Modification of salivary multilayer for improved oral lubrication

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Abstract

Background

Modification of saliva film effectively enhances lubrication for both dry-mouth patients and healthy individuals. This process focuses on altering the salivary multilayer in mouth by adjusting mucin interactions to alleviate dryness. The structure and properties of mucins, polymers, and physiological factors—such as lubricity, papillae height, and tongue density—are all related to the success of these modifications. In this review, we present three methods with distinct lubrication effects: physical, chemical, and physiological.

Scope and Approach

We discuss three modifications of the salivary multilayer that enhance lubrication at sliding interfaces in the oral cavity: electrostatic attraction, covalent grafting, and laser therapy. This review provides insights into oral lubrication, addressing key questions: what lubrication is, why do we need oral lubrication, and how can we achieve optimal oral lubrication. Advanced techniques for elucidating interfacial adsorption and the applications of surface modifications are also emphasized.

Key Findings and Conclusions

Modulating salivary multilayer is a promising approach to enhance lubrication and create a more comfortable eating experience. This strategy is vital for both food scientists and healthcare professionals, as it helps reduce oral friction and alleviate dry mouth symptoms. The interaction of mucins in salivary film is a key for effective modification. In this review, the effectiveness of chemical grafting outperforms electrostatic attraction on xerostomia, providing more durable lubrication. Low-level laser lightning is another therapy for salivary gland dysfunction. We aim to inspire innovative designs for artificial saliva and biomimetic devices through these modifications at oral bio-interfaces, ultimately improving salivary hypofunction and addressing mechanistic challenges in oral lubrication.

Key words: Oral lubrication, saliva, salivary multilayer, dry mouth, food-saliva interactions

1.Introduction

Lubrication, a dynamic and complex process in oral cavity, occurs simultaneously during food oral processing. It protects human interfaces from tribological contacts and sliding motions, influencing hydration and surface lubricity. Saliva adhered to oral surface normally functions as a typical bio-lubricant and natural emulsifier offering a comfortable sensation inside the mouth (Ma et al., 2022). Specifically, salivary proteins (e.g. proline-rich proteins and different types of mucins) play significant roles in improved lubricity of the entire oral cavity due to their high water-holding

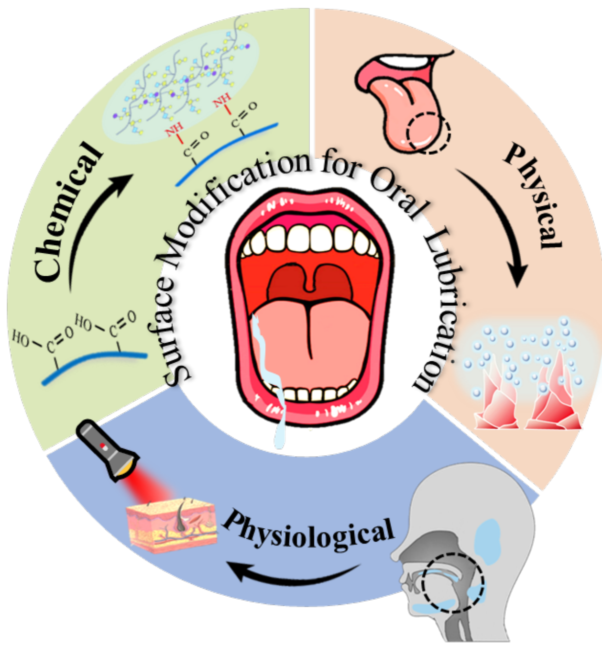

Fig. 1. **Schematic illustration of overview of this review.** This covers three main modifications for optimized oral lubrication: electrostatic attraction, chemical grafting, and laser treatment. Such knowledge will provide newly perspectives for solving problems of lubrication, inspiring the design of lubricants such as artificial saliva, food colloids with good lubricating performance at interfaces in the oral cavity.

properties during routine consumption. Lack of those proteins may impair oral lubrication, and even lead to dry-mouth syndrome (xerostomia) (Łysik et al., 2019), particularly in the elderly (Kim, 2023). Salivary hypofunction may be related to two different conditions or causes: hyposalivation and changes in salivary composition. The former is defined as a symptom of reduced saliva secretion that is an objective measurement closely related to the subjective feeling of dryness (Ericsson, 1959). Changes in both secretion volume and composition will alter the rheological and tribological properties of saliva as well as its lubrication behaviour in the oral cavity.

Bio-tribological mechanism of oral lubrication is critical to explain the changes in lubricity occurring in human oral cavity. The hydration capacity of salivary conditioning films (SCF) is the main factor for oral lubrication (H. Wan, C. Ma, et al., 2020). More specifically, mucins and other proteins presented on SCF are good at forming hydration film with low friction or wear on mucosal tissues such as digestive tract, genitourinary tracts, and oral cavity (McGuckin et al., 2011; Thornton et al., 2008). The backbone of mucin polymer could also be modulated through modifications for biomedical applications with appropriate physical and biochemical properties at interfaces (e.g. hydration and lubrication), which means artificial regulation is necessary for better lubrication behavior inside the mouth (Crouzier et al., 2015; Park et al., 2023).

In past decade, many researchers have elaborated on the importance of modification for improved oral lubrication (Gonzalez-Estanol et al., 2022; Qian et al., 2024; Soltanahmadi et al., 2023). Most of them mainly focused on modifying foods and substrates used in tribological experiments by interacting with mucins, α-amylase, and proline-rich proteins in saliva (Mosca & Chen, 2017; Sanni et al., 2022). For example, the modification in structure and properties of foods with high lubricity for the elderly (Qin et al., 2024); the design of artificial saliva (Hu et al., 2021; Jeroen Vinke et al., 2020) and stimulants for patients with xerostomia (Melo et al., 2023; Reyad et al., 2020; Riley et al., 2017). However, while there is no doubt that bulk properties of food materials have an important influence on oral lubrication, the effects of multilayered saliva film should never be underestimated. Furthermore, neither stimulants nor commercial saliva offer long-term relief and have ideal boundary lubrication compared to real human saliva with specific characteristics (slippery but not slimy, runny but not watery) (Katsnelson, 2023). Thus, it's urgent to clarify the mechanisms of excellent lubrication behavior at the microscopic level in the oral cavity and provide novelty thinking of designing foods with ideal interfacial lubrication.

Very recently, we proposed a multilayer salivary model, based on Yakubov's description of the salivary film (Mu & Chen, 2023; Yakubov, 2014). The model successfully addresses functional as well as compositional variations within a saliva film. Many studies have further confirmed that changes in the multilayer structure of SCF could potentially change the lubrication performance (Agorastos et al., 2022; Araiza-Calahorra et al., 2024; Lesme et al., 2024; Zhang et al., 2024). For instance, the lubricating behavior at sliding surfaces varies with changes in the mucins present on adsorbed saliva films (e.g. structure and extent of glycosylation). Alterations of supercharged proteins and polypeptides also affect lubrication (Ma et al., 2020; Veeregowda et al., 2012). Besides, surface characteristics of the human tongue (e.g. hydrophobicity, papilla density, and type) in real oral conditions also influence the roughness and integrity of lubrication film, then changing the lubrication status (Ni et al., 2021; Zhong et al., 2024). Tribological data from recent studies further supported the feasibility of modifications on saliva multilayers to improve oral lubricity in the oral cavity (Chang et al., 2020; Kerr et al., 2023; Riquelme et al., 2021).

