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Review Article

Effect of high-pressure steam sterilization on the stability of medicine and food homology oral liquid: from the perspective of chemical composition and physical phase

Xiao-Rong Wei[1,†], Jun Tang[1,†], Guo-Tao Xue[1], Fang-Yu Xiang[1], Ding-Kun Zhang[1,2], Meng-Qi Li[3], San-Hu Fan[4], Tai-Gang Mo[4], Jun-Zhi Lin[5] (✉), Hao-Zhou Huang[6] (✉), Li Han[1] (✉)

[1] State Key Laboratory of Southwestern Chinese Medicine Resources, Pharmacy School, Chengdu University of Traditional Chinese Medicine, Chengdu 611137, China
[2] Sichuan Provincial Engineering Research Center of Innovative Re-development of Famous Classical Formulas, Tianfu TCM Innovation Harbour, Chengdu University of Traditional Chinese Medicine, Pengzhou 611900, China
[3] Pharmacy department, Sichuan Nursing Vocational College, Chengdu 610100, China
[4] Sanajon Pharmaceutical Group, Chengdu 610000, China
[5] TCM Regulating Metabolic Diseases Key Laboratory of Sichuan Province, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu 610072, China
[6] State key Laboratory of Southwestern Chinese Medicine Resources, Innovative Institute of Chinese Medicine and Pharmacy, Chengdu University of Traditional Chinese Medicine, Chengdu 611137, China
[†] Xiao-Rong Wei and Jun Tang contributed equally to this work.

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Abstract: Oral liquid has the advantages of large drug loading, simple preparation and rapid effect. The substances of medicine and food homology (SMFH) are mostly developed into the form of oral liquid and prepared by high-temperature steam sterilization (HPSS). However, due to the complex composition of the solution, it is easy to be affected by HPSS and produce a series of unstable phenomena, which has become the key to hinder the development of the medicine and food homology oral liquid (MFHOL). Based on the characteristics of HPSS, this paper analyzed the chemical composition and physical phase interaction in the solution, discussed the mechanism and influencing factors of MFHOL instability induced by this method, as well as put forward feasible future solutions. Through the analysis and summary of the literature on oral liquid instability, it was found that HPSS can cause dramatic changes in the chemical composition of MFHOL, lead to changes of the physical phase, as well as produce a series of chain reactions, which seriously affect its stability. At the same time, this paper introduced the new sterilization technology that can be applied to the production of MFHOL in the future, put forward the personalized sterilization program and the establishment of intelligent continuous sterilization system according to the characteristics of SMFH. So as to provide the corresponding theoretical basis for the efficient and reasonable sterilization of MFHOL, in order to promote its further development.

Keywords: medicine and food homology; oral liquid; stability; high-pressure steam sterilization; phase state; physical and chemical properties

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Introduction

Amidst the burgeoning global sub-healthy population, the awareness of health through diet is increasing, and the employment of dietary therapy as an alternative to pharmacotherapy for the prevention and treatment of diseases presents extensive application potential. The evolution of the dietary therapy concept has a rich historical lineage, with its earliest documentation in the Yellow Emperor Canon of Internal Medicine (Huang Di Nei Jing) over three millennia ago in China: "Grains, meats, fruits and vegetables, all are nourishments; without errors, one upholds righteousness", which is the earliest principle of dietary therapy[1]. In the Western tradition, its origins can be traced to the era of Hippocrates (circa 460–370 BC), who proposed the philosophy that 'medicine resembles food, and food resembles medicine'[2]. As the era progresses, the U.S. Food and Drug Administration and the Japanese Ministry of Health, Labour and Welfare have also endorsed the concepts of 'food as

Address correspondence to Jun-Zhi Lin, 582097013@qq.com; Hao-Zhou Huang, 1539889839@qq.com; Li Han, hanliyx@163.com

therapeutic' and 'medicine and food integration', with the goal of utilizing functional foods to modulate physiological states. In addition, India, South Korea, Thailand and other countries also have a long history of homologous culture of medicine and food, and have had a certain impact on modern health awareness, especially Indian Ayurvedic medicine, which pays special attention to the balance effect of medicine/food on the human body[2]. It has been predicted that by the year 2028, the market for health foods, encompassing medicine and food homology products, will expand to a valuation of 3,885.4 billion yuan, signifying a vast application landscape[3].

The SMFH are frequently developed into the application form of oral liquid, favored by consumers for their palatability and significant therapeutic effects. Statistically, at present, a total of 79 types of SMFH in the homologous catalogue of medicine and food issued and periodically updated by the Chinese Health Commission have been developed into a diverse range of oral liquids[4-6], including Ganoderma lucidum, ginseng, Sanlejiang, and American ginseng oral liquids, with an average annual market sales reaching billions[7]. These MFHOL serve not only to enhance cognition, combat fatigue, reduce lipid levels, and regulate blood sugar, but also to bolster immunity and significantly contribute to the prevention and treatment of numerous diseases.

Currently, the predominant method for sterilizing oral liquid is HPSS, because the steam possesses a higher heat capacity and strong penetrating ability, making it suitable for the sterilization of solid, semi-solid, and liquid preparations[8], which can effectively kill a variety of microorganisms and their spores, and with its simple, easy-to-operate, and low-cost equipment, it is widely adopted in the pharmaceutical industry for liquid preparation sterilization[9]. However, due to the instability of the chemical composition and the complexity of the phase state in the MFHOL, the unstable phenomenon of clarity reduction precipitation and stratification often occurs after HPSS, which has become an obstacle restricting its development. The composition of MFHOL is complex, including polysaccharides, flavonoids, saponins, quinones and alkaloids etc.[10]. These components form complex phase states in the solution, and high-temperature processing can induce transformations in these components and their phase states. For instance, the hydrolysis of corilagin and chebulagic acid at high temperature produces ellagic acid precipitation[11]. Furthermore, due to the increase of temperature, the association colloid in the polyphenol oral solution ages and precipitates[12]. Currently, due to the lack of understanding of the clarity change of these SMFH under HPSS, the clarity problem of MFHOL after HPSS always exists and is difficult to solve, which has become a bottleneck problem in the development of such products.

This paper reviewed instability phenomenon, mechanism and influencing factors caused by HPSS technology on MFHOL, as well as the influence of this sterilization on the current new delivery system. Combined with the composition of SMFH, this paper discussed more advanced and reliable sterilization methods in the industrial production of MFHOL, as well as the future application potential and scenarios. This provides a reference for the industrial application and development of oral liquid sterilization technology for the MFHOL

1 Current research on the influence of HPSS on the stability of MFHOL

HPSS currently serves as the predominant method for sterilizing oral liquid products, but it can result in the degradation of certain bioactive components and alterations in the appearance of the final product at high temperatures, which can adversely affect the quality and therapeutic efficacy of the oral liquid (Fig. 1). Hence, it is imperative to elucidate the mechanisms underlying the influence of the prevalent HPSS on the stability of oral liquid formulations, to ensure effective sterilization without compromising the integrity of active constituents and preserving the clarity of the liquid.

1.1 Effect of HPSS on the physical stability of MFHOL

Under high-temperature conditions during HPSS, droplet speed accelerates, and collision frequency increases, so that the droplet will continue to coalescence, resulting in unstable phenomena such as flocculation, coalescence and even emulsion breaking. In addition, with increased emulsion storage time, the Zeta potential decreases, reducing electrostatic repulsion and causing droplet agglomeration, which affects emulsion stability and diminishes the flavor and efficacy of the medicinal and food oral liquid[13]. Almond beverages are oil-in-water emulsions. Following high-temperature sterilization, particles within the beverages undergo flocculation, leading to precipitation and subsequently separating from the continuous phase. As storage time extends, the extent of precipitation increases compared to initial levels, indicating a decline in emulsion stability over time[14]. Walnut-based emulsions, inherently thermodynamically unstable, show an increase in droplet particle size with rising sterilization temperature, leading to decreased emulsion stability. Exceeding the walnut protein denaturation temperature of 67.5 °C, extended sterilization time results in significant denaturation of walnut protein, leading to precipitation, color change, and other signs of emulsion instability. These changes can critically affect the quality and acceptability of walnut-based emulsions[15].

Elevated temperature enhances the Brownian motion of particles within the suspension and decreases its viscosity. According to Stokes' Law, the stability of the suspension will be reduced, leading to flocculation and precipitation. In addition, high temperatures may destroy the hydration film, diminishing particle repulsion and promoting agglomeration. The ellagic acid precipitation in Sanlejiang oral liquid increases with temperature because high temperatures undermine the protective effect of polyphenol associations on ellagic acid, leading to precipitation. Meanwhile, high temperatures will reduce its Zeta potential and liquid viscosity, contributing to decreased stability and precipitation[16]. HPSS can increase the size of ginkgo biloba beverage, potentially due to protein denaturation and carbohydrate aggregation under high temperatures. In the process of sterilization of ginkgo biloba beverage, it was found that the Zeta potential of the beverage decreased while the fluidity increased and the viscosity decreased. Large particle size and low viscosity can compromise solution stability, leading to particle accumulation and precipitation. Therefore, HPSS will reduce the physical stability of ginkgo biloba beverage[17].

Mulberry is rich in functional components such as anthocyanin, polyphenol and polysaccharide, which have good antioxidants and hypoglycemic effects. Studies have shown that temperature will have a significant impact on the degradation of anthocyanin, which will lead to the change of color of the oral liquid containing anthocyanin. With the increase of temperatures, the stable xanthine ion in the solution will be transformed into the chalcones structure. The color of the accelerated anthocyanin faded, and the red color of the solution became significantly lighter[18, 19]. Therefore, the oral liquid containing such ingredients

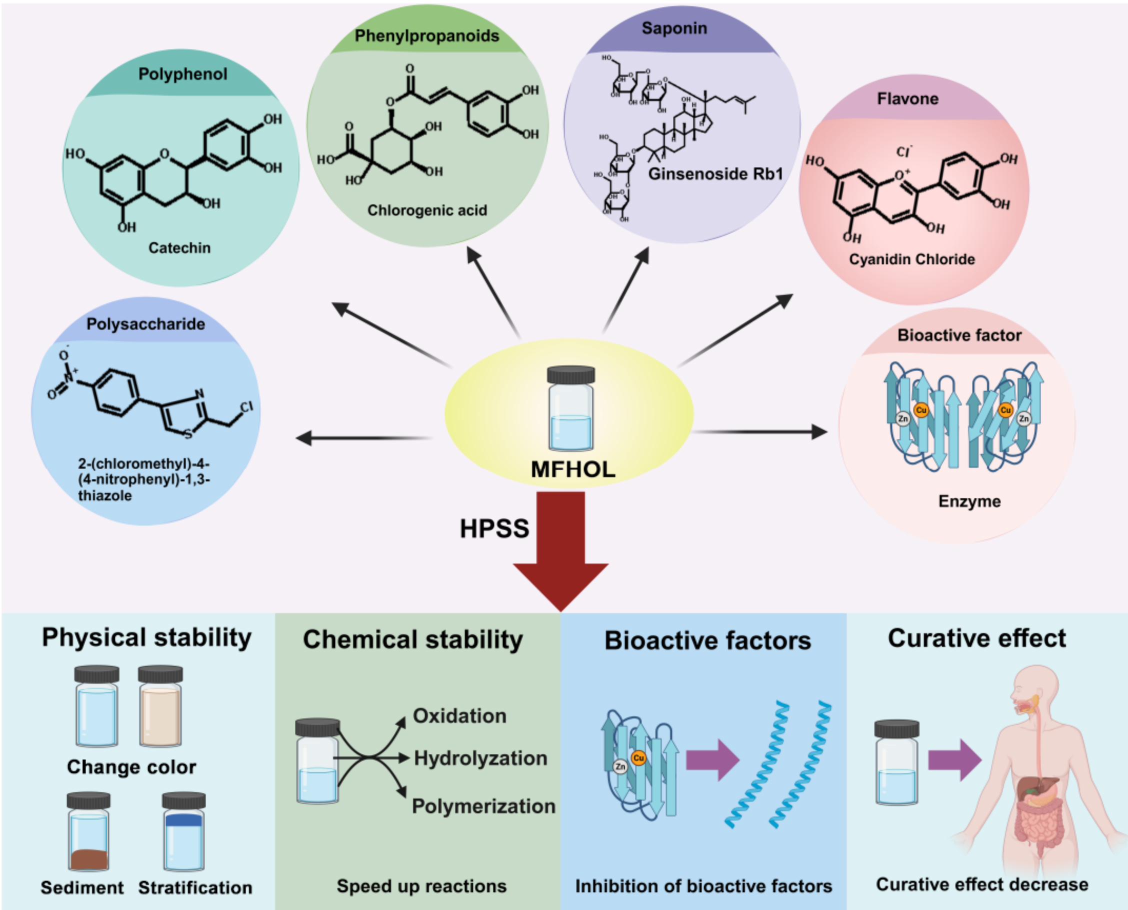

Figure 1 Effect of HPSS on the instability of MFHOL. "Created in BioRender.com".

should choose a low temperature sterilization method to prevent the reduction of the active ingredient content, while not affecting the appearance of the oral liquid.

1.2 Effect of HPSS on the chemical stability of MFHOL

High temperatures will cause hydrolysis, oxidation, