous reviews have detailed the use of nanocellulose in cosmetics, paper, textile, biomedicine, and food industry<sup>25,27,34,35</sup>, but it appears that not many have discussed its potential as a functional substance for health and disease management. Therefore, this review article will discuss the potential of nanocellulose as a functional ingredient for metabolic syndrome based on its physicochemical properties and its effects on processes that may affect metabolic biomarkers, the health implications it may entail, and the potential application for nanocellulose as functional food.

## CELLULOSE AND NANOCELLULOSE

Cellulose is the most widely available and abundant biopolymer on Earth, most well-known as the structural and reinforcement component in cell wall of plant.<sup>24</sup> Approximately  $7.5 \times 10^{10}$  tons of cellulose are produced every year<sup>36</sup> by not only plants but also bacteria, fungus, tunicates, and some species of invertebrates and amoeba.<sup>26</sup> Structurally, cellulose is a linear polysaccharide consisting of glucose monomer units that carry three hydroxyl groups each.<sup>24</sup> Each cellulose fiber is formed by a bundle of cellulose crystals linked along microfibrils that are tightly connected by hydrogen bonds and enclosed with matrix components namely hemicellulose, pectin, and lignin. About a quarter of dietary fiber in grains and fruits and one third in vegetables are made up of cellulose.<sup>37</sup> As an insoluble fiber, cellulose increases fecal volume and undergoes fermentation by intestinal microflora which produces beneficial byproducts like short-chain fatty acids.<sup>38</sup>

Using certain methods, cellulose can be broken down into its nanoscale components or commonly known as 'nanocellulose'. Nanocellulose generally describes various nanomaterials derived from cellulose with at least one dimension in the nanometer range.<sup>27</sup> There are two major methods to obtain nanocellulose: top-down and bottom-up.<sup>27</sup> Top-down methods involve enzymatic or chemical or mechanical treatments to isolate nanocellulose from lignocellulosic residues. The bottom-up method involve production of nanocellulose from glucose by bacteria. These methods produce the three main types of nanocellulose, namely nanocrystals cellulose (NCC), nanofibers cellulose (NFC), and bacterial nanocellulose (BNC).

Both NCC and NFC are produced through top-down methods from materials like wood, potato tuber, sugar beet, seed fiber, grasses, wheat straw, bark, marine animals (tunicate), and algae.<sup>24,25</sup> The extraction of NCC begins with acid hydrolysis to remove amorphous regions of the material. Afterwards, free acidic molecules and impurities are removed using dilution and washing along with centrifugation and extensive dialysis. Lastly, the NCC particles are stabilized as uniform suspension by sonication. The diameter of NCC ranges from 5-70 nm with various lengths depending on its source material, starting from 100-500 nm for plant cellulose and 100 nm to several  $\mu\text{m}$  for algae and tunicate cellulose.<sup>24</sup> NCC appears as rigid, long needle-like nanoparticles under electron microscope observations.<sup>39</sup> NCC carries a negative surface charge.

On the other hand, NFC is mostly isolated through mechanical treatments such as high-pressure homogenization, grinding, waring blender, or microfluidizer.<sup>26</sup> These treatments are meant to break the side aggregations and delaminate the individual microfibrils. Pretreatments like 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) oxidation are often applied beforehand to weaken interfibrillar hydrogen bonds, to reduce the energy consumption needed in NFC extraction, and to convert primary hydroxyl groups of cellulose to carboxyl groups.<sup>26,40</sup> NFC has a diameter of 5-60 nm and length of several  $\mu\text{m}$ . NFC has a more flexible structure than NCC due to its alternating crystalline and amorphous regions.<sup>24</sup>

Unlike NCC and NFC, BNC is extracted using the bottom-up method where bacteria synthesize cellulose in a pure form, requiring no treatments to remove impurities or contaminants. Glucose chains and cellulose molecules are generated inside the bacteria and then extrude out through pores on the cell surface, before assembling and further aggregating into nanofibrils.<sup>26,41</sup> Bacteria that can be used to produce BNC are *Aerobacter*, *Achromobacter*, *Agrobacteriuj*, *Pseudomonas*, *Rhizobium*, *Salmonella*, *Zooglea*, and *Escherichia*, but so far only *Gluconacetobacter* can produce BNC for commercial use.<sup>42</sup> The diameter of BNC is around 20-100 nm.<sup>24</sup>

