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Glycation influencing lubrication: Tribology principles derived from nature to inspire future food colloid design

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Abstract

Glycation, *i.e.*, the covalent reaction between reactive carbonyl groups of sugar with biomolecules such as protein, lipid, or DNA, is integral to many physiological functions, including biolubrication. Although glycation, also commonly termed as "Maillard reaction", has been used extensively to modify flavors and stabilize food colloids, its applications for achieving desired oral lubrication performance of food are in its infancy. This review discusses glycation as a biolubrication tool to provide stimulus to future designing of food colloids. Specifically, we examine how glycation drives biolubrication of soft tissues with examples of lubricin and mucin as "brush-like", nature-engineered, high performance, aqueous lubricants. Recent advances in Maillard conjugation to modify tribology, rheology, adsorption, or surface hydrophobicity of dietary proteins are covered. Lastly, we transfer molecular rules from polymer physics to food colloid science to inspire repurposing glycation of dietary proteins to rationally design the next-generation of lubricious alternative protein-based foods that are often delubricating.

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Introduction

Glycation is a natural process that occurs when a reactive carbonyl group of a monomeric or a polymeric carbohydrate molecule (*e.g.*, glucose, starch, non-starch polysaccharides) reacts with a biomolecule such as a protein, lipid, or DNA to form a new Amadori compounds *via* covalent interaction. When an enzyme is used for such glycation reaction, this is termed as glycosylation, although "glycation" and "glycosylation" are often used in literature synonymously. A series of glycation reactions between amino acids and reducing sugars occurring during food processing was pioneered by Louis Camille Maillard in 1912 [1], which is termed as Maillard reaction. Later, in the 1970s, it was recognized that similar reactions also occur in the body, leading to the formation of advanced glycation end products [2]. Glycation has been associated *in vivo* with various pathologies including diabetes, cataract [3], renal diseases and cardiac failure [4,5], neurogenerative diseases [6], and so on and thus essential to understanding of many life processes. On the other hand, glycation has been exploited in the last two decades for numerous technological applications including wound healing, maintaining protein stability, preserving tissue structure, and infection prevention [7–9]. Complex glycation reactions have now found increasing applications for designing pharmaceuticals [10–12] and controlled delivery vehicles for nutraceuticals [13–15], and so on.

Interestingly, glycation of proteins has been evidenced in nature as a key tool to provide biolubrication of various soft-to-hard tissue-tissue and tissue-implant interfaces. Lubrication is essential for proper functioning of biological surfaces such as the oral cavity, eyes, and joints among many others. The principal lubricating components present on all these biological surfaces are essentially glycoproteins playing a crucial role in protecting biological surfaces by reducing friction [16,17]. For example, glycation of proteins has been reported to contribute to the creation of a durable, lubricious tear film that protects the ocular surfaces from damage [18]. Studies on synthetic lubricants have demonstrated that such covalent conjugation often act by modulating the viscosity of lubricants [19–21]. Besides liquids and gels, glycation has been also shown to enhance the lubricating properties of oral dosage forms such as tablets and capsules by reducing wall friction between the powder and the surface of equipment such

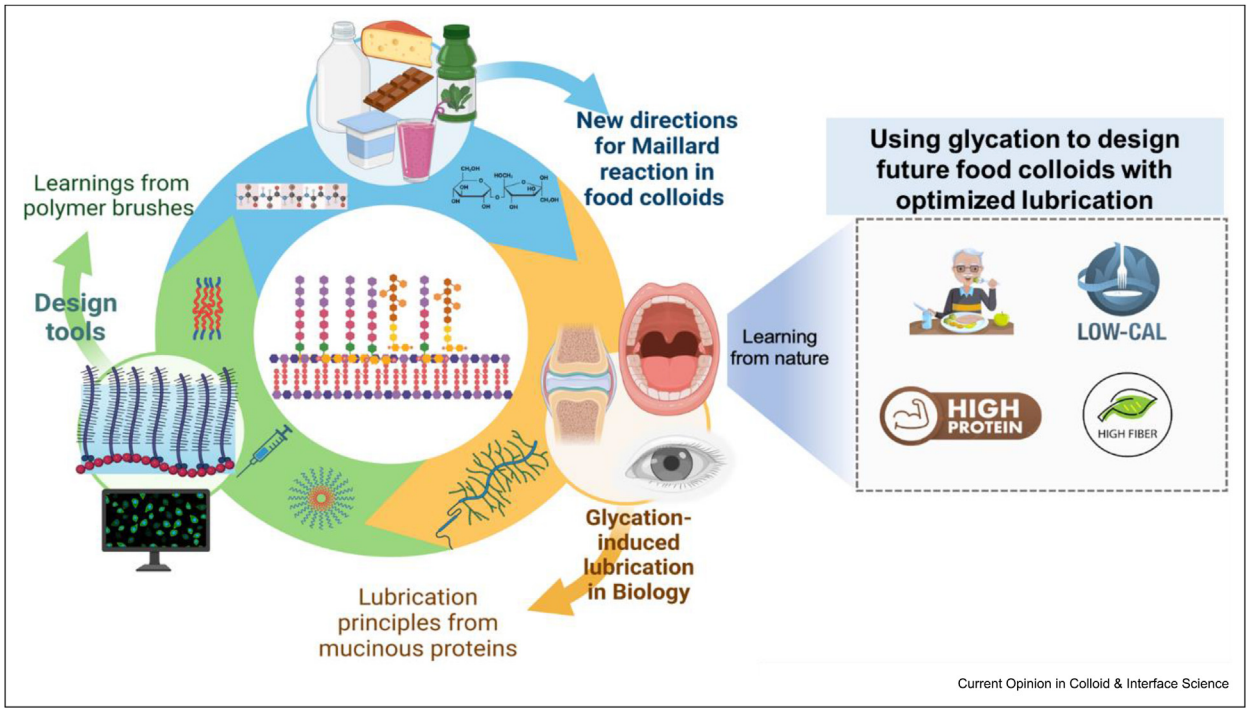
as blender as well as particle-particle adhesive forces, considerably improving the lubricating performance [22–24]. However, such tribological realms of Maillard reaction have been rarely studied in the food community until recently [25–29].