In this review, we focus on the structural mechanisms of salivary lubrication and soft tribology occurring at the sliding interfaces during food oral processing. We then briefly introduce the theory of tribology and the multilayered structure of saliva, which are fundamental to understanding lubrication and will help us better grasp the mechanisms of oral lubrication. It also highlights the modulations of salivary architecture that often get underestimated in literature studies. Three main methods of surface modification inside the oral cavity, including physical, chemical, and physiological modifications, have been identified and discussed in detail in this review. A schematic illustration of modifications in this review is shown in Fig. 1. Detailed mechanistic insights into how each method (physical, chemical, physiological) specifically impacts the structure and function of the multilayer can be found in Table. 1. Novelty about the research and research gap with the previous research: (1) Modulating oral lubrication from the perspective of multilayered saliva film, while revealing the structural mechanisms and effectiveness of these methods during oral processing. (2) We propose combining saliva modification with clinical tests to provide strong evidence of its lubrication effects on patients with xerostomia. However, this still requires further exploration by researchers. (3) The advancement of new technologies provides us with greater motivation to delve into the exploration of interfacial behavior at the microscopic level in the oral cavity. Such as quartz crystal microbalance with dissipation monitoring (QCM-D) and dual polarisation interferometer (DPI) (Weston et al., 2023; Zembyla et al., 2021); mid infrared (MIR) spectroscopy (Bel'skaya et al., 2020; Ni et al., 2021); atomic force microscopy (AFM) (Koehler et al., 2024), surface plasmon resonance (SPR) (Guerreiro et al., 2017; Navarro et al., 2020) and X-ray photoelectron microscopy (XPS) (Biggio et al., 2023; H. Wan, C. Lin, et al., 2020). This review paves the way for designing next-generation artificial saliva for xerostomia and bio-mimicked devices with ideal interfacial properties, such as electrostatic tongue, by modulating the interaction of mucins in the multilayered saliva film.

2. Tribology in the oral cavity

2.1 The theory of tribology

2.1.1 Why tribology important in the analysis for oral processing?

The study of food oral processing and its impact on texture sensation has been increasingly concerned since the 1960s. Food scientists have realized that the texture sensation is influenced not only by food material but the food-saliva interaction inside the mouth. Rheology is a powerful tool to explain the mouthfeel of food products by analyzing the flow and deformation of materials (such as viscosity, elasticity, shear thinning and texture). It particularly focuses on how material responds to applied forces, revealing the connection between texture and oral sensation (Caffyn, 1954). It holds a dominant position in quantifying texture perception and inspires critical thinking in designing food products possessing good flavor and nutrients for the elderly (Stading et al., 2023). However, it has limitations in interpreting sensory attributes that are related to relative surface movement. More than a decade ago, the concept of "the rheology-tribology transition" was first proposed by Chen and Stokes (2012) (Chen & Stokes, 2012), recognizing the shift in the dominant mechanisms of oral texture sensation from initially bulk phase deformation to later surface movement.

Rheology-tribology transition is usually accompanied by a reduction in both the particle size of food and the gap between the tongue and hard palate during food consumption (Chen & Stokes, 2012). For example, continuous mastication reduces the particle size of food materials to sub-millimeters before being swallowed (Liu et al., 2024). Simultaneously, the salivary film thins due to shear-thinning behaviors, and tribology becomes the primary factor influencing the oral sensation. Under conditions of strain and rheological shear, the deformation of filiform papillae affects the

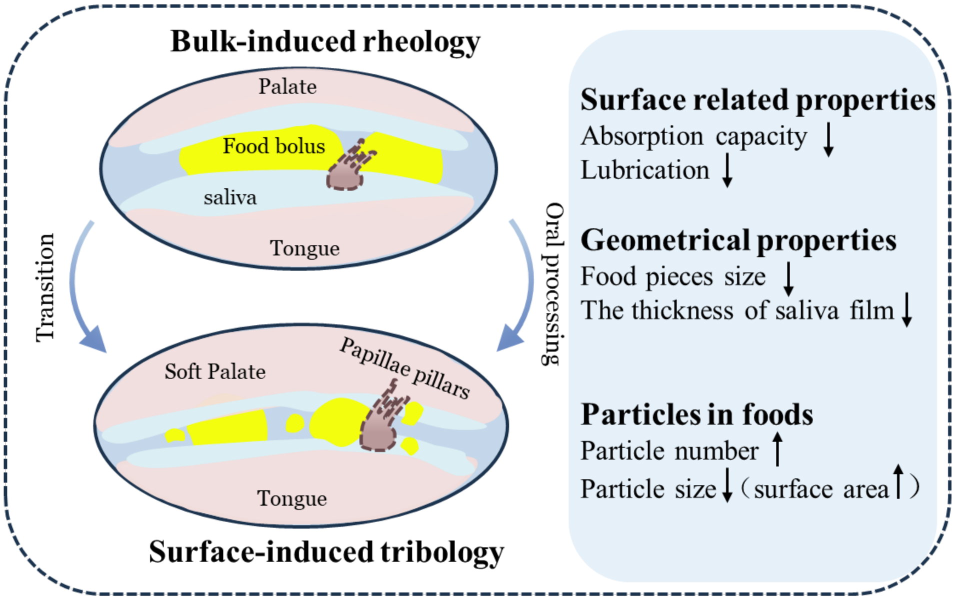

Fig. 2. **The transition from rheology to tribology during oral consumption.** This transition can roughly be divided into two stages for solid or semi-solid food: the rheological stage and the tribological stage. In the early stage, there is a large gap between the tongue and the palate at the front of the mouth, indicating that oral sensation is determined by the bulk properties of the food material. After a series of relative motions occurring at interfaces, the salivary flow decreases and the dominant property shifts to the tribological performance of the saliva film, which can be analyzed through tribological measurements.

roughness of the tongue surface, thus changing mouthfeel perception (Sarkar et al., 2019). Fig. 2 illustrates the various changes during this transition in food oral processing. It is obvious that rheological data alone cannot explain all oral behavior, such as the sensations of lubrication and astringency experienced during eating. Tribology paves the way for studying the surface-related properties of food materials and provides insights into sensory perception during food oral processing (Sözeri Atik et al., 2024).

Unlike rheology, tribology is more like a system property influenced not only by the properties of food materials but also by the two contacting substrate surfaces inside the oral cavity. Soft tribology mimics real human oral conditions by introducing a fluidic layer that behaves as a salivary film while using polydimethylsiloxane (PDMS) as the frictional surface (Shewan et al., 2019). The combination of tribology and rheology offers significant advantages for a comprehensive understanding of texture sensation in the oral cavity. For instance, Schädle and co-workers (2022) (Schädle et al., 2022) studied the texture sensation of mayonnaise samples with different fat contents by conducting both rheological and tribological measurements. They discovered that the friction in full-fat mayonnaise decreases because of the lubricating film formed by fat droplets. Glumac and Chen (Glumac & Chen, 2020) also synchronize rheology and tribology behaviour concerning oil/ fat perception. However, discrepancies between the analytical data and the results of the human sensory tests are often inevitable due to the lack of consideration of saliva. Therefore, the incorporation of multilayered structure of the salivary film into rheology and tribology analyses is crucial.