General physicochemical characteristics of cellulose was found to be improved in nanocellulose. Due to its smaller size, nanocellulose has larger specific surface area which indicated more exposure of free hydroxyl groups on the surface. These hydroxyl groups develop hydrogen bonds that give nanocellulose a reactive surface for associations with substances.<sup>43</sup> This was supported by the findings of an inverse relationship between cellulose particle size with water holding capacity, swelling capacity, and oil-holding capacity.<sup>31,44</sup> Similarly, Dubey et al reported that water holding-capacity and swelling capacity of nanocellulose were, respectively, 7.3 times and 9 times higher than cellulose.<sup>32</sup> Swelling capacity can affect the fermentation of fiber, further proven by another study where nanocellulose has higher fermentability than cellulose.<sup>31</sup> Apart from that, nanocellulose has low toxicity as well as good biocompatibility and biodegradability.<sup>45,46</sup> Cellulose is generally found to be biocompatible with minimum to no adverse effects, but it is not highly biodegradable for the human body due to the lack of cellulolytic enzymes. Although still not readily degradable, nanocellulose were biodegraded at a relatively faster pace than cellulose because of its higher surface area.<sup>47</sup> Nanocellulose also has shear-thinning properties where they cause decreased viscosity in fluid under shear force, making it beneficial for the processing and storage of fluids.<sup>48</sup> Another interesting property is the capability of nanocellulose to accumulate at oil-water interface in emulsions to form a physical barrier that prevents the emulsion droplets from coalescing.<sup>49</sup> Other properties of nanocellulose include high aspect ratio, high stiffness and tensile strength, low density, rheological properties, barrier properties, and mechanical reinforcement.<sup>25</sup> The stark differences in properties between cellulose and nanocellulose clearly imply distinct biological activities.

## FUNCTIONAL ACTIVITIES OF NANOCCELLULOSE

A food or substance is considered 'functional' when it evokes positive biological effects that provides protection from diseases through mechanisms other than fulfilling nutritional needs.<sup>12</sup> The functional activities of fiber are generally determined by the type of fiber, either soluble or insoluble fiber.<sup>38</sup> Soluble fiber forms viscous gels in the stomach, resulting in delayed gastric emptying and consequently reduced glycemic response<sup>50</sup>. Insoluble fiber inflates the volume of food bolus, increases gastrointestinal transit time, and improves intestinal function, causing reduced absorption of triglyceride and cholesterol.<sup>38,51</sup> All types of dietary fiber undergo fermentation in the large intestine, directly influencing the balance of gut microbiome and determining the generated fermentation products.<sup>51</sup> Since nanocellulose has its own distinguished properties, it is possible that it might not entirely have the exact same effects as cellulose on the processes in the gastrointestinal tract and its metabolic implications. It is important to identify the types of functional activities nanocellulose possess to determine the exact health benefits it may provide as well as the proper application methods to sustain its functional activities. The following is an overview of studies that examined the potential functional activities of nanocellulose, especially in the gut.

### Effects on Lipid Digestion and Absorption

As with other dietary fibers, nanocellulose has shown potential hypolipidemic activities in simulated gastrointestinal digestion models. The addition of nanocellulose resulted in slower lipid digestion and lower lipolysis rates.<sup>29,52-56</sup> DeLoid et al reported that NFC significantly reduced fatty acid hydrolysis up to 48.4%.<sup>29</sup> Similarly, another study used NCC to stabilize emulsions and it generated less free fatty acids compared to gum Arabic-coated emulsions during simulated digestion.<sup>52</sup> Sarkar et al also found that the use of 3% NCC reduced the rate and degree of lipid digestion, going as far as to 8 times and 3 times lower, respectively.<sup>56</sup> Increasing the concentration of nanocellulose appeared to enhance the inhibition effect as the lowest amount of hydrolysis products was mostly found at the highest concentration studied, around 1-3% dry weight.<sup>52,53,56</sup> In addition, nanocellulose exhibited excellent cholesterol adsorption capacity, reportedly adsorbing 99.99% (8.5 mg/dry weight fiber) of cholesterol, which was significantly higher than cellulose (84%, 7.1 mg/dry weight fiber).<sup>53</sup> Furthermore, a study using an *in vitro* triculture small intestinal epithelial model revealed that NFC reduced the absorption of triglyceride by 35% and free fatty acids by 54%.<sup>29</sup> Mackie et al also found that NCC caused significantly less absorption of saturated fat.<sup>30</sup>

