

## Chemical And Physical Evaluation Of Herbal Artificial Saliva Formulations-Scoping Review

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### ABSTRACT

Saliva plays an important role in physiological function. Alteration in saliva production results in serious health problems that affect patient oral health-related quality of life (OHRQoL). the purpose of the research was to investigate the chemical and physical evaluation of natural artificial saliva formulations. Methods, the data synthesis protocol for a rapid review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol (PRISMA-P). Electronic databases were searched on articles published in 2004-2024. evaluating Chemical and physical properties of herbal artificial saliva formulations in preclinical study. Results, Identification from the Science Direct and PubMed databases obtained 332 scientific articles and 3 articles met inclusion criteria. *Basella alba* Linn. (Ceylon Spinach mucilage) shows non-Newtonian characteristic fluid, similar to normal human saliva. It has antioxidative activity, adhesion inhibition, and non-toxic. *Propolis* extract and *Aloe vera* extract showed minimal effect on viscoelastic properties but were still in the range of normal human saliva. *Dioscorea batatas* (Yam tuber mucilage) viscosity shows non-Newtonian characteristic fluid and antibacterial activity by influenced the enzymatic activity of lysozyme and peroxidase. Conclusion, Chemical and physiological evaluation shows that herbal plant extract has the potential to be used as an artificial saliva constituent. It had a viscosity in the range of normal human saliva with several advantages in terms of pharmacological activity.

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## INTRODUCTION

Saliva plays important roles in oral cavity, such as speaking, swallowing, cleansing, buffering, lubrication, remineralization, and antimicrobial activity. (Alhejoury et al., 2021; Sharma, Samanta, Guha, & Mishra, 2023) Saliva production is affected by various factors such as emotional conditions (upset, stress, and anxiety), salivary gland dysfunction, aging, systemic disease, medication, chemotherapy, and radiotherapy. Reduced saliva secretion causes serious health problems like altered taste and smell, ingestion, tooth caries, and burning tongue. (Lysik, Niemirowicz-Laskowska, Bucki, Tokajuk, & Mystkowska, 2019) The average

daily flow of total saliva is approximately 1 to 1.5 L. A decrease in salivary flow rate, less than 0.1 mL per minute in resting saliva and 0.5-0.7 mL per minute in stimulated saliva, caused hyposalivation. (Lysik et al., 2019) The chronic decrease in salivary secretion (hyposalivation) that causes dry mouth is called xerostomia, that is the subjective complaint of dry mouth associated with quantitative and qualitative changes in saliva. (Piaton, Duconseille, Roger-Leroi, & Hennequin, 2021; Wan, Vissink, & Sharma, 2020) Around 25 % of the elderly experience xerostomia. (Vinke, Kaper, Vissink, & Sharma, 2020) Xerostomia could lead to caries and mucosal infection affecting patient oral health-related quality of life (OHRQoL). (Purdie et al., 2023)

Generally, symptomatic therapy for xerostomia is artificial saliva which can provide adequate hydration, lubrication, and viscosity similar to natural saliva, relieving discomfort in the mouth. (See, Mohammadi, Han, Mulligan, & Enciso, 2019) A previous study concluded that artificial saliva reduces the symptoms of dry mouth in xerostomia patients significantly. (Ingle, 2020; Marimuthu, Han, Mohamad, & Azman, 2021; Vinke et al., 2020)

Artificial saliva must be chemically and physically similar to normal human saliva. (Alhejoury et al., 2021) Artificial saliva composition generally contains rheological modifiers, electrolytes, preservatives, and sweeteners. Rheological modifiers include xanthan gum, guar gum, carboxymethyl cellulose (CMC) and glycerol. Rheological and lubricating properties are important in tissue protection, speech, and swallowing. (Lysik et al., 2019) Besides that, the protective ability of artificial saliva must be considered such as antimicrobial properties and re-mineralizing properties. In the oral cavity, more than 700 species of bacteria have been identified. (Deo & Deshmukh, 2017) However, commercially available artificial saliva doesn't inhibit the adhesion of bacteria. (Lysik et al., 2019) Re-mineralizing properties in the artificial saliva are also important. The oral cavity is in a constant cycle of demineralisation and remineralisation. Saliva contains essential ions that can promote enamel remineralisation. Consequently reducing in saliva volume affects this function. (Farooq & Bugshan, 2020) Furthermore, several artificial saliva contain very low PH due to citric acid content, which increases the potential risk of enamel erosion. (Aykut-Yetkiner, Wiegand, & Attin, 2014). A recent study shows artificial saliva containing herbal substances is promising but there is limited data on the effectiveness of these preparations. (Bugarin-Castillo et al., 2024) Therefore the main purpose of this study was to investigate the chemical and physical evaluation of natural artificial saliva formulations.

## METHODS

The data synthesis protocol for the rapid review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol (PRISMA-P) guidelines. (Moher et al., 2015)

### Study selection Criteria

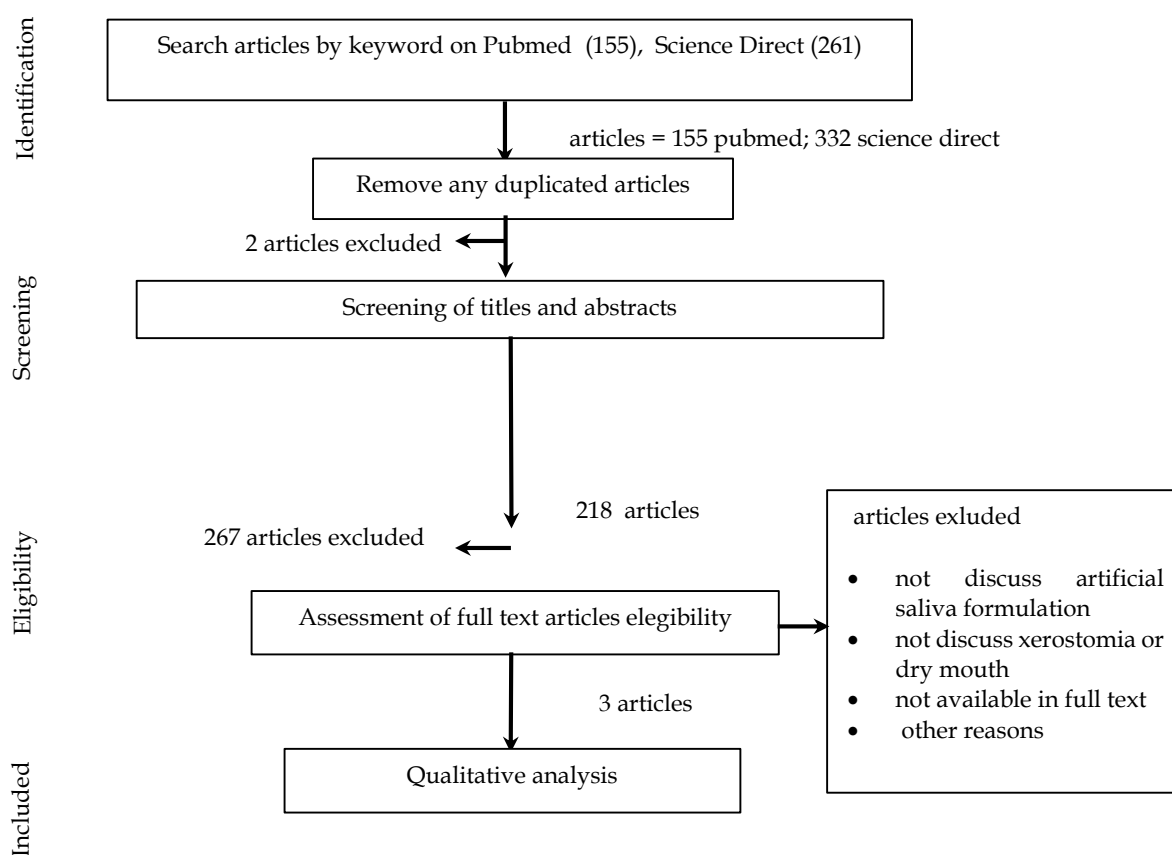
The question was formulated following the PICO protocol : (Roever, 2018). Population, herbal artificial saliva formulation. Interventions, Chemical and physical assessment of herbal artificial saliva formulations. Control, Placebo or other artificial saliva. Outcomes, Chemical and physical evaluation results of natural artificial saliva formulations.

### Literature search strategy

A systematic search of the scientific literature was conducted using Science Direct and PubMed database using Boolean operators and keywords ((artificial saliva or saliva artificial or saliva substitutes) AND (xerostomia or dry mouth)) AND (natural or herbal or extract). Inclusion criteria were articles published in 2004- 2024, available in full text, preclinical study, clinical study, and published in English. Criteria for exclusion were: articles with off-topics, and reviewed articles.

## RESULTS AND DISCUSSION

Identification from the Science Direct and PubMed databases obtained 332 scientific articles. The following extraction process by PRISMA method screening obtained 3 article match with defined criteria and enter entered the qualitative data synthesis stage. The selected articles were analyze using a narrative approach. The research process is outlines in Figure 1.



**Figure 1** Flowchart of article search based on the PRISMA method(Fracasso et al., 2023)

The extracted articles were briefly shown in Table 1.

**Table 1** The Results of chemical and physical evaluation from Selected Article

No	Author	Natural Source	Formulation	Result	Important Result (conclusions)
1	Manosroi, et al., 2020(Manosroi et al., 2020)	<i>Basella alba</i> Linn. (Ceylon Spinach mucilage)  Natural human saliva (standard)	Ceylon Spinach mucilage, CaCl <sub>2</sub> ·2H <sub>2</sub> O, KCl, Na <sub>2</sub> HPO <sub>4</sub> , NaH <sub>2</sub> PO <sub>4</sub> ·H <sub>2</sub> O, NaF, paraben	non-Newtonian pseudoplastic flow (8.9 ± 0.2 cP), the viscosity decreased with increased shear rate, the wetting time (12.50 ± 2.24 min) similar to the normal human saliva, antioxidative activity, adhesion inhibition, non-toxic	<i>Ceylon Spinach</i> mucilage artificial saliva formulation show non-Newtonian flow and has the potency to be used as artificial saliva.
2	Srisomboon, et al.(Srisomboon, Intharah, Jarujareet, Toneluck, & Panpisut, 2024)	propolis extract aloe vera extract Biotene Oral Rinse (standard)	propolis extract 5% / aloe vera extract 5% / combination of propolis extract 2.5% + aloe vera extract 2.5%, Methyl-p-hydroxybenzoate, MgCl <sub>2</sub> ·6H <sub>2</sub> O, CaCl <sub>2</sub> ·2H <sub>2</sub> O, KCl, K <sub>2</sub> HPO <sub>4</sub> , KH <sub>2</sub> PO <sub>4</sub> , Sodium carboxymethyl cellulose	The viscosity of extract formulation is lower than standard, Propolis (5.24±0.05 mPa.s), aloe vera (4.46±0.03 mPa.s), Propolis+ aloe vera (4.77±0.09 mPa.s), Biotene (13.45±0.03 mPa.s) All formulations showed viscoelastic properties of natural saliva, the saliva substitute containing propolis extract demonstrated superior remineralizing actions.	The propolis and aloe vera extracts increased the viscosity of the artificial saliva. The viscosity lower than that of the commercial formulation but still within the range of normal human saliva

No	Author	Natural Source	Formulation	Result	Important Result (conclusions)
3	Kho et al(Kho, Park, Chang, & Kim, 2014)	<i>Dioscorea batatas</i> (Yam tuber mucilage/YTM)	<i>Dioscorea batatas</i> muchilago, 0.021 M Na <sub>2</sub> HPO <sub>4</sub> / NaH <sub>2</sub> PO <sub>4</sub> , pH 7.0, containing 36 mM NaCl and 0.96 mM CaCl <sub>2</sub>	The viscosity values of YTM showed a non-Newtonian fluid. YTM influence on the enzymatic activity of lysozyme or peroxidase	YTM artificial saliva formulation has viscoelastic characteristic similar to human saliva and enhances the enzymatic activity of lysozyme on hydroxyapatite surfaces.

1 cP=1 mPa.s

The chemical and physical properties of artificial saliva should be as close as possible to normal human saliva such as lubricating properties, mucoadhesive function, tissue protection, speech, and swallowing (Alhejoury et al., 2021; Foglio-, 2018). Rheological characteristics such as viscosity and viscoelasticity, are important in assessing whether artificial saliva mimics the properties of normal human saliva. (Farinone, Foglio Bonda, Foglio-Bonda, & Pattarino, 2018). Saliva is a non-Newtonian fluid, which means that its viscosity varies with shear rate. (Lysik et al., 2019) Viscoelasticity shows an indirect behaviour between a viscous solution and an elastic solid. The sticky consistency/viscosity of normal saliva shows that it is a non-Newtonian fluid. At a shear rate of about 0.1-1 litre/s (resting saliva), the viscosity of saliva is much greater than the viscosity during chewing and speaking at shear rates of about 60 and 160 litre/s. This dependence of viscosity on shear rate is called pseudoplasticity and is essential for normal function. (Alhejoury et al., 2021)

Artificial saliva formulations generally consist of rheological modifiers such as hydroxyethyl cellulose, CMC, sodium carboxymethyl cellulose (SCMC) and as thickening and lubricating agents.(Manosroi et al., 2020) However, they have a greater viscosity than normal human saliva. Therefore novel artificial saliva uses mucin or xanthan guar gum as a thickening agent which have non-Newtonian pseudoplastic flow and closer physicochemical properties to human normal saliva.(Alhejoury et al., 2021) Several plants contain mucilage that can be used as an alternative thickening, moisturising and lubricating agent in artificial saliva formulations. They also have bioactive compounds with potential pharmacological activity as an advantage.(Manosroi et al., 2020)

*Basella alba Linn* exhibited viscosity and rheological properties comparable to those of natural human saliva, a non-Newtonian pseudoplastic fluid that represents a crucial physical attribute of human saliva. The optimal artificial saliva formulation demonstrated a viscosity of  $8.9 \pm 0.2$  cP, closely approximating the viscosity of natural human saliva ( $9.0 \pm 0.1$  cP). Additionally, the viscosity exhibited a decline with increasing shear rate, a phenomenon observed in human saliva.(Marcinkowska-Gapińska, Linkowska-Świdzińska, Świdziński, &

Surdacka, 2018; Wagner & McKinley, 2017) Indicating the non-Newtonian pseudoplastic flow of the formulation which is the same as the natural saliva. The wetting time of the artificial saliva formulation mucilage derived from Ceylon spinach ( $12.50 \pm 2.24$  minutes) was comparable to the normal human saliva ( $10.87 \pm 1.79$  minutes). It plays an essential role in the oral cavity. Saliva has significant importance in the protection of oral tissue, the facilitation of speech, and the act of eating. (Alhejoury et al., 2021) The food that can be wet in a few minutes will facilitate chewing and swelling. A shorter wetting time can enhance food swallowing in patients with xerostomia and hyposalivation. The mucilage from Ceylon Spinach possesses an antioxidant activity that is suspected to come from the flavonoid content in the plant. Moreover, the mucilage from Ceylon Spinach inhibits *S. mutans* adhesion on the tooth surface which could prevent dental caries. (Manosroi et al., 2020)

Propolis extract and aloe vera extract artificial saliva formulation gave the viscosity range from 4.46-5.24. It is still in the human saliva viscosity range (2.75 mPa.s - 15.51 mPa.s) although under Biotene viscosity (13.63) as standard. However, none of the formulations showed viscosity reduction in increased shear rate thus showing the absence of non-Newtonian behavior. CMC in the formulation was Newtonian fluid which has a greater viscosity (sticky consistency) than normal human saliva and also from other saliva substituents such as carbomer, hydroxyethyl cellulose, and mucin. (Farinone et al., 2018; Foglio-Bonda, Foglio-Bonda, Bottini, Pezzotti, & Migliario, 2022) Therefore to enhance the rheological properties, novel artificial saliva formulations use mucin or xanthan guar gum as a thickening agent which has non-Newtonian pseudoplastic flow and closer physicochemical properties to human normal saliva. (Alhejoury et al., 2021) Moreover, mucin provided greater comfort and longer post-application effectivity. (Austin et al., 2024)

The propolis formulation was demonstrated to enhance dentin remineralization. The activity proposed provides evidence that flavonoid content in propolis may reduce demineralisation and promote remineralisation of dentin. (Srisomboon et al., 2024) Propolis enhances enamel microhardness levels and promotes remineralization. (Ali et al., 2021; Anani, Elasser, Niazy, Jamil, & Elsharkawy, 2023). YTM may be considered a suitable substitute for saliva, given its physical and biological properties. The viscosity values were found to be very similar to those of human saliva. Furthermore, YTM has been demonstrated to enhance lysozyme activity. Lysozyme and peroxidase are widely distributed in various biological fluids, including saliva, which had antibacterial activity. YTM in artificial saliva formulation will provide antibacterial activity in salivary hypofunction patient. (Kho et al., 2014)

## CONCLUSION

Chemical and physiological evaluation shows that herbal plant extract has the potential to be used as an artificial saliva constituent. It had viscosity within the range of normal human saliva with several pharmacological activity advantages.

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