2.1.2 The Stribeck curve

The Stribeck curve was first proposed by Richard Stribeck in 1902 for the description of frictional behaviour between two lubricated surfaces with relative movement (Stribeck, 1902). Three main regimes of the ideal Stribeck curve in Fig. 3a indicate different lubrication performances under specific entrainment speeds as well as lubricant viscosity and surface load (Nguyen et al., 2017). These regimes include boundary lubrication at low entrainment speeds, low viscosities, and high surface load; mixed lubrication at moderate speeds, viscosities and surface load; and hydrodynamic lubrication at high entrainment speeds, viscosities and low surface load. Based on the Stribeck curve, the frictional coefficient (μ) is a function of fluid viscosity, entrainment speed, and load. Furthermore, the contact angle, surface wettability, and roughness of

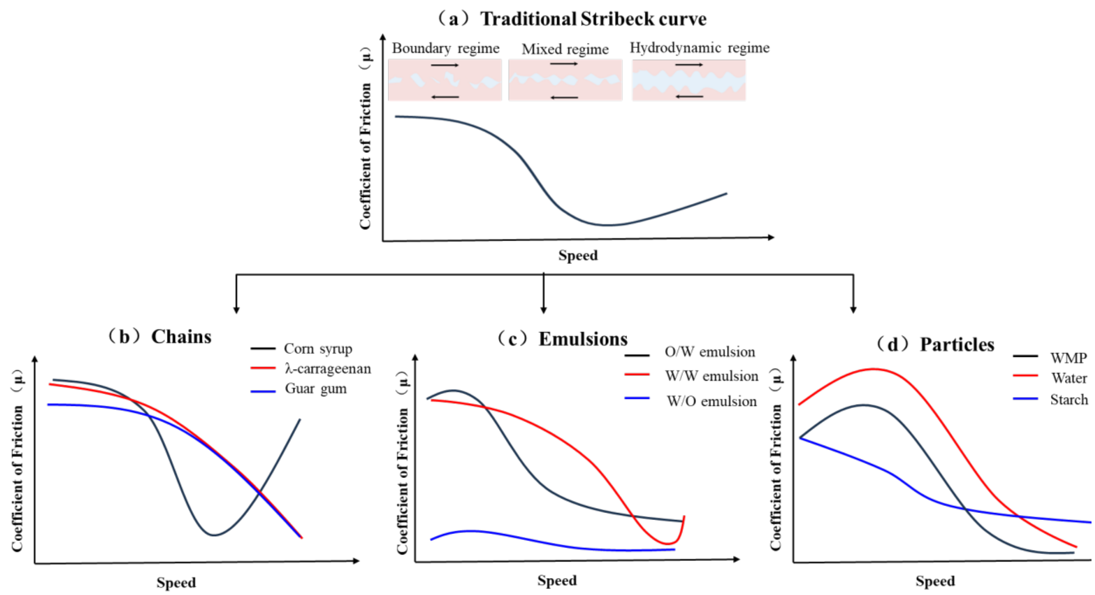

Fig. 3. Ideal Stribeck curve under specific conditions (different entrainment speed, the viscosity of foods, and applied load), where μ is the friction coefficient (a). The lubrication behavior of molecular chains (b), emulsions (c), and particles (d), which are reproduced from (Douaire et al., 2014; Fan et al., 2021; Garrec & Norton, 2012; Sarkar et al., 2017; Torres et al., 2018; G. E. Yakubov et al., 2015; You et al., 2023), respectively.

food material also affect the shape of the curve. It is important to note that fluids in multiphasic food systems deviate from simple fluids that behave as a continuum (Selway et al., 2017), leading to more complexity due to multicomponent and/or multiphase interactions. In this section, our main concerns are the influences of biopolymer chains, emulsion droplets, and various particles on lubrication behaviour.

The lubrication behavior changes following various chain behaviors in the solutions (Morris et al., 1981). Researchers have investigated diverse chain expansions of polysaccharide solutions, highlighting the significance of polysaccharides' conformation during food consumption (Fu et al., 2024; Hamilton & Norton, 2016; Hu et al., 2024; Ji et al., 2022; Yang et al., 2020). The conformation of polysaccharides is highly correlated with the value of the Mark-Houwink coefficient, reflecting different chain behaviors from extended-coil to rigid-rod (Garrec & Norton, 2012). The random-coil conformation in polysaccharides causes lubrication failure at low entrainment speed due to polymer exclusion between two surface contacts. For instance, the friction coefficient of guar gum increases because of the inability of random coil chains in aqueous environment, such as blockage and polymer exclusion (de Vicente et al., 2005; Zinoviadou et al., 2008). Polysaccharides with various chain expansions exhibit different friction behaviors, including Newtonian corn syrup, non-Newtonian λ-carrageenan, and guar gum (Fig. 3b). The frictional values of λ-carrageenan with an expanded chain and guar gum with a random coil are increased compared to corn syrup in boundary and mixed regimes, which can be attributed to the enhanced chain expansion of polysaccharides. However, the alignment and disentanglement of these chains also influence the exclusion performance at the surfaces and change the lubrication behaviour within the oral cavity.

Different emulsions have different friction performance. Notably, oil-in-water (W/O) emulsion offers the best lubrication properties in the boundary and mixed regimes during oral consumption (Fig. 3c). This superior performance is attributed to the incorporation of oil droplets and enhanced viscosity, which effectively supports the load and reduces the μ in the boundary regime. However, as the speed and load increase, the frictional coefficient tends to rise. Research conducted by Douaire et al. (2014) has investigated the influence of water content in W/O emulsion on lubrication behavior in the boundary regime, indicating that a water content of 60 % leads to decreased friction (Douaire et al., 2014). Furthermore, emulsion-saliva interactions involve processes such as salt-induced aggregation, depletion flocculation, bridging flocculation, and coalescence. A recent study has shown that oleogel-in-water HIPEs (high internal phase emulsions) perform better lubrication when mixed with saliva, as undiluted emulsions with cohesive properties accelerate the formation of food bolus between sliding surfaces (Zhang et al., 2024). In contrast, water-in-water (W/W) emulsions, which are shear-thinning liquids, exhibit high frictional values (You et al., 2023). While the friction coefficient decreases due to the formation of lubricious film containing water droplets, the overall lubrication properties are generally poor compared to W/O emulsions. This reduction in lubrication in water-in-water emulsions can be attributed to the inability of water droplets within a water continuous phase to provide effective bearing, thus limiting their lubrication effect.

Soft particles, mainly including protein aggregates, microgels (Sarkar et al., 2017), and whey protein microparticles (Liu et al., 2016; Olivares et al., 2019), perform various lubrication behaviors. These particles serve as lubricants at interfaces due to their “load-bearing” properties, allowing them to easily be entrained into two frictional contacts, thereby enhancing lubrication performance (Lim et al., 2022). As depicted in Fig. 3d, water has a higher friction coefficient compared to other particle systems. The μ dramatically decreases with the introduction of emulsion microgel particles that possess high lubrication (Torres et al., 2018). The excellent lubrication properties can be attributed to the incorporation of the oil phase (e.g. sunflower oil) and starch content (10 wt % and

20 wt %, respectively) in the microgel. These components effectively bear the loads while simultaneously forming a lubricious film composed of oil droplets within the gap between two sliding surfaces. Compared to water without soft particles, the friction in aqueous dispersions containing whey protein microgel (WPM) particles is relatively low in both the plateau boundary and mixed lubrication regimes. Those can be attributed to the layer formed by particles with load-bearing capabilities serving as "surface lubricants" between the asperity contacts. However, the lubrication performance of WPM is poorer than that of emulsion-containing microgel particles, possibly due to the presence of oil droplets in emulsions. Fan et al. examined the lubrication properties of oil-in-water emulsions when fat particles are introduced into sliding contacts by using 3D printed tongue. Their findings indicate that the layer constructed by fat droplets effectively separates the gap, facilitating reduced friction at low entrainment speeds (Fan et al., 2021). Additionally, the thickness of lubricious film and surface friction are also related to particle size, particle number and the hydrophobicity of the substrates (Torres et al., 2018). Regarding microgel particles, the Stribeck curve of the native whey protein solution exhibits significantly higher friction coefficients in the boundary and mixed lubrication regimes. Such high interfacial friction observed in the mixed lubrication regime may result from the protein being squeezed out from the two contacts and the absence of a hydration layer at interfaces. In fact, the lubrication properties are influenced by both the concentration of WPM and the hydrophobicity of the substrates used.

2.2 The multilayer structure of saliva film

Various phenomena, such as emulsification, lubrication, adsorption, and adhesion, occur at the oral interfaces, influencing friction behavior and food-saliva interactions. Many studies have attempted to understand oral behaviour of various food materials (Elizabeth Aguilar Fernández et al., 2024; Pematilleke et al., 2020; Soltanahmadi et al., 2022; Vilgis, 2024; Zhang et al., 2024). However, the focus of most research has been on the structure and properties of food material, with very little attention given to adsorption and interfacial behaviour as well as the multilayered structure of saliva.