There are several mechanisms underlying the effects of nanocellulose on lipid digestion. Considering its larger surface area and high water-holding capacity, nanocellulose can reduce free water content in digesta, thereby increasing the viscosity.<sup>54,55</sup> The viscosity was particularly increased after gastric digestion, most likely due to high ionic strength that compressed the electric double layer and allowed NCC to interact through van der Waals forces and hydrogen bonds.<sup>54,57</sup> Highly viscous digesta resulted in slower digestion and lower absorption of lipid as it prevented the bulk diffusion across intestinal lumen.<sup>33</sup>

Examinations under various microscopy systems demonstrated that nanocellulose formed a surrounding structure that encapsulates and attaches to fat droplets, thus limiting the adsorption of lipase and preventing the hydrolysis of fat droplets.<sup>29,52,56</sup> NCC formed a strong, rigid, densely packed coating on the surface of fat droplets.<sup>52</sup> Closer examination revealed that nanocellulose bridged together small emulsion droplets in a raspberry-like floc that was similar with emulsion microgel particles.<sup>56</sup> Similarly, NFC were found to form a honeycomb-like lattice with fat droplets attached to its structure.<sup>29</sup> This was also confirmed by Winuprasith et al who reported that NFC may have adsorbed to the surfaces of several fat droplets at once, creating a tight cluster bond.<sup>55</sup> Although it has not been proven yet in the current studies, high nanocellulose concentrations were assumed to ascertain lipid droplets becoming wholly surrounded by cellulose nanocrystals, leaving no uncovered gaps that are accessible for lipase or bile salts.<sup>52,56</sup>

Another mechanism involved the sequestration of bile salts by nanocellulose through hydrogen binding with hydrophilic groups.<sup>52,56</sup> Liu et al found that NFC at 2% (w/w) caused significantly lower bile acid diffusion rate than control (5.48% vs 8.0%) with a bile acid retardation index of 27, owing to higher viscosity from the binding of cellulose nanofibrils to bile acid.<sup>53</sup> Fiber-bound bile acid is excreted through the feces, as confirmed by Lu et al that observed higher total bile acid levels in fecal matter of rats fed with NCC.<sup>33</sup> The decrease of available bile acid hindered the displacement of interfacial materials at the surface of fat droplets, further preventing the adsorption of lipase-colipase complexes on fat droplets.<sup>29</sup> Insufficient bile acid would also stimulate the utilization of cholesterol for bile acid production, consequently reducing lipid and cholesterol absorption.<sup>53</sup> Furthermore, bile acid is necessary for the solubilization and removal of lipolytic products from the surface of fat droplets. Accumulation of such products like free fatty acids and monoacylglycerols would hamper further digestion processes such as hydrolysis by pancreatin.<sup>29,55</sup>

### Effects on Carbohydrate Digestion and Absorption

Carbohydrate digestion occurs starting from the mouth and all the way into the intestines, meaning that there are many possible sites where nanocellulose can affect the process. A linear relationship was found between the addition of NFC and the decrease of *in vitro* glucose diffusion, with significant differences observed starting from 0.5% of NFC.<sup>28,58</sup> As the concentration rose from 0 to 2%, NFC steadily reduced glucose diffusion rates from 22.4 to 9.5  $\mu\text{mol}/\text{minute}$ .<sup>28</sup> Retardation effect of fiber on glucose absorption in jejunum was quantified using glucose dialysis retardation index (GDRI) and 2% nanocellulose recorded a maximum value of 50%, much higher than fiber fractions from wheat bran (34.8%) and oats (29.7%).<sup>59</sup> Moreover, the digestion of starch with 1.1% NFC revealed significantly reduced glucose release.<sup>28</sup>

Nanocellulose also exhibited inhibitory effects on enzymes linked with carbohydrate digestion, particularly amylase. Amylase is an enzyme produced by saliva and pancreatic juice and functions to hydrolyze starch into maltose and glucose. The rate of hydrolysis by amylase declined with 1-2% of NFC, resulting in only approximately 70% of glucose was released after 6 hours of digestion.<sup>28</sup> Likewise, Ji et al reported that an inverse relationship between the activity of  $\alpha$ -amylase and NCC concentration. Results from infrared spectroscopy and circular dichroism analysis suggested changes in the structure of  $\alpha$ -amylase, confirming that NCC affected its activity by associating with  $\alpha$ -amylase, possibly through weak non-covalent interactions and hydrogen bonds.<sup>60</sup> Similar effects were found with glucoamylase. It was supposed that the hydroxyl groups in NCC migrated into protein's interior and form hydrogen bonds with atoms in the backbone.<sup>60</sup>

Glucose diffusion rates are determined by solution viscosity and the amount of glucose adsorbed in the fiber. Higher nanocellulose concentrations result in higher viscosity, causing an increase in the thickness of unstirred water layer next to the intestinal membrane and eventually making it harder for nutrients to be absorbed.<sup>28</sup> Furthermore, nanocellulose could bind three times more glucose than cellulose, reportedly 35.6% compared to only 12.8% of 200 mM glucose.<sup>28</sup> This effect was still prominent even at low glucose concentrations.<sup>28</sup> Nsor-Atindana et al also reported suppressed glucose release and diffusion in starch digested with NCC suspension, attributing it to the increased viscosity since the inhibition effect was higher in more viscous samples containing smaller-sized NCC particles.<sup>61</sup>

### Effects on Gut Microbiome

For the last decade, gut microbiome has been a great interest of study for its vital role in maintaining various bodily functions. Numerous studies showed that compromised gut bacteria contribute to the development of various diseases, including metabolic syndrome.<sup>62</sup> The consumption of prebiotics such as dietary fiber was reported to help improve gut barrier integrity and microbiota balance, thus it was reasonable to assume that nanocellulose could do the same.<sup>62</sup>

Several studies have described the beneficial effects of nanocellulose on gut microbiome and its metabolic products.<sup>31,32</sup> Using pH value as the index of fiber fermentation, studies have found that the addition of nanocellulose reduced pH during fermentation, suggesting that short chain fatty acids were abundantly produced. The decline of pH was greater in nanocellulose with the least particle size.<sup>31,32</sup> Lower intestinal pH provides protection against pathogenic bacteria and stimulates the growth of beneficial gut microbiome such as *Lactobacillus* and *Bifidobacterium*. This result was supported by Lopes et al who found that NFC may possess antibacterial activity against Gram-positive bacteria such as *Escherichia coli* but had no effect on *Lactobacillus reuteri*.<sup>46</sup>

Results from *in vitro* fermentation using human feces revealed that the number of *Bifidobacterium* bacteria significantly increased with 1% nanocellulose after 4-hour fermentation.<sup>31</sup> Interestingly, the bacteria count rose as the particle size decreased, with the smallest sized nanocellulose constantly having the highest number of bacteria throughout 24-hour fermentation. Accordingly, the amount of generated short-chain fatty acids was also size-dependent. A direct correlation was found between specific surface area of cellulose with the concentration of total short-chain fatty acids with R values of 0.837-0.988.<sup>31</sup> The same results were observed during *in vivo* experiment where faecal matter of rats orally fed with nanocellulose had significantly higher *Bifidobacterium* count and short-chain fatty acid concentrations in comparison to non-cellulose and microcellulose fed groups.<sup>31</sup>

Similarly, Dubey et al detected higher levels of acetate, propionate, and butyrate during simulated fermentation of reduced size cellulose in contrast to the original-sized one.<sup>32</sup> Acetate had the highest concentration, followed by propionate and lastly butyrate. In contrast, Nsor-Atindana et al reported butyrate as the highest, and then propionate and acetate.<sup>31</sup> However, their *in vivo* experiment revealed similar results as Dubey et al. The differences in short-chain fatty acid production may be attributed to the variation of intestinal microbiota profile among individuals.<sup>32</sup> Regardless, increased short-chain fatty acids appears to be the main mechanism for various health benefits provided by gut microbiome.