In foods, glycation reactions under controlled reaction conditions have been reported to improve the stability of protein-stabilized emulsions when subjected to various environmental conditions [30–34]. Glycation offers steric sterilization to the dietary protein-stabilized emulsions [33,35] against coalescence and flocculation, and in turn impact the rheological characteristics of foods, such as viscosity, elasticity, and flow behavior. Besides rheology, the glycation of proteins has recently been shown to impact tribological properties in food proteins [26,29,36,37]. The surface charge and hydrophobicity of proteins are modified through glycation, thus affecting their interactions with surfaces [38]. To sum it up, a thorough understanding of tribology of glycated systems omnipresent in nature may inspire future food design with lower calories or higher proteins without compromising mouthfeel and optimized lubricity, as well as enable tailoring food catering to specific oral processing needs [39] (Figure 1).

Herein, we present our current understanding of glycation and/or glycosylation in biological systems in lubrication context, and how this can be translated to food colloid science. The role of glycation for food applications such as those for modifying flavour/color, antioxidants, and emulsion-stabilizing properties are considered to be beyond the scope as they been reviewed elsewhere [40,41]. In addition, the details of oral tribology covering fundamental principles and applications can be read in previous reviews [42–45]. We focus here on how glycation in saliva, tear and synovial fluids containing mucinous glycoproteins such as mucins and lubricins contribute to the so-called *hydration lubrication* in nature. We discuss specific design rules of brush polymers used in polymer science to achieve ultra-low friction that can be used in context of glycation in food colloid science to modulate food lubricity. We then examine the very few food tribological studies on glycation of dietary proteins that have surfaced in the last half decade. We also examine recent advances in glycation in food colloid studies that have been used to reduce surface hydrophobicity of plant proteins, which can potentially improve their hydration lubrication performance.

We envisage deriving insights from nature will act as a true springboard for creating the next generation of foods (Figure 1), where oral friction is an issue such as those in alternative proteins [46–48] and we finally highlight the technological and mouthfeel challenges

Figure 1



Schematic illustration of overview of this review. This covers learning "glycation-induced lubrication" from nature and design rules that have been applied in polymer physics to induce brush-led lubrication. Such knowledge will inspire the design of next-generation food colloids with just-right lubrication performance such as low-calorie, high-protein, high-fiber diets as well as food for vulnerable population.

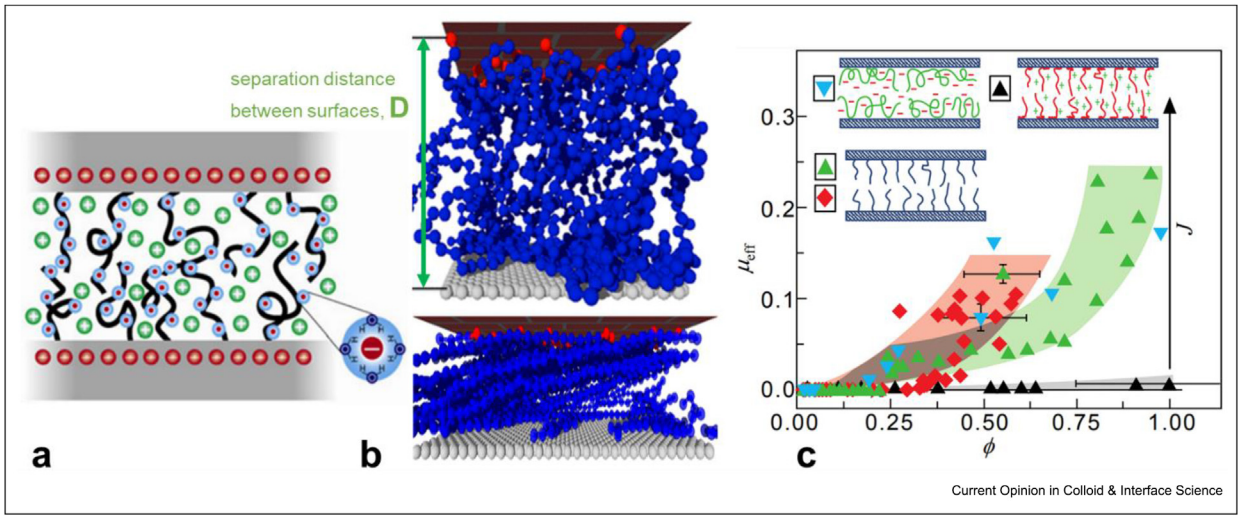
that need to be overcome. Ultimately, this review offers a new *lubrication dimension* for food colloid scientists to explore and repurpose the *age-old tool* of Maillard reaction.

Tribology of glycated and/or glycosylated systems in biology

The biological fluids such as synovial fluid, tear, and saliva act as effective nature-engineered aqueous lubricants. They are integral in reducing friction between the interacting tissues and protect them against wear and tear. Often, these lubricants in nature achieve ultra-low friction coefficient (μ) (*i.e.* the force to slide the surfaces past each other divided by the normal force compressing the counter surfaces) in the range from 0.01 towards the vanishing magnitudes of <0.001, known as superlubricity [49]. Such biolubrication is linked mechanistically to glycosylated proteins such as mucins, lubricins containing counter-ions. In fact the brush-like architecture of the glycans, *i.e.* the carbohydrate moieties attached to the polypeptide backbone in these glycated mucinous proteins is considered as the key structural basis underpinning such biolubrication under reasonably high physiological pressures of 10 MPa or more [50]. Hence, it is crucial to give a brief overview of brush-to-hydration lubrication principle in this review in the context of biology, though excellent reviews by Klein [50–53] are necessary reads in this regard.