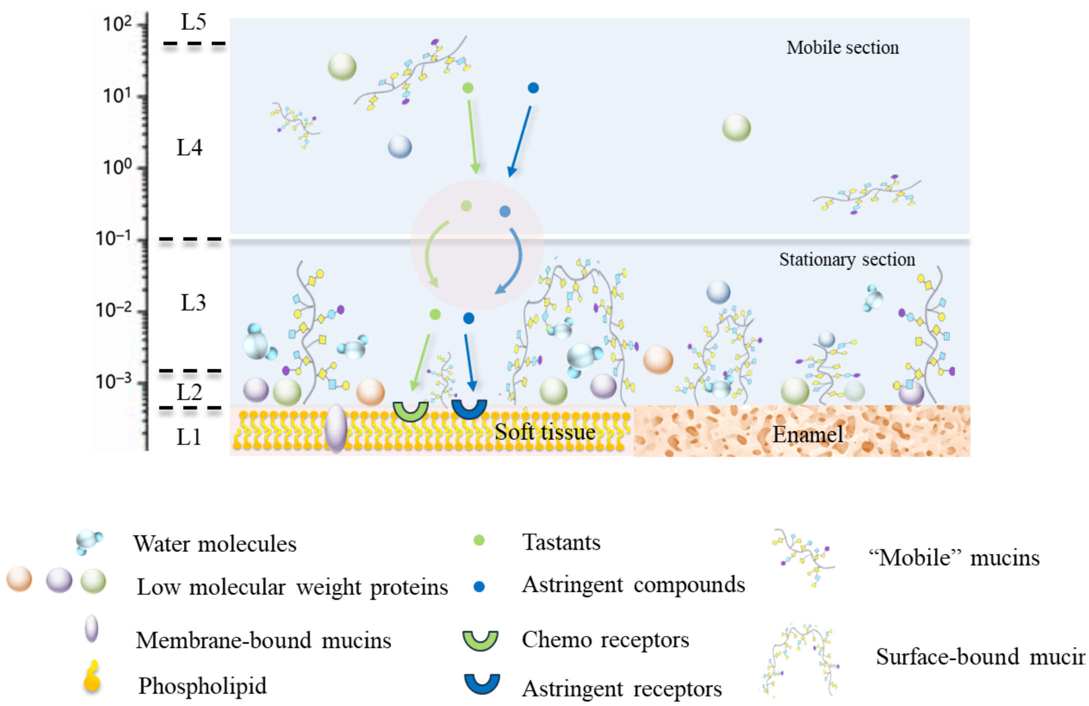

Fig. 4. **The multilayered structure of saliva film in the oral cavity.** The saliva film is fabricated by five sub-layers each with different functionalities. Herein, we introduce two sections based on the fluidity of mucins in the bulk saliva: the mobile section and the stationary section. The former (comprising layers 4 to 5) is responsible for transporting food components to the tongue surface, providing wetting, emulsification, and lubrication. Many low-molecular-weight salivary proteins are present in the latter one (comprising sub-layers 1 to 3), which adheres strongly to the soft tissues, providing effective lubrication. This figure is inspired and reproduced with modifications from (Mu & Chen, 2023).

Sufficient evidence indicates that oral lubrication performance is associated with mucins resulting from the heavy glycosylation of many salivary proteins (Mortazavi et al., 2024). Therefore, there is no doubt that the structural changes of the saliva film are vital for elucidating the tribological behavior and lubrication mechanisms at oral surfaces during food oral processing.

As shown in Fig. 4, the salivary film is a five-layered structure composed of different salivary proteins (proline-rich proteins, cystatins, statherin, etc.), each with different functions including lubrication, food transportation, enzymatic and colloidal interactions, and emulsification of fat/oil droplet (Gleb E. Yakubov et al., 2015). We can divide this five-layered structure into two different sections: the mobile section and the stationary section. The mobile section consists of three sub-layers composed of different components with various functions. Mucins in this section possess a unique microstructure characterized by loops and brushes. These special structures form a hydrated lubrication layer by attracting and binding water molecules, establishing a connection with the air or food. This layer also plays a crucial role in transmitting food components to the tongue surface for taste sensation (Macáková et al., 2010), providing wetting, emulsification, and lubrication. Throughout this process, the adsorption ability of protein is a key influencing the exchange of components and oral friction. On the other hand, the stationary section of the salivary film contains many other salivary proteins that adhere strongly to the tongue, mucosa, or palate, enhancing oral lubrication by catching large-molecular-weight mucins.

The layered microstructure is essential for lubrication performance. As mentioned previously (Section 1), numerous studies have found that frictional behavior can be changed by altering the structure of the saliva film in the oral cavity. Smart and Bryant (Smart & Bryant, 2023) emphasized that surface composition affects interfacial bonding, which further influences water retention capacity. The formation of lubricious mucin layers depends on the adsorption effectiveness of salivary proteins in the stationary section. Any alteration of salivary proteins will result in different outcomes in frictional behavior at oral interfaces. Lubrication failure occurs when the mucins with loops and brushes in sub-layer 3 are removed at a low surface load (Macáková et al., 2010). The aggregation of large proteins in sub-layer 2, caused by the presence of polyphenols, also leads to poor lubrication, resulting in astringency perception and influencing the whole eating experience (López-Solís et al., 2024a). This change in protein composition occurring at L2 or L3 leads to microstructural damage in the multilayered saliva film, negatively affecting lubrication behavior by increasing the frictional coefficient. However, the variation of proteins is not always detrimental to the formation of hydrated lubrication layers with lubricating ability. The performance of the absorbed film could be improved by deliberately introducing proline-rich proteins into the oral system. Furthermore, research has revealed that a combination of high molecular weight mucins and relatively low molecular weight proteins is highly beneficial for maintaining lubricating capability inside the oral cavity (J. Vinke et al., 2020). Such a combination could be applied in the design of artificial saliva for vulnerable populations. These studies suggest that lubrication behavior during oral processing can be manipulated by modulating the salivary structure.

Table. 1. Summary of three main modifications applied in interfacial lubrication.

Type	Methods	Material	Mechanisms	Changes in lubrication behavior	Applications	References
Physical	Electrostatic attraction	Lactoferrin and β-lactoglobulin	Changing the surface charge of mobile section interacts with mucins in the stationary section.	Mucin coverage increased from 0.61 to 1 mg/m²; friction coefficient reduced from 0.07 to 0.01.	Designing nature-mimetic aqueous lubricants and alleviating dryness sensation.	(Pabois et al., 2023; Sarkar et al., 2009)
	Hydrophobic forces	Condensed tannins, catechins	Control the hydrophobicity of the components in the mobile section to inhibit polyphenol–protein complexation.	Protein precipitation causes astringency, and oral lubricity has been decreased.	Regulating the astringency related to oral lubrication in beverages (coffee, red wine and tea.)	(James et al., 2023; López-Solís et al., 2024b; Wang et al., 2024)
	Chain behavior	Polysaccharides	Alter the structure of salivary mobile section by regulating polymer conformation.	Polysaccharides with maximum chain expansion perform better lubrication in the boundary regime.	Designing non-oil-based formulations for low-fat Foods.	(Garrec & Norton, 2012)
		Glycans with brushes	Alter the structure of salivary stationary section by limiting chain entanglement of glycans based on "steric-entropic type" repulsion.	Minimizing viscous and frictional dissipation while supporting high contact pressures with low μ values.	Oral lubrication	(Raviv et al., 2003; Zappone et al., 2007
Chemical	Covalent grafting	Poly (ethylene glycol) (PEG)	Introduce new functional groups through grafting to alter the microstructure of mucins in the stationary section, forming layered or network structures to enhance the water retention capacity of the lubricant layer.	Lubrication performance has been increased at pH 7 by inhibiting desorption.	Drug delivery	(Lee & Spencer, 2008)
		Chitosan		Friction coefficient lowered to 0.047; relief time extended to 3.3 min for patients and 7.2 min for healthy individuals.	Oral delivery and lubrication	(Kim et al., 2015; H. Wan, A. Vissink, et al., 2020)
		Recombinant supercharged polypeptides		Prolonging the lubrication time from 3 to 21 min.	Artificial saliva for xerostomia	(H. Wan, C. Ma, et al., 2020)
	Glycation	Mucinous proteins	Facilitate the formation of bottle-brush-structured proteins in the stationary section.	Brush polymers achieved ultra-low friction, decreasing from 0.01 to below 0.001.	Designing food colloids with optimized lubrication	(Sarkar & Gul, 2024)
		Fish gelation		Glycosylation ensured lubrication properties, measured at 0.131 on day 1.	Designing foods with good lubricity	(Miao et al., 2024)
Physiological	Low-level laser therapy	Laser	Stimulate the nerves surrounding the salivary glands, thereby enhancing the transmission of nerve signals and promoting saliva secretion.	Salivary flow rate increased from 0.58 mL/min before LLLT to 0.65 mL/min after.	Oral lubrication for xerostomia	(Ribeiro et al., 2024)
	Submandibular gland transfer	—		The incidence of severe dry mouth was significantly reduced to 16.7%.	Treatment for patients with gland dysfunction.	(Chang et al., 2020)

Notes: Modifications also have limitations in their applications, which need further improvement. 1) Physical: The weak electrostatic interaction force and its susceptibility to being washed away lead to short-lasting oral lubrication, indicating a need for further research on regulating polymer chain behavior. 2) Chemical: The health risks of chemical reagents used in the modification process, such as HCA, NHS, and EDC, limit clinical research. 3) Physiological: Laser therapy's lubrication effects may weaken within a few months, and high radiation doses can lead to irreversible xerostomia, impacting gland function.

3. Modulating microstructure of the salivary multilayer: physical, chemical, and physiological approaches

Oral lubrication is a topic sparking hot debates in the field of food sensory science. There are many foods with lubricating properties (smoothness, creaminess, and slipperiness) in our daily life, such as jelly, chocolate, or liquid yogurt, facilitating safe swallowing and offering a pleasant experience during food consumption. However, phenolic compounds in food (like wine, tea, or coffee) owing to the precipitation of salivary proteins may cause discomfort feelings in the oral cavity, such as drying, roughening, shrinking and puckering (González-Muñoz et al., 2022). For a desirable eating experience and the specific needs of various consumers, both food materials and salivary protein compositions require modifications to achieve an enhanced oral lubricating capability. In the 1990s, researchers had already discovered that the repulsion between brush polymer and fluid layers keeps the surface apart, significantly decreasing friction at contact surfaces (Klein et al., 1994). This inspires us to speculate that similar brush and loop microstructures with varying elastic modulus within salivary film may also reduce friction or wear inside the oral cavity. For this, how to modulate the salivary microstructure to reach beneficial lubrication is definitely a major challenge. Herein, we briefly outline three possible approaches based on the interactions between saliva and food materials: physical, chemical, and physiological methods.

3.1 Physical modification

The lubrication performance changes following physical modifications of the salivary film (Celebioglu et al., 2020). Electrostatic interactions, hydrophobic forces, and chain entanglement are three main physical forms of food-saliva interactions. Electrostatic complexation is the most prevalent method in altering the microstructure of the multilayered saliva film (Gibbins et al., 2014; Zembyla et al., 2021). We assume that better lubrication can be achieved through modulating surface charge between electrostatic interactions. The mechanism is the interactions between salivary mucin and other proteins or polysaccharides that change oral lubrication behavior (Sarkar et al., 2009). Salivary mucins (MUC 5B and MUC 7) function as a hinge to form a hydration layer due to their highly glycosylated regions, which enhance water trapping abilities offering lower friction at sliding interfaces (Amerongen et al., 1995; Tabak, 1995).

Colijin et al. (Colijn et al., 2022) modulate the electrostatic interactions to explore the interfacial adsorption of emulsion droplets through changing surface charge of complexation on the oral film with mucins. The data of Quartz Crystal Microbalance with dissipation monitoring (QCM-D) and Dual Polarising Interferometry (DPI) shows that cationic emulsions have strong adsorption on salivary film due to the interaction with opposite surface charge (Fig. 5b). One study further explained the mechanisms of salivary lubrication from macro to nanoscale based on electrostatic interactions, revealing that hydrated mucin is a key to oral lubrication while lactoferrin function as a "binder" between mucin-surface trapping water molecules within the complex network (Xu et al., 2020). A similar study also investigates the effect of mucin content on the adsorption behavior of emulsions (Sarkar et al., 2009). The experimental data have shown that mucin coverage of lactoferrin (cationic emulsion) is larger than β-lg-stabilized emulsion (anionic emulsion) due to its electrostatic attraction, 0.6 mg/m^2 and 1 mg/m^2 respectively, which means emulsions with positive surface charge may have a larger potential to provide high lubricity inside the oral cavity.

Additionally, electrostatic binding also prevents desorption from the hydrophobic surface, achieving permanent lubrication after swallowing. The desorption rate of microgel-reinforced lubricant compared to commercial saliva substitutes (23–58% desorption) can be controlled within 7 % while maintaining high viscosity and also aids boundary lubrication under different dry mouth conditions (de-papillated tongue and papillated tongue) (Pabois et al., 2023). Tribological data have shown that the friction coefficient of lubricant based on lactoferrin protein is lower than commercial saliva (0.07 ±0.03 at 0.01m s^{-1}) significantly reducing the friction between two sliding contacts in the boundary and hydrodynamic region, 0.01 ± 0.01, at 0.01 m s^{-1} and 0.01 ± 0.01, at 0.25 m s^{-1}, respectively.

However, electrostatic repulsions vary with change of pH, charge density, and ionic strength. It can alter the intramolecular and intermolecular interactions, hence impact oral lubrication performance (Silva et al., 2012). Specifically, ionic concentration has been proved largely influences the lubricative abilities of mucin in the boundary and mixed regime (Feldötö et al., 2008; Hughes et al., 2019; Macáková et al., 2010). QCM-D analysis supported that increasing the concentration of sodium ions enhance the lubricity of mucin films between two relative motion surfaces at oral condition. (Weston et al., 2023). Boyd et al. (Boyd et al., 2020) have also elucidated that the mobile layer of salivary film expands under low ionic strength conditions, exhibiting weak polyelectrolyte behavior and successfully preventing structural collapse for boundary lubrication.

Hydrophobic interactions may cause astringent sensation leading to lubrication failure (Pires et al., 2020) when polyphenolic molecules (from unripe fruits, coffee, tea) exist in the oral cavity

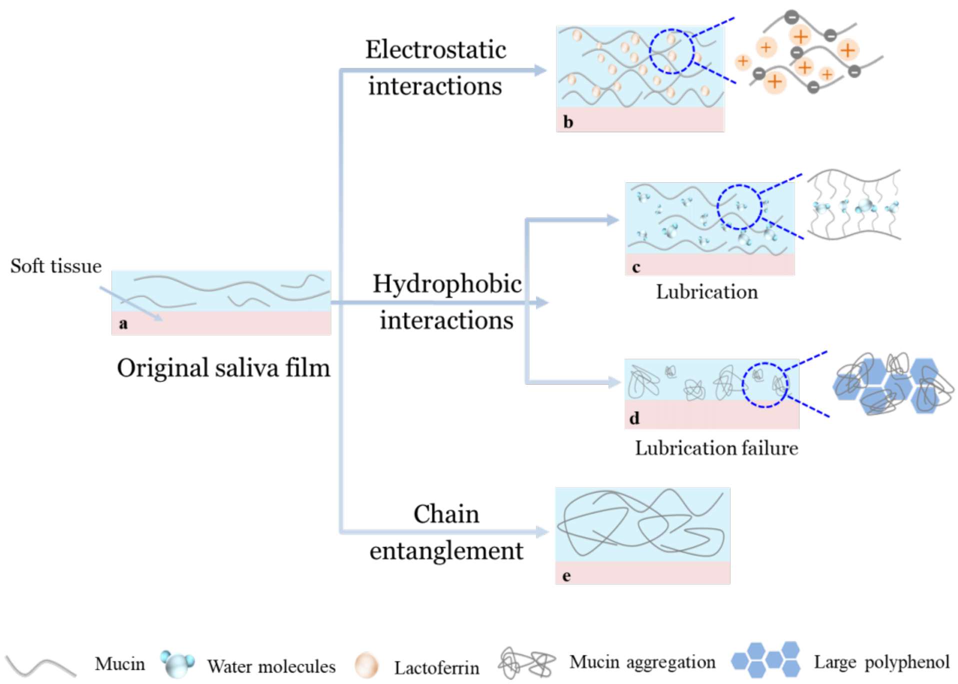

Fig. 5. **The underlying mechanisms of physical modification** including electrostatic complexation, hydrophobic interactions, and steric entanglement. (a) is original saliva film with limited lubricity in the oral cavity. After a series of interactions, the thickness of the saliva film has clearly increased by interplaying with mucins such as (b) and (c). But the modifications do not always enhance the oral lubrication, they may cause mucin aggregation (d) and chain entanglement (e), leading to lubrication failure.

(Fig. 5d). For instance, the interactions between salivary proline-rich proteins and polyphenol (e.g. condensed tannins, catechins) may produce a dryness sensation compromising lubrication that depends on the degree of glycosylation of mucins in the oral cavity (Wang et al., 2024). The protein precipitation/aggregation caused by polyphenol–protein complexation reaction is the main factor in the loss of lubricity and wetting abilities inside the oral cavity during consumption (Biegler et al., 2016; Gibbins & Carpenter, 2013; Ma et al., 2016). It also alters the salivary microstructure and rheological behavior. The mechanisms of astringency have the potential to improve oral lubrication by modulating the hydrophobicity of the components in the mobile section, thus inhibiting the interaction between polyphenols and mucins. Additionally, this can prevent astringent sensations in the oral cavity without compromising the beneficial properties of stringent molecules for human health. Those molecules have anti-inflammatory properties, anti-cancerous effects, and antioxidant activity (James et al., 2023). Furthermore, hydrophobic interaction may slightly inhibit friction damage by forming lubricating monolayers at the oral interfaces (Fig. 5c) when neutral emulsion interacts with low molecular weight salivary proteins in the stationary layer at low ionic strengths (Dresselhuis et al., 2008).

Entanglement and Expansion of polymer chains is another key factor for oral lubrication relevant to oral processing, medicine delivery (mucoadhesive oral patches), and the design of oral-care products (Ryu et al., 2020). For instance, glycans may change tribological behavior, resisting large contact pressures as glycans have limited entanglement (Fig. 5e) due to "steric-entropic type" repulsion. Furthermore, it can slide easily at interacting surfaces, allowing water molecules retained in interfacial surfaces while exhibiting great lubrication (Raviv et al., 2003; Zappone et al., 2007). Garrec and Norton (2012) further investigate the influence of different chain structures on lubrication, such as polysaccharides with random coil, extended chain and rigid-rod (Garrec & Norton, 2012). They indicated that the friction coefficient of random coil solutions increases with concentration (from 0.19 to 0.28) due to polymer blockage and exclusion within a certain concentration. However, the other two decrease as concentration increases. Additionally, interchain entanglement could further stabilize food systems to provide good (Sarkar et al., 2009) thermal stability, acid stability, salt stability, and shear stability (Nimaming et al., 2024; Zhang et al., 2023). So far, there is very few research on regulating the behavior of polymer chains to achieve low oral friction.

These physical modifications have the potential to alter the microstructure of the salivary film, thereby improving oral lubrication. It primarily modulates the surface charge of food materials in the mobile phase, allowing for better interaction with mucins in the stationary phase. It facilitates the trapping of more water molecules within network by strengthening electrostatic interactions. However, the lubrication layer formed through weak electrostatic interactions can be easily rinsed by daily activities such as eating and drinking, making it difficult to achieve long-lasting oral lubrication. Additionally, for patients who have significantly lost mucin on the tongue surface, the lubrication effectiveness of this physically adsorbed hydrated layer is quite limited.

3.2 Chemical modification

Mucins with brush structure facilitate mucinous binding to hydrophilic and hydrophobic substrates, improving lubrication behavior (F. Wan et al., 2020). However, the mucin films formed by surface adsorption can be easily damaged after repeated friction inside the oral cavity. To ensure appropriate surface coverage of mucins or to prevent its surface loss is hugely important for oral care as well as for the eating experience. Herein, two possible approaches (grafting and glycation) from chemical perspectives will be discussed.

Stable covalent grafting is an excellent strategy for strengthening the binding of mucins to material surfaces. It is a main chemical technology to modify the surface lubrication of food materials, referring to combining appropriate branched or functional side groups on a macromolecular chain through chemical bonding. Therefore, we hypothesize that graft mucins with amine groups onto surfaces with carboxylic acid groups through stable covalent linkages, favoring the formation of multilayered mucin film via layer-by-layer assembly (Fig. 6a). Jiang et al. (Jiang et al., 2022) covalently links bovine submaxillary mucin to different substrates, resulting in a highly stable mucin film. It retains almost 100% of mucins on soft surfaces compared to passively absorbed film after daily rinsing. The layered structure of mucins significantly increases the quantity of mucins at the interface, providing significant potential for optimal lubrication. These graft copolymers are friction modifiers to enhance boundary lubrication via constructing a lubricious film between sliding surfaces (Kerr et al., 2023). For instance, grafted hyaluronic acid enhances articular lubrication as well as increases resistance to surface damage by forming a viscoelastic gel (Li et al., 2021; Yu et al., 2012). Based on effective lubrication in articular joints, researchers have found that poly (ethylene glycol) (PEG) is a good candidate for further modification among water-soluble polymers. Modified-PEG is an excellent lubricant additive possessing low friction, excellent lubricity, self-healing capacity, and biocompatibility under boundary conditions, which achieves long-lasting lubrication at the interfaces (Z. Wang et al., 2023). For example, thiolated polyethylene glycol and mucin can quickly create hydrated layers resisting oral friction through chemisorption. A similar conclusion on lubricating properties of grafted PEG has also been made by Lee and Spencer (2008) through tribological experiments (Lee & Spencer, 2008). The excess of grafted polymer at pH 7 enhances lubrication properties by inhibiting the desorption of initially adsorbed polymers under tribostress conditions. Meanwhile, a mucoadhesive polymer, made up of a chitosan backbone grafted with catechol moieties through carbodiimide chemistry, has been developed to provide adequate lubrication via mucin recruitment (Kim et al., 2015). More specifically, the conjugated catechol forms covalent linkages with amines and cysteine residues of mucin, facilitating the formation of a double layer after rinsing treatment. In another similar study, the data supported by friction experiments have shown that different conjugation degrees of chitosan-catechol (7.6%, 14.5%, and 22.4%) have different lubrication performances (H. Wan, A. Vissink, et al., 2020). The highest degree of conjugation in grafted polymer results in a softer and thinker top layer. It enhances water retention capacity, hence yields a lower friction coefficient (0.047 ± 0.0031) and extended relief time (3.3 ± 1.3 min for patients and 7.2 ± 0.3 min for healthy individuals).

The fabrication of recombinant supercharged polypeptides (SUPs) enhances the duration of oral lubrication by forming a hydrated and soft layer, on the top of residual mucin layer on the tongue surface through mucin recruitment (Veeregowda et al., 2013). In 2020, Wan et al. (H. Wan, C. Ma, et al., 2020) introduced two cysteine residues into the polypeptide chains, forming disulfide bridges through genetic engineering. Experimental data further indicate that SUP, with 108 positive charges and two cysteine residues, could be the most promising candidate for restoring oral lubrication. It forms a layered structure with good water-holding capacity due to the disulfide bridges when exposed to saliva flow, prolonging the lubrication time from 3 to 21 min.

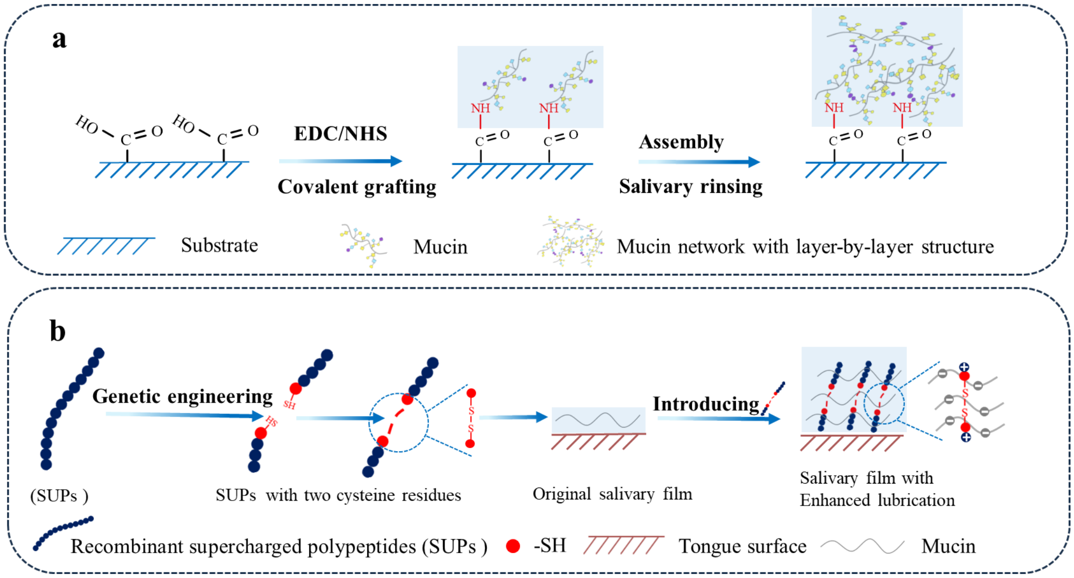

Fig. 6. **Chemical grafting can enhance oral lubricity through the formation of a layer-by-layer structure of mucins.** The figures of (a) and (b) draw inspiration and are reproduced from the works of (Jiang et al., 2022) and (H. Wan, C. Ma, et al., 2020), respectively.

Glycation is a useful strategy for maintaining lubrication at bio-interfaces involving a covalent reaction between sugars with carbonyl groups and biomolecules (Sun et al., 2023). This chemical process also termed as “Maillard reaction” occurs not only in foods but also inside the human body (Monnier et al., 1984). This process is crucial for the structural and functional expansion of proteins (including the formation of a brush-like structure of mucins), affecting interactions with surfaces and texture perception (Sarkar & Gul, 2024). Generally, highly glycosylated proteins offer excellent adsorption efficiency and stabilities (Li et al., 2024; Miao et al., 2024), providing boundary lubrication and wear protection at interfaces. A basic understanding of glycosylation sheds light on designing foods with good lubricity and high nutrient content for vulnerable people (Araiza-Calahorra et al., 2023; Fan et al., 2024). To illustrate the influence of glycosylation on lubrication, Huang et al. (Huang et al., 2020) developed modified fish gelatin through glycosylation to achieve desirable lubrication properties. Tribological data indicated that glycosylation could enhance internal lubrication of emulsion, as well as improve emulsion resistance ability to pressure. The friction coefficient of fish gelatin glycosylated with OSA - gum Arabic is 0.131 ± 0.001, 0.147 ± 0.000, and 0.167 ± 0.001 for Day1， Day 7, and Day 14, respectively. In contrast, the friction coefficient of fish gelatin is 0.143 ± 0.007， 0.159 ± 0.007, and 0.161 ± 0.011 for the same days, respectively. A similar study conducted by Wang et al. in 2023 further elucidated the effects of glycosylation on the structural and functional properties of fish gelatin (Y. Wang et al., 2023). Their results revealed that the conjugates of modified fish gelatin exhibited excellent lubrication abilities inside the oral cavity. A recent study also demonstrated that conjugates formed through the Maillard reaction can be used to stabilize Pickering emulsions (Du et al., 2024). It forms a three-dimensional network by self-assembling, providing adequate lubricity and comfortable sensation in the oral cavity.

Grafting and glycation complement physical modifications by forming layer-by-layer mucin structures with good lubricity, creating a comfortable eating experience. It also largely prevents the surface loss of mucins, ensuring optimal surface coverage. However, the chemical reagents used in the modification process, such as 3,4-dihydroxy hydrocinnamic acid (HCA), N-Hydroxysuccinimide (NHS) and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC), may pose health risks to humans. Therefore, cytotoxicity tests are essential to ensure that the dosages used are within a reasonable range.

3.3 Physiological modification

Physiological characteristics such as age, gender, and health status have a significant impact on saliva secretion and dry mouth sensation. One study revealed that age plays a crucial role in the dryness sensation in the oral cavity through collecting experimental data from forty-two healthy

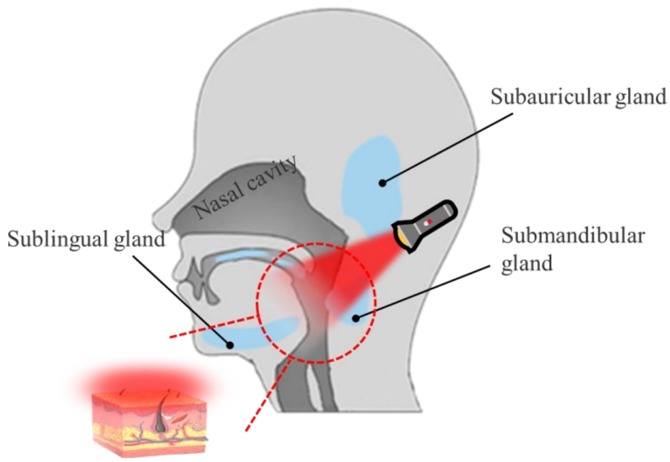

Fig. 7. **Laser treatment of main glands inside the mouth for alleviating xerostomia.** The tip of the tool is in contact with specific points on the major salivary glands on the patient's skin during LLLT treatment. Laser light is transformed into beneficial energy for cells after a series of mechanisms. This process promotes cellular repair and regeneration, leading to enhanced healing of wounds, tissues, and injuries, while alleviating xerostomia.

participants (mean age = 65 years; 20 females) (Rogus-Pulia et al., 2018). Females exhibit a stronger association between reduced salivary flow rate and xerostomia compared to males. The overall prevalence of xerostomia was found to be 43.6 %, with females comprising the majority at 61.2% (Morita et al., 2023). Based on this research, scientists expanded the scope of their study to include 1405 individuals aged from 35 to 74 years old, investigating the influence of other factors on the dryness sensation, such as systemic disease and alcohol consumption. The result shows that these factors are positively correlated with xerostomia, leading to a higher incidence of dry mouth syndrome (accounting for 71.2 %) (Adolfsson et al., 2022; Stankeviciene et al., 2021). The surface microstructure of the human tongue also influences lubrication sensation in the oral cavity such as papillae height and density on the tongue surface (Glumac et al., 2023). Although experimental analysis exhibited a slightly positive correlation between tongue surface roughness (54.6-140.0 μm) and the oral friction coefficient (0.299-1.505) (Wang et al., 2022), the topographic features of the human tongue are still highly individual, which is not the point in this review.