On the contrary, Khare et al reported possible adverse reactions on gut microbiome due to ingested nanocellulose. The gavage feeding of rats with 1% NFC resulted in decreased intestinal bacteria species, including *Caprococcus catus* that contributes to the production of short-chain fatty acids and *Bacteroides acifaciens* that is linked with increased insulin levels.<sup>63</sup> However, notable reduction of potential pathogenic and disadvantageous bacteria was also observed, such as *Tannerella* spp. that is known to stimulate foam cell formation.<sup>63</sup> More studies are required to be able to gain a complete picture of the effects of nanocellulose on gut microflora.

### **Health Implications of the Functional Activities of Nanocellulose on the Components of Metabolic Syndrome**

The previous overview shows that nanocellulose clearly has functional impacts on various processes in the gastrointestinal tract. These impacts may amount to beneficial health effects in the body, including improvements of the components of metabolic syndrome.

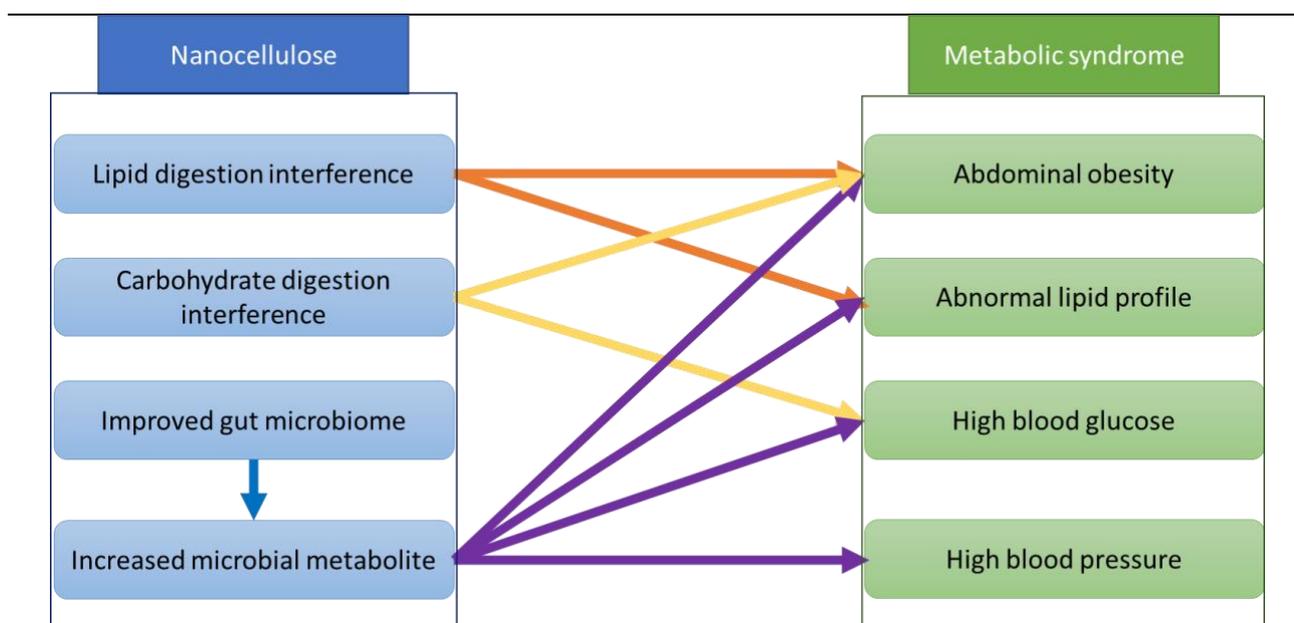
Abdominal obesity, commonly measured by waist circumference, serves as a practical screening tool for metabolic syndrome. It demonstrates the accumulation of fat in visceral tissues which eventually triggers the release of various peptides that contribute to the development of metabolic syndrome. The overload of fat storage arises from energy imbalance, mainly due to excessive energy consumption with fat being the highest contributor. Fiber is well-known to reduce energy intake and obesity by affecting digestion rate through increasing viscosity of digesta in the gut, lowering gastric-emptying rate and limiting digestive enzyme activities on nutrients.<sup>50</sup> As a result, the presence of nutrients in the intestines is prolonged and the absorption is delayed, leading to altered secretion of appetite control peptides namely glucagon-like peptide 1 (GLP-1) and cholecystikinin (CCK).<sup>64</sup> Reduced appetite and greater satiety result in lowered energy intake and eventually decreased waist circumference and body fat in the long term, as shown in previous studies.<sup>18,65,66</sup> Lambert et al provided pea fiber for 12 weeks and reported significant depletion in energy intake and body fat.<sup>18</sup> Similar digesta viscosity-enhancing effects were observed with nanocellulose during artificial digestion, suggesting that it would also have the same weight loss promoting effects as other fibers. Moreover, nanocellulose exhibits fat-entrapping capacity that is comparable to chitosan, which has been proven to achieve weight loss and diminished visceral fat even though subjects were not given specific diet restrictions.<sup>67</sup>