Hydration lubrication principle is schematically shown in Figure 2a with evidence gathered from computational simulation (Figure 2b) and experimental studies (Figure 2c). Briefly, when brushes (*i.e.* glycans in case of biology) are rubbed under low to moderate compressions in between tribo-contact surfaces, the glycans may have limited glycan-glycan entanglement. This is due to excluded volume effects arising from soft (long-range) "steric-entropic type" repulsion, and thus, glycans can easily slide past each other supporting large contact pressures [54,55] with minimal viscous and frictional dissipation generating low μ values. Under these moderate compressive forces, the thickness (d) of the overlapped region of the glycans, *i.e.* $d \sim D^{-1/3}$, where D is the separation distance between the tribo-contact surfaces [52] (Figure 2b). In this case, the brushes do not interpenetrate [55] and the water molecules can move relatively freely with a low viscous fluid-like character under tribo-shear. In addition, the trapped mobile counter-ions (Figure 2a) within the hydrated shells can elevate the osmotic pressure of the

Figure 2



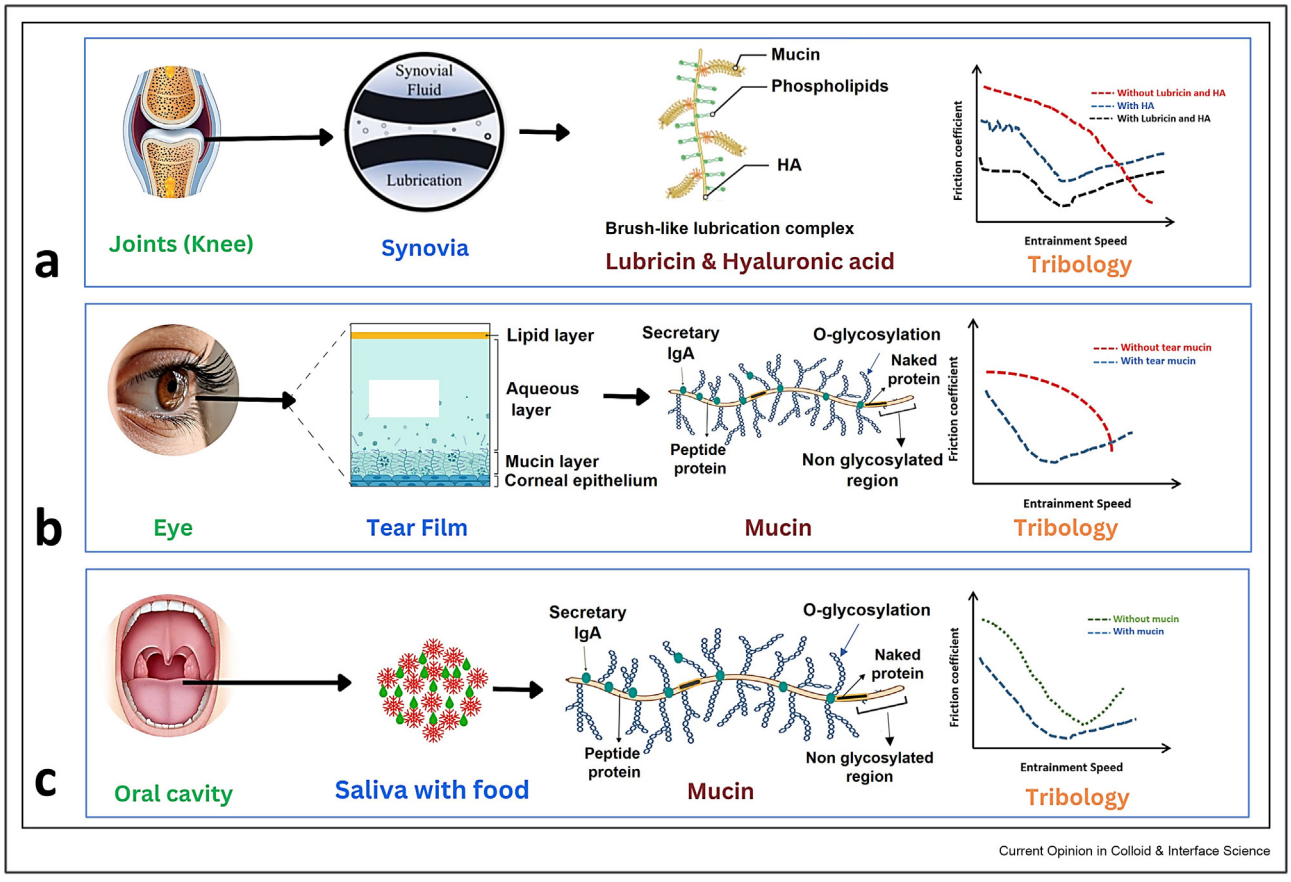
Lubrication principle in brush-like polymers evidenced *via* simulation and experimental approaches. a. Schematic illustration of polymer brushes [53] where there is little interpenetration between brushes. Under higher compressions, the hydration shells on the monomers act *via* the hydration lubrication mechanism with the counter-ions (green circles) in the hydrated shell increasing the osmotic pressure of the polymer supporting the load. **b.** Molecular-dynamic simulation-based snapshots [56] of dextran polymer-brush systems (M = 20 chains with 50 beads per chain, with grafting density ρ = 0.075 LJ units) against-wall surface (**top**). Red beads are tethered, blue beads are non-tethered, gray beads are wall particles, and flat walls are flat (indicated as "brick walls") and their tribo-shearing at relative wall speed of 0.01 (LJ) units) (**down**). The brush consists of M = 20 chains with N = 50, and the separation is D = 8 (4 nm). **c.** Experimental data [54] on effective friction coefficient (μ_{eff}) with volume fraction φ of compressed polymer for different lubricants when sheared in the range of 250–500 nm s^{-1}. Red (and associated scatter), green (and associated scatter) and blue symbols are for neutral, charged and cationic polymer brushes, respectively as visualized with corresponding cartoons showing the counter ions. The black symbols and corresponding gray band are from synthetic polyelectrolyte brushes created using diblock copolymer poly (methyl methacrylate)-block-poly(sodium sulphonated glycidyl methacrylate) copolymer (PMMA-b-PSGMA brushes). At the jump point *J*, the polymer is ploughed away from the contact surfaces and the friction increases suddenly. Figures are reproduced in **a** [53] under the terms of the Creative Commons Attribution 2.0 International Licence and produced in **b** and **c** with permission from ACS [56] and Springer [54], respectively.

polymer chains to support the load. Using non-equilibrium molecular dynamic simulations (Figure 2b), Singh et al. demonstrated [56] repulsive forces between dextran chains and the counter surface resulting in a separation like that seen in hydrodynamic regime, irrespective of speeds. In other words, essentially there is no boundary-like regime [56] even at lower speeds due to brush-induced lubrication, *i.e.* entropic prevention of interdigitation of the polymer brushes.

At higher compressions on the other hand, upon eventual overlap of these hydrated glycans, with larger $D \sim R_g$, *i.e.* the radius of gyration of the polymer, the entropic factors would matter little, and the water shells tethered to the glycans may act now *via* the hydration lubrication mechanism (Figure 2a). Experimental work by Raviv et al. [54] (Figure 2c) revealed that charged or neutral polymers with/without being anchored to a substrate offer very low effective friction coefficients (μ_{eff}) at low volume fractions $\varphi \lesssim 0.3$, where aforementioned brush-induced entropic factors prevail. However, the fluidity of the hydration shells by the counter-ions is the governing factor to achieve larger frictional dissipation particularly at higher volume fractions.

With this background of lubrication principles in mind, we now cover the two key mucinous glycoproteins in biology, *i.e.*, lubricin secreted in the synovial joint and mucins in tear and saliva. The details of structure of these glycoproteins are available in previous literature [57]. Here, we examine how specifically glycation plays a key role in influencing tissue-lubricity *via* hydration lubrication (Figure 3). In other words, we raise question on whether absence of glycation is detrimental to biolubrication.

Figure 3



Schematic illustrations of key glycosylated structures in biology acting as high-performance nature-engineered lubricants. Examples are shown from **a.** joint, **b.** ocular and **c.** oral lubrication where glycosylated structures such as lubricin and mucin are omnipresent in biological tissues interfaces to provide lubrication. In case of synovial fluid in joints, a highly glycosylated glycoprotein, lubricin in **a** comprising of 30–50 % β(1–3)Gal-GalNAc [58] offers the desired low friction coefficients in synergy with hyaluronic acid [59,60] in cartilages. High molecular weight, highly negatively charged, glycosylated mucins (0.5–40 MDa) in **b.** tear films and **c.** saliva in the case of ocular [61] and oral [28,62,63] surfaces, respectively, reduce friction *via* brush-like hydration and viscous lubrication mechanisms.

Learnings from lubricin

Synovial fluid, a dense extracellular matrix fluid, surrounds the human diarthrodial joints and is mainly composed of chondrocyte-secreted glycoproteins, *i.e.* lubricin of ∼250 kDa monomeric molecular weight encoded by the gene proteoglycan; a linear negatively charged polysaccharide, hyaluronic acid, and phospholipids [64,65]. Lubricin comprises of nearly equal mass proportion of polypeptide and oligosaccharide chain with a central mucin-like region, one chondroitin sulphate/heparin -rich domain and one hemopexin-like domain in the *C*-terminal and two somatomedin B homology domains in the *N*-terminal [66]. The cartilages slide over each other during movement and the μ ranges from 0.0005 to 0.04 in cartilages in presence of the synovial fluid [67]. Studies into the lubrication of synovial joints (joints that contain synovial fluid) have been conducted for more than three centuries, beginning with the first written reference to the subject in 1743 [68], and a number of theories regarding the lubrication mechanism in the joints have been proposed since then. Although there is an increasing body of literature providing transcending mechanisms behind how synovial fluid lubricate cartilages, it is now well-documented experimentally that hyaluronic acid on its own offers negligible boundary lubrication benefits [69]. On the other hand, several research have identified the important role of lubricin, a highly O-linked glycoprotein being responsible in providing the brush-like lubrication (Figure 3a) in joints.

Using a combination of *in vitro* and *ex vivo* work using rodents and bovine models, lubricin was shown to self-assemble and reduce adhesion between contacting surfaces and reduce friction [70,71]. Using surface force apparatus, purified human lubricin has been experimentally shown to reduce friction by an order of magnitude ($\mu = 0.02-0.04$) in negatively charged surfaces compared to that of hydrophobic surfaces [55]. Although lubricin is often considered as a protagonist in the ultra-low lubrication in synovial fluids [72], synergy with hyaluronic acid reducing the friction further *via* altering the viscosity and benefiting elastoviscous transition in Stribeck curves cannot be ignored (Figure 3a) [60]. Nevertheless, within the glycoprotein itself, the extensive glycosylation of lubricin creating water-reservoir to support loading and shear stress has been considered as the key structural factor behind hydration lubrication. Glycosylation seems essential for creating an amphoteric nature of lubricin. In particular, *N*-acetyl-galactosamine saccharides covalently linked to the polypeptide through the oxygen molecules of serine and threonine side chains in the central serine/threonine/proline (STP)-rich domain offer a negative charge and positively charged lysine and arginine residues in the *N* and *C* termini [73]. Such amphoteric property may facilitate its efficient biolubrication function. Biolubrication mechanism was further evidenced by loss of lubricity of lubricin by almost 80 % on enzymatic hydrolysis of purified human and bovine lubricin by recombinant glycosidases, causing removal of 54 % or less of O-linked $\beta(1-3)$Gal-GalNAc chain [58], highlighting the importance of glycosylation.

Learnings from mucins

Mucins like lubricins are glycosylated bottle-brush-structured proteins of high molecular weight of around 641 kDa for mucin monomers are found in the saliva, tear films (Figures 3b and 3c) among many other internal linings of the body, bearing hydrophilic hydroxyl, carboxyl, sulfate, and amino groups, and forms lubricating gels [74]. The ocular surface is also constantly lubricated by a thin film of tears, which is composed of a mixture of mucins, lipids, and electrolytes. In fact mucins coating the hydrophobic corneal epithelium are considered as lubricants of the corneal and conjunctival epithelial surfaces layers of the eye facing the eyelid during the eyelid blink whilst the lipid molecules form a protective barrier on the ocular surface and reduce evaporation of tears [75,76] (Figure 3b). Both membrane-bound mucins MUC1, -4 and -16, and the gel-forming mucin MUC5AC have been associated with lubrication function at ocular surfaces [77]. Similarly, both gel-forming and surface active mucins, *i.e.* MUC5B and MUC7AC, respectively, have been known to be present in human saliva [78].

Although a pure dispersion of heavily glycosylated mucin cannot replicate the complex tribological behavior of real saliva due to the combination of other factors such as ions, small molecules, low molecular weight macromolecules driving the lubricity [62,79,80], mucin is still considered a leading structural contributor to the obtained lubrication in human saliva [81] (Figure 3c). Both saliva and tear-film are shear-thinning liquids [61,82] and their lubrication principles *via* mucin combine both brush-like hydration [51] and speed-dependent "viscous lubrication" [80,83] mechanisms.

It may be thus intriguing to ask what happens to the lubrication behavior of mucins when the glycosylation is artificially removed? Similar to that in lubricin [58], it has been demonstrated recently that the β-elimination of glycans from the mucin results in a 3.5-fold decrease in hydration and an increase in friction coefficients by two orders of magnitude with $\mu \sim 1$ [84]. In fact, deglycosylation of MUC5B and MUC7 has also been reported to be a leading cause of dry mouth associated pathology and lubrication failure situation [85,86]. The mechanism of lubrication failure on deglcosylation can be explained by 1) loss of hydration lubrication at the molecular scale, 2) bridging effects [87] between deglycosylated mucins bringing the contact surfaces in close vicinity and increasing the frictional dissipation.

However, such deglycosylation was restored when a bioconjugate of lectin type protein such as wheat germ agglutinin + polyethylene glycol (PEG, 40 kDa) was physisorbed on the deglycosylated mucins [84].

Besides enzymatic approach of deglycosylation, an interesting study in personal care applications showed how mechanical shear *via* different kinds of tooth-brushing devices leads to deglycosylation of the mucins associated with the salivary condition film and consequently resulted in increased μ [88]. In particular, authors showed that manual and sonic brushing resulted in lesser degree of deglycosylation as compared to powered rotary oscillatory device. The powered rotary oscillatory device resulted in an order of magnitude higher surface roughness of the salivary conditioning films (5.37 nm) and μ was $\sim$0.63 as compared to the manual and sonic brushing. Computing the glycosylated oxygen ($\%O_{glyco}$) using experimental surface elemental analysis of the salivary film, authors [88] correlated such increase in friction to the degree of deglycoslyation in mucins when subjected to the powered rotary oscillatory device-based brushing.

Due to increasing incidences of osteoarthritis, dry eyes, dry mouth and associated lubrication failure situation is soft tissues, there has been growing interests to design analogs for these mucinous glycoproteins in nature. Often polymeric brushes such as polyethylene glycol (PEG) chains of various chain lengths are used to provide high load-bearing, superlubricity, and wear resistance capability [89]. Having discussed that glycation is imperative to provide the much needed biolubrication, a question lies whether glycation of peptide chains with sugars of various chain lengths by chemical routes or Maillard reaction can offer lubrication functionality similar to those of lubricins and mucins. A very elegant work [90] in this regard is the recent fabrication of lubricin mimetic using chondroitin sulfate conjugated to collagen type II-binding peptide or hyaluronic acid-binding peptide [90] via EDC (1-ethyl-3-[3-dimethylaminopropyl] carbodiimide hydrochloride) conjugation chemistry. Particularly, the bioconjugates with collagen Type II peptides were effective in reducing kinetic friction in bovine cartilage-glass contacts similar to that in presence of synovial fluids highlighting the effectiveness of nature-inspired glycation chemistry offering tribological benefits. Overall, this section highlights the importance of glycation in biolubrication in soft tissues and now we move forward with our current understanding on using glycation to improve tribological performance of food colloids.

Tribology of glycated systems in food colloids

Although glycation has been used a tool in food colloids for decades to improve emulsion stabilization in various environments by virtue of creating steric stabilization [91–94], its crucial role in manipulating lubrication performance remain unnoticed until very recently. In fact, Sarkar et al. were the first to pinpoint Maillard reaction as a potent tool to modify hydration lubrication of proteins in a review in 2019 [28]. Since then, there has been three key studies where glycation has been used either directly or indirectly to modify lubrication performance in food colloidal systems (Table 1).

The first study in this direction was using fish gelatin glycated by gum Arabic for stabilizing emulsions [26]. Although the Maillard reaction with gum Arabic did reduce the viscosity of the emulsions (Table 1) and did not influence μ considerably versus the non-glycated fish gelatin-stabilized emulsion system, the glycated systems did demonstrate a stable lubricity irrespective of entrainment speeds across storage time over two weeks unlike the non-glycated systems (Figure 4a). We propose such non-significant effect of glycation on μ might be attributed to the use of gum Arabic, which is a rather anomalous low viscosity polymer [95] and thus does not provide the sufficiently large high-shear-rate limiting viscosity to enable lowering of μ in the fluid film regimes [27]. Although the exact degree of glycation and the influence of glycation of the fish gelatin itself versus when present in the emulsified system were not reported, this is an interesting study showing tribology results in glycated food colloids for the first time.

In the second study, work in our laboratory [29] demonstrated a direct evidence of Maillard conjugation on tribology using whey protein and dextran as the protein and polysaccharide, respectively. Here, it was shown that conjugation reduced the μ in mixed regime versus single/mixed biopolymer systems despite their almost identical second plateau viscosity (*i.e.*, viscosity at 2000 s^{-1}, η_{2000}). The system was further microgelled and this showed an unprecedented *superlubricity* with boundary $\mu \sim 0.002$ at speed of 0.001 m s^{-1} in a rolling-sliding contact (Figure 4b). We hypothesized such superlubricity due to the dextran chains sticking out of the microgels facilitating a 'brush-like' lubrication similar to those explained before (Figure 2b). However, such benefits were not replicated in a tongue-mimicking system 3D tongue-mimicking setup [96] operating under pure sliding. It might be intriguing to ask whether such superlubricity would be retained in the non-microgelled conjugated system was lying flat and tethered on a planar surface (rather than being microgelled) similar to most polymer brushes, which require future attention.

Inspired by these findings, our laboratory carried out the first work [37] on improving tribological properties of alternative proteins by Maillard reaction with pectin using potato protein as the model plant protein (Table 1) with degree of conjugation of 20 % and 33 %.

Table 1

List of Maillard reaction studies that have surfaced in the last five years in food colloids with evidenced modification of rheology, tribology, or surface hydrophobicity of animal- and plant-derived proteins via glycation with simple sugars or polysaccharides [26,29,37,105–119].

Protein	Monosaccharides	Polysaccharides	Viscosity (η, mPa.s)	Friction coefficient (μ)	Surface hydrophobicity (H_o)	References
Casein		Pectin (citrus), arabinogalactan	NE	NE	↓ H_o	[106]
		κ-carrageenan	↓ η	NE	NE	[107]
Egg white protein	Glucose	Maltodextrin, Dextran	↑ η	NE	NE	[108]
Fish gelatin		Gum Arabic	↓ η	= μ	NE	[26]
Whey protein		Dextran	= η	↓ μ	↓ H_o	[29, 109, 110]
	D-Tagatose		NE	NE	↓ H_o	[29, 109]
		Gum acacia	NE	NE	↓ H_o	[111]
Peanut protein isolate	Xylose				↑ H_o	[112]
	Glucose		NE	NE	↑ H_o	[113]
		Pea starch (maltodextrin, 14.6 dextrose equivalent)	NE	NE	↓ H_o	[114]
Pea protein isolate	D-Arabinose		NE	NE	↓ H_o	[115]
		Guar gum	NE	NE	↑ H_o	[105]
Potato protein		Pectin	↑ η	↓ μ	NE	[37]
Soy protein isolate		Dextran	NE	NE	↑ H_o	[116]
		Gellan gum	↑ η	NE	↑ H_o	[117]
		Pectin (citrus, apple)	NE	NE	↓ H_o	[118, 119]

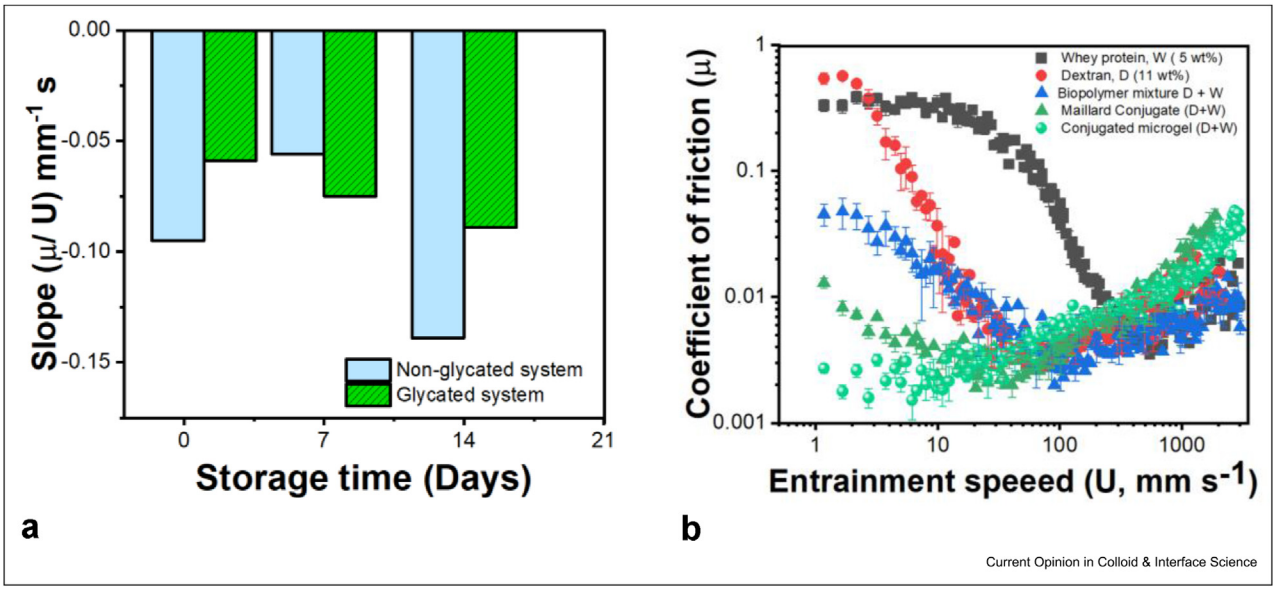
*NE: Not examined
= similar, no significant change; ↓ significantly lower, ↑ significantly higher in conjugated systems than that of the biopolymer mixture/ controls.
Shaded regions in light green indicate this is examined.

Potato protein despite having significantly high solubility as compared to many, if not most, plant proteins demonstrates high friction in both macro [46,97] and nanoscale contacts [98]. Potato protein–pectin glycoconjugates particularly at higher degree of conjugation (33 %) demonstrated higher boundary and mixed lubrication performance than the potato protein when a viscosity-scaled entrainment speed parameter was employed. However, distinct advantage over unconjugated mixtures with pectin on lubrication performance was not obvious from this study. This raises the questions about how free pectin in these systems contributed to the tribological behavior as opposed to the ones conjugated to potato protein, which needs further attention in literature. Also, the degree of conjugation tested was in a narrow window [37] and a detailed work on degree of conjugation, pH, and temperature of conjugation will be a necessary undertaking.

Future prospects for glycation in food colloids: deriving design rules from polymer science

There is now increasing interests to use dietary proteins to replace calorie-dense fat and design low calorie foods [99] and also for formulating foods with high protein for vulnerable population to address malnutrition issues [39] (Figure 1). However, often formulation with proteins leads to delubrication and increased oral friction [42,100] and recent studies have shown that such oral friction issues tend to worsen in case of formulations with alternative proteins [46–48], which are inherently aggregated, have limited solubility and also have high surface hydrophobicity. Maillard reaction with sugars can be thus a new strategy in this direction to improve hydration of proteins [101], particularly for alternative proteins which suffer from high surface hydrophobicity and consequently impaired lubricity. Recent studies on

Figure 4



Examples where Maillard reaction has been used in food colloid design to influence lubrication performance. a. Bar graph replotted from the data shown in paper [26] showing storage time has no effect in Maillard conjugated fish gelatin + gum Arabic-stabilized emulsion (green stripped bar) versus non-glycated fish-gelatin-stabilized emulsion (light blue non-stripped blue bar). The slope represents the onset of the mixed regime in the friction curve obtained using a rheo-tribo setup with rough solid substrate (3 M Transpore Surgical Tape 1527-2)-based tribopairs. **b** Friction curves replotted from the data shown in paper [29] showing Maillard conjugate of whey protein (5 wt%) + dextran (11 wt%) (green triangle) show lower friction than whey protein (5 wt%) (black square), dextran (11 wt%) (red circle), their mixtures (blue triangle) whilst when the conjugate was microgelled (green circle), it showed superlubricity. These friction curves are obtained using a ball-on-disc set up with hydrophobic polydimethylsiloxane (PDMS-PDMS) smooth tribopairs.

plant proteins demonstrate that Maillard reaction can help to reduce surface hydrophobicity of sparingly soluble legume proteins, such as soy protein and pea protein [102–104], when conjugated with mono- or polysaccharides under certain conditions (Table 1). However, often surface hydrophobicity may increase depending upon the processing conditions such as incorporation of severe heat treatment during Maillard reaction, which may denature and unfold the protein, and increase surface hydrophobicity as seen in case of pea protein + guar gum conjugates [105] (Table 1).

Shaded regions in light green indicate this is examined

We hypothesize that reduced surface hydrophobicity may be an indirect measure of improved lubricity, simply by exploiting hydration lubrication. Nevertheless, such conjecture should be investigated in future with well-design experiments. Unlike polymer brushes, foods are not tethered to oral surfaces. Hence to create desired lubrication behavior, one needs (1) sufficient degree of surface hydrophobicity in the food proteins to bind to weakly polar oral surfaces [120] when saliva is limiting and (2) enough polysaccharide chains bound to these protein backbone to provide brush-like lubrication performance. Now, we discuss few of the design rules learning from nature that might be useful when fabricating the next Maillard reaction in the lab with improving lubricity as an anticipated benefit. We also highlight challenges in implementing such designs keeping in mind the food science boundaries.

Chain length of protein backbone and polysaccharides as brushes

First, it is important to ask what should be the chain length of the proteins and the polysaccharides for Maillard conjugation? The works by Spencer's group on poly(L-lysine, PLL) [121], where 375 kDa PLL backbone demonstrated better lubricity compared to a 20 kDa one (with other conditions remaining constant) simply by virtue of adsorption strength. Getting inspiration from this work, it appears that a protein backbone might be more beneficial to get higher adsorption strength and desired lubricity rather a smaller peptide for conjugation in food colloids. Also, hydrolysis of proteins might result in bitter-tasting hydrophobic peptides which might not be acceptable for food applications [122], even if such bitterness is masked to a certain extent by glycation.

Second, does chain length of the polysaccharide matter in lubricity? Since data from food community is restricted to two different macromolecules, *i.e.* pectin [37] and dextran [29] without focusing on chain length;

it is difficult to derive at definitive conclusions. However, using the same PLL backbone example, but now changing the chain length of the grafted brushes using PEG chains from 2 to 5 kDa [123], it was demonstrated that the higher molecular weight PEG chains offered thicker lubricant film with reduced μ over the entire range of entrainment speed than the low molecular weight counterpart. Such improved lubricity with increased chain lengths was further evidenced recently using biopolymers such as hyaluronic acid with different molecular weight (35 kDa, 240 kDa, 1.8 MDa) [124]. In the gelatin (gel)-covered mica surfaces, coating with high-molecular weight hyaluronic acid maintained a low μ of <0.001, with no increase in μ even when the maximum pressure >100 atm was applied. This was attributed to the high molecular weight hyaluronic acid strongly adsorbing to the surface with energies of orders of magnitude higher k_BTs (k_B being the Bolzmann constant and T is the temperature) as compared to few k_BTs in the medium and low molecular weight counter parts. Hence, one might approach using long chain polysaccharides such as pectin, xanthan, gellan gum, and so on when glycating to proteins to offer viscous lubrication benefits unlike using monomers, such as glucose, xylose. Also, such monomers do not seem to improve surface hydrophobicity of proteins (Table 1).

Degree of conjugation deriving principles from grafting density

Having understood the importance of chain lengths, it is important to think about the degree of conjugation on lubrication. The closest proxy for degree of conjugation from polymer physics would be grafting density (σ_g) where $\sigma_g = (\rho\ h\ NA)/M_n$) where ρ is the bulk density of the polymer brush, h is the thickness of the brush, NA is Avogadro's number, and M_n is the number-average molecular weight) [125]. Here $\rho = \Gamma/h$, where Γ is the surface coverage of the polymer brush chains. Therefore, σ_g can also be represented as $\sigma_g = (\Gamma\ NA)/M_n$.

Thinking structurally about σ_g, the brushes in case of end-grafted polymers range from so-called "pancake" and "mushroom"-type structure at low σ_g, followed by a transition state with to a typical, highly stretched out "brush" regime at high σ_g, largely driven by steric, entropic, and osmotic factors [126]. A recent simulation work investigated the effect of σ_g on lubrication, where σ_g of model polymer was changed from $\sigma_g = 0.015$ to 0.15 where critical transition σ_g was 0.025 [127]. Increasing σ_g resulted in decreased μ values particularly in the transition state from mushroom-like regime ($\sigma_g = 0.015$) into the brush regime ($\sigma_g = 0.075$) due to entropic factors. However, the effect of σ_g mattered little once it had reached the brush regime. This is also seen in experimental works with dextran [128], where increasing σ_g of dextran chains reduced μ until a critical point governed by increased quantity of water associated with brush layer and consequently increased film hydration supporting the load.

Noteworthy, for food colloids, such grafting is done by Maillard reaction, which is not as controllable as those reported in synthetic polymerization. In particular, higher degree of conjugation might require prolonged heat treatment, which may result in adverse effects of denaturation of the proteins and reduction in hydration. Also, higher molecular weight polysaccharides with high viscosities might offer lower molecular motion and reduced ease of reaction with carbonyl groups of protein during Maillard reaction and thus reduced degree of conjugation. For instance, recent study on conjugation of soy protein with low acyl gellan gum [117] (Table 1) shows that surface hydrophobicity increased and solubility decreased in conjugate with 42 % degree of conjugate versus 25 % largely associated with processing-induced denaturation of proteins. This is not surprising as higher gellan gum concentration increased the system's viscosity and, therefore, reduced degree of interaction with soy protein molecules during glycation and subsequently resulted in lower degree of conjugation. However, due to the higher concentration of gellan (despite lower degree of conjugation), these systems had sufficiently high viscosity and lower surface hydrophobicity. On the other hand, higher degree of conjugation (33 %) with pectin in fact improved lubricity in case of potato protein [37]. This suggests that an intelligent interplay of polysaccharide concentration and degree of conjugation is needed to achieve desired viscosity effects, hydration, and lubricity.

Molecular structure and charge density

Often the properties of glycans such as stiffness and charge density can have significant impacts on hydration lubrication, largely driven by surface separation as well as Coulombic interactions. An elegant non-equilibrium molecular dynamic simulation study [127] with various chain stiffness revealed that μ decreased with increasing persistence length. In other words, brushes having stiffer chains aligned themselves along the shear direction easily, so the friction decreased rather than increasing. Although such studies have not been experimentally replicated in a glycated structure in food colloids, a recent work on polysaccharides [129] also show that rigid rod-like polysaccharides such as xanthan gum show higher lubricating capacity than flexible polysaccharide (guar gum) when compared at similar molecular weight levels.

Charge density is also a contributing factor when thinking about conjugation for lubrication benefits. Comparing frictional dissipation of grafted layers of charged and neutral bottle-brush macromolecules using molecular dynamics simulations [130], it was revealed that charged brushes offer an order of magnitude lower μ

than the corresponding neutral macromolecule, purely by exploiting the dominant role of counter-ions in the lubrication process [54]. A recent study using *in vitro* and *in vivo* approaches [131] demonstrated that grating chitosan with zwitterionic phosphorylcholine headgroups containing both negative (PO_4^-) and positive ($N^+(CH_3)_3$) charged groups can be also beneficial. Although having overall neutral charge, addition of side chains with high charge densities can combine large amount of water molecules to form high level of hydration sheaths providing ultralow friction (Figure 2a). Again the studies on glycated food proteins with varying charge densities measuring tribological performance remain to be studied but tribological studies on pure polysaccharides [129,132], as well as one study on conjugates [37] show that anionic polysaccharides with high charge densities such as pectin might have a beneficial effect on lubrication.

Processing conditions

As one might expect, processing factors such as pH, time, and temperature of glycation are crucial to achieve the desired lubrication effects. Too much heat, prolonged heating or extreme pH and ionic conditions can result in denaturation of the protein which might reduce hydration [98,133] and subsequently impair lubricity. Recent studies reveal that ultrasound can be used as an interesting tool to improve degree of conjugation with increasing/decreasing effects on surface hydrophobicity depending upon the ultrasound power and type of sugars used [111,115] (Table 1). However, how such novel processing treatment affects viscosity, hydration and lubricity remains to be studied.

To sum it up, one can reasonably hypothesize that glycating proteins with extensive chain length of stiff polysaccharides with sufficient charge density should allow optimizing hydration lubrication. Such tool will also allow enhanced viscosity giving potential "sensory thickness" and such viscosity if existing at high shear rates further translates to lubricious behavior giving rise to fluid film lubrication.

Conclusions

This review delves into the ways in which glycation approaches have been used in nature-engineered aqueous lubricants such as saliva, tear, and synovial fluids to prevent lubrication failure in soft tissues to fabricate nature-inspired food design. We explained the importance of hydration lubrication highlighting the steric-entropic factors associated with brush-like polymers as well as hydration lubrication mechanism of counter-ions within the hydration shell showcasing classic examples of mucinous proteins in biology. We paint the versatility of simulation and experimental work done in end grafted brush-induced lubrication in polymers alongside few recent studies in food-based glycoconjugates. This provides a thinking toolbox showcasing that subtle plug-and-play of chain lengths, degree of conjugation, charge densities, and processing variables may enable designing future food colloids particularly for making Maillard conjugates with desired viscosity and lubrication performance. We anticipate that the molecular rules described in this review when exploited within the known food science boundaries can help to develop sustainable and healthy foods such as alternative protein-rich foods with lesser surface hydrophobicity, optimized lubricity and mouthfeel and also foods for vulnerable population with special oral processing needs.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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