Clinical intervention is required to alleviate or improve oral discomfort when salivary gland is damaged due to salivary gland hypofunction after radiation treatment. Laser is a powerful tool that can effectively alleviate xerostomia and significantly reduce oral friction (Legouté et al., 2019; Simões et al., 2010). As shown in Fig. 7, during the treatment, the tip of the tool makes direct contact with the patient's skin (on the subauricular and submandibular glands) or the floor of the mouth (sublingual glands). The laser light transforms into beneficial energy for cells by regulating various metabolic, biochemical, and photophysical processes, which helps alleviate the dry mouth sensation (Saleh et al., 2014). Studies *in vitro* confirmed the effects of laser therapy on salivary gland hypofunction (Onizawa et al., 2009; Plavnik et al., 2003). A low-level laser therapy (LLLT) has been reported to improve the dry mouth sensation and to change salivary flow by irradiating the subauricular, submandibular, and sublingual glands in a fixed period (Ribeiro et al., 2024). To avoid adverse impacts on tissues, such as thermal and cytotoxic effects, radiation power is normally maintained within a range of 0.05 to 0.5 W (Huang et al., 2009). Saleh et al. (Saleh et al., 2014) further investigate the effects of laser therapy (830 nm, 100 mW) on simulated salivary flow in patients with pre-existing hyposalivation and xerostomia *in vivo*, indicating that there is no significant difference between the control group and laser group. Nevertheless, both xerostomia and the quality of life-related to oral health showed improvement. On the other hand, Nascimento et al. (Nascimento et al., 2023) judge the effectiveness of LLLT on patients by combining salivary flow rate (objective parameters) and questionnaires (subjective parameters). They observed a decrease in xerostomia and a slight increase in the salivary flow rate (0.58 mL/min before and 0.65mL/min after LLLT), which is consistent with an early study by Cowen et al. (Cowen et al., 1997). The long-term effects of radiotherapy on glandular structure may cause different outcomes of LLLT in patients. More interestingly, submandibular salivary gland can be transferred and shielded to submental space (outside the radiation field), preventing xerostomia induced by radiation and enhancing the mean weight of saliva from 0.73 g to 1.65 g (Liu et al., 2011). One study revealed that among 43 patients who received salivary gland transfer, 81 % had none or only mild dry mouth, and 19 % had moderate to severe dry mouth. Those suggest that surgical transfer significantly works on xerostomia (Jha et al., 2003). Chang and colleagues (2020) modified the technique of submandibular gland transfer by preserving the ipsilateral facial artery and vein. Those may result in better outcomes and no complications, such as postoperative facial edema and swelling (Chang et al., 2020). Incidence of severe dry mouth in the group undergoing submandibular gland transfer was significantly reduced to 16.7%.

Dietary treatments are often the first choice for patients with xerostomia because they are readily available and carry low risks and discomfort, including yogurt, lemon juice and even Chinese herbs (Murugesh et al., 2015) (Wei et al., 2022). However, the effectiveness of these treatments tends to be mild and often inadequate for patients with severe oral dryness. Thus, low-level laser therapy (LLLT) is a necessary approach to achieve powerful and lasting effects.

Although laser therapy treatment has longer-lasting effects compared to physical and chemically modified treatments, there still seems to be a consensus that the effects of LLLT are likely to diminish after a few months (Gonnelli et al., 2016; Wibawa et al., 2018). Additionally, radiation doses exceeding 60 Gy may cause irreversible xerostomia, influencing treatment effectiveness and glandular function (Cheng et al., 2011).

To note, it is challenging to distinguish mechanisms of interactions from one another due to the presence of synergistic effects in this section. Synergy commonly occurs between physical interactions and chemical grafting. For example, recombinant supercharged polypeptides, comprising two cysteine residues and 108 positive charges mentioned before, have the potential to restore salivary flow in the oral cavity through the synergistic interaction between electrostatic complexation and disulfide bridges formed by two sulfhydryl groups (H. Wan, C. Ma, et al., 2020). From a certain perspective, Synergistic effects of physical and chemical interactions facilitate the formation of a robust layer-by-layer structure of saliva film, making it less susceptible to being rinsed by daily food consumption. It enhances the water retention capacity of the saliva film, maximizing the moisture and comfort in the oral cavity.

4. Conclusion and future perspectives

Modifications of salivary multilayers that enhance the impact of mucins on the tongue surface within the oral cavity are of particular importance for oral lubrication and the alleviation of xerostomia. We here demonstrated that three layers with different mechanisms may be promising options for this purpose, as they possess the ability to modify the multilayered saliva film, generating surfaces with good lubricity at the interface. Electrostatic adsorption layer, covalent grafted mucin layer, and even laser therapy for severe xerostomia are all based on the existing mucins that are present on the tongue surface. Mucins possess unique structures of loops or brushes that provide water retention abilities while forming a lubricating layer. Modified mucins with layer-by-layer or network structures significantly enhance their water retention capacity, remarkably alleviating the dryness sensation and providing a comfortable eating experience. The effects of these modifications vary significantly. Generally, the lubricating layer formed through electrostatic binding is too weak to withstand the rinsing of daily consumption. In contrast, grafting strategy compensates for this deficiency by providing a strong anchoring effect, ensuring that dietary activities do not disrupt the mucin layer to a certain extent. However, chemical agents used in grafting process may pose risks to human health. The first two methods are common choices for ordinary patients with dryness. However, patients with radiotherapy-induced xerostomia have already compromised salivary glands and have no sufficient salivary flow, and they must use laser therapy. Among three modifications, laser therapy offers the longest-lasting effects (up to several months), yet the mechanisms of its interaction with salivary multilayers or mucins remain unclear and require further exploration by researchers.

This review aims to address oral lubricity by examining the possibilities of modifying salivary film via physical, chemical, as well as physiological approaches. Specifically, modification improved lubrication by creating a strong mucin network on oral surfaces that retains water molecules and bears surface pressure. We hope this review will inspire diverse thinking about oral lubrication. New discoveries and clinical testing are waiting to be made, but a series of research gaps and challenges need to be addressed. A few examples of the same are given below:

- Theoretically, chain length of the polymer can be modulated to interact with mucins for reduced friction due to the unique structure of mucins (Yan et al., 2004). However, few studies investigate the influence of interactions between the chain entanglement of polymer and mucins on oral lubrication. We believe that investigating the chain behavior of polymers plays a very important role in controlling interfacial friction, and it inspires us to design the structure of polymers with good lubricity.

- The development of artificial saliva and functional foods may be further improved by taking into consideration different oral conditions, including the presence or absence of a pre-absorbed salivary film at interfaces. Lubricants that solely emulate salivary components may no longer meet the specific needs of patients as their relief time is short, and they can be easily rinsed away by food or drink. The residual mucins on oral surfaces are crucial to designing the next-generation commercial saliva to achieve effective and longer-lasting lubrication.

- Most current studies on oral lubrication use SiO_2 or PDMS substrates, and even pig tongue to mimic the geometry and topography of the human tongue. Linking data *in vitro* from tribological experiments with the data in the human oral cavity *in vivo* may difficult due to the presence of pre-absorbed mucins and the papillated surface on the tongue (Andablo-Reyes et al., 2020). Additionally, tongue surface varies with the oral environment. For instance, patients with different degrees of dry mouth syndrome have varying amounts of papillae, mucin content, and water-holding capacity. It is hard to emulate their tongue surface to investigate oral lubrication. There is still a challenge to design a triboelectric electronic tongue and even a bio-mimicked sensor with natural human characteristics (such as lubricity, papillae height and density) in the field of tribology and biomedical applications (Han et al., 2022; Zhang et al., 2016).

- Numerous studies have demonstrated that physical, chemical, and physiological modifications can alleviate the sensation of dryness and enhance oral lubrication. However, those modifications primarily focus on the theoretical aspects of lubrication and lack clinical data to support the key concepts. There is an urgent need to connect theoretical concepts with real-world applications by investigating the actual effectiveness of these modifications in patients with xerostomia or dry mouth syndrome.

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