Another component of metabolic syndrome that may be ameliorated by nanocellulose is dyslipidemia. Dyslipidemia mostly occurs from a combination of high-fat diets with sedentary lifestyle, so a switch to low-fat with high fiber diets is commonly recommended to reduce elevated cholesterol and triglyceride levels.<sup>68</sup> Fiber demonstrates lipid lowering effects through several mechanisms.<sup>69</sup> First, it lowers overall energy intake by increasing satiety as previously explained. Secondly, it entraps bile acids and increases fecal excretion of bile acid and cholesterol, consequently decreasing bile acid re-absorption. Because of that, hepatic uptake of cholesterol is amplified to produce bile acids, thus reducing total cholesterol and low-density lipoprotein (LDL) cholesterol levels.<sup>70</sup> As mentioned, a similar fiber-bile acid relationship was observed with nanocellulose and further supported by animal studies that reported hypocholesterolemic effects. In a 28-day long study on ovariectomized rats, Lu et al found that NCC significantly decreased plasma total cholesterol and low-density lipoprotein cholesterol (LDL-C).<sup>33</sup> Several other studies affirmed that particle size reduction of cellulose improved its functional effects in lowering serum cholesterol in rats.<sup>71,72</sup> Further examination in animal studies revealed that NCC affected the expression of hepatic and ileac genes that are linked with cholesterol homeostasis. Further examination revealed that NCC caused the down-regulation of HMG-CoA reductase which is the rate-controlling enzyme for cholesterol biosynthesis, whereas mRNA levels of ASBT and IBABP that modulate intestinal absorption of bile acids were up-regulated.<sup>33</sup> This effect is most likely attributable to enhanced short-chain fatty acid production, especially butyrate.<sup>73,74</sup> This lipid-lowering capacity of nanocellulose would surely be beneficial in both the prevention and therapy of metabolic syndrome and other related illnesses like cardiovascular disease.

Furthermore, nanocellulose may have positive effects for glucose response by attenuating blood glucose levels using combined properties from both insoluble and soluble fibers. Insoluble fibers increase bulking of food matrix with its high water-binding capacity which leads to reduced glucose diffusion and suppressed increment of blood glucose.<sup>75,76</sup> Administration of insoluble barley fiber has been found to cause significantly ( $p < 0.01$ ) lower blood glucose levels in subjects with hyperglycemia when compared to placebo.<sup>75</sup> Soluble fibers delay gastric emptying and affects carbohydrate-related enzymes in the small intestine, resulting in lessened glucose and insulin response.<sup>15,50</sup> Both fibers also play a role in microbial metabolite production which includes various short-chain fatty acids that evoke the release of intestinal hormones linked with insulin and glycemic regulation.<sup>50</sup> All these mechanisms underlying hypoglycemic effects in the body were also observed with nanocellulose, thus indicating its possible efficacy in improving glycemic control. In addition, results from animal studies confirm the hypoglycemic capacity of nanocellulose. The administration of TEMPO-oxidized NFC with glucose and glycerol trioleate to mice resulted in decreased postprandial blood glucose, plasma insulin, and triglycerides.<sup>77</sup> Glucose-dependent insulinotropic polypeptide (GIP), which is involved in insulin secretion and fat metabolism, was also reduced.<sup>78</sup>

As for other parameters of metabolic syndrome, nanocellulose may cause betterment through stimulation of gut microflora and the production of short-chain fatty acids (SCFAs). SCFAs has been recognized as an important key for metabolic health as they are involved in numerous pathways that are linked with metabolic and inflammatory responses.<sup>79,80</sup> SCFAs, mostly acetate and propionate, modulate the expression of genes involved in blood pressure regulation. Propionate mediates GPR41 receptor which induces reduction of blood pressure.<sup>81</sup> Furthermore, SCFAs activate free fatty acid receptors (FFAR), specifically FFAR2, which is mainly activated by acetate and propionate, and FFAR3, which is activated by propionate and butyrate.<sup>62</sup> Both FFAR2 and FFAR3 trigger the secretion of intestinal hormones, such as GLP-1 that stimulates glucose-dependent insulin secretion and inhibits glucagon release, thus improving insulin resistance and overall glycemic control.<sup>82</sup> SCFAs were also found to reduce the expression of FXR which regulates triglyceride homeostasis.<sup>17</sup> That might be the plausible mechanism for lowered serum triglycerides when rats were provided heavy cream with 1.0% NFC. Serum triglycerides were curtailed by 36% at 1-hour post-gavage and the effect remained consistent after 2 hours.<sup>29</sup>

Altogether, the functional activities of nanocellulose appear to be beneficial for the treatment of metabolic syndrome. However, more research is needed to further verify this as some studies reported adverse effects instead. Andrade et al revealed no significant changes in the lipid profile nor blood glucose levels of rats fed with NFC for thirty days.<sup>35</sup> Another study examined the effect of oral NFC treatment in rats for 4-6 weeks, discovering that it caused negative effects instead, specifically dysregulation of glucose homeostasis, decreased lean body mass, and elevated body fat.<sup>83</sup> Generally, studies about the *in vivo* functional properties of nanocellulose are still limited and most are animal experiments while human studies are scarce.



Graphic 1. The link between the functional activities of nanocellulose with the components of metabolic syndrome that may be affected.

### Potential Application of Nanocellulose in the Management of Metabolic Syndrome

Dietary changes are a major part of the lifestyle modification required for the prevention and treatment of metabolic syndrome. Increasing fiber is one of the most prescribed modifications as it has repeatedly shown beneficial impacts on individual components of metabolic syndrome. Besides the wholefood sources of fiber, various innovations through chemical, thermal, and enzymatic processing have been made to expand the utility and application of fiber.<sup>84</sup> Nanocellulose is a result of those innovations and with its small size and improved functionality, it has great versatility in its application to support the fulfilment of dietary recommendations to ameliorate metabolic syndrome. There are two plausible ways to use nanocellulose as a therapeutic ingredient: as a dietary supplement or as a food additive to make functional food. Dietary fiber supplements are commonly found nowadays and are mostly presumed to be able to give the same health benefits as whole fibers but has a high risk of causing gastrointestinal distress due to significant differences in stool viscosity.<sup>85,86</sup> However, further studies are still required to verify if the same impact would be found with nanocellulose supplements.

The use of nanocellulose as an additive in food would most likely reduce the potential gastrointestinal disturbances and have other benefits both on bodily health and the quality of food. With its high water-holding capacity, nanocellulose can be used as an additive to produce low-calorie food. Most processed food products have high energy density because of their low water content, thus increasing the water content would lead to reduced energy density.<sup>87</sup> Incorporating nanocellulose may be used to lower energy density of processed foods up to < 1.6 kcal/g.<sup>88</sup> Furthermore, nanocellulose has shown great potential as an emulsion stabilizer, making it suitable for application in commonly high-calorie emulsion food products such as dressings, toppings, sauces, puddings, and others.<sup>27,49</sup> Several patents have been established for the use of nanocellulose to replace fats completely or partially in toppings, fillings, gravies, etc.<sup>27,89</sup> Aside from reducing initial energy content, the addition of NFC to high-fat food models has been proven to exhibit strong interference effect on fat digestion.<sup>29</sup> The effect was observed in food models with various fat types, containing varied amounts of saturated and unsaturated fat as well as fatty acid profiles. The highest inhibition effect (48.4% reduction) was found in heavy cream and it was postulated that fatty acid chain length played a big role in determining the extent of interference by nanocellulose.<sup>29</sup> This finding suggested that nanocellulose can be used as an additive in high-fat food to counter the negative impacts of excessive fat intake.

On top of that, nanocellulose may improve the quality of specific food contents and enhance its functional properties; in this case, it is starch. Starchy food is prone to retrogradation which causes detrimental effects on its quality, but the addition of NCC has been shown to inhibit both long-term and short-term retrogradation.<sup>90</sup> Ji et al mixed NCC with various types of gelatinized starch and discovered that it led to significantly higher resistant starch content and lower digestible starch content. The resistant starch content rose ~30% for corn, ~23% for pea, and ~20% for potato starch.<sup>60</sup> Resistant starch is the part of starch that cannot be digested by enzymes in the small intestine, but is fermented by gut microbiota in the large intestine. Various health benefits can be obtained from consuming resistant starch, including improved glycemic and

insulinemic response, improved blood lipid profile, reduced fat accumulation, increased satiety, and prebiotic effects.<sup>91</sup> These physiological effects are certainly favorable in the treatment of metabolic syndrome.

As a source of fiber, nanocellulose can be incorporated into food to provide the benefits of increased fiber consumption. To date, the main challenge in supplementing fiber in food is the noticeable effect on the appearance, taste, texture, and flavor of food.<sup>92</sup> These concerns are no longer found in the application of nanocellulose, particularly BNC, as it can acquire and reproduce the natural color and flavor of a modified culture medium, thereby not causing major changes to organoleptic properties.<sup>93</sup> The addition of 10% BNC in Chinese meatball showed slight changes in texture but overall similar sensory properties to control.<sup>94</sup> No off-flavors nor changes to texture and mouthfeel was detected in nanocellulose-modified hamburger.<sup>95</sup> Likewise, Sangnark et al confirmed fiber with large particles elicited adverse effects on the grain of bread and reduced overall acceptability of bread, whereas bread with smaller-sized fiber (<0.075) at the same concentration obtained sensory scores remarkably close to the control bread containing 100% wheat flour.<sup>96</sup> This further confirms the promising potential of nanocellulose as a fiber fortificant in food, although additional studies may be required to determine the limit of possible nanocellulose addition before it begin to cause undesirable sensory changes.

Overall, the application of nanocellulose in food may not only provide beneficial effects from the addition of nanocellulose itself, but also on the organoleptic and nutrient quality of food, thus producing a palatable and healthy food that supports the betterment of metabolic syndrome.

## CONCLUSION

Functional food is seen as a favorable option to answer the need of health-stimulating therapies with minimum adverse effects. The development of food technology offers a new type of functional fiber which is nanocellulose. Nanocellulose is the nanoscale counterpart of cellulose, demonstrating improved physicochemical properties including larger specific surface area, higher water-holding capacity, higher swelling capacity, biodegradability, steric barrier properties, low density, and gelling properties. It also boasts various functional activities in the gut, such as impaired lipid and carbohydrate digestion and enhanced gut microflora as well as increased short-chain fatty acid production. These activities may translate to hypocholesterolemic properties, hypoglycemic activities, and prebiotic effect that are beneficial for the treatment of metabolic syndrome. In addition, nanocellulose can improve the quality of food without causing unwanted organoleptic changes with less risk of causing gastrointestinal distress, making it suitable for the production of functional food. Evidently, there are still many gaps to explore considering the currently limited studies, especially from animal and human studies, that opens the opportunity for urgently needed studies to confirm the positive results from *in vitro* studies as well as to detect possible adverse effects that may arise from applications in biological systems. As the interest of nanocellulose for food and health continue to rise, we can look forward to more findings from further research in the upcoming years and possibly even actual applications of nanocellulose for health management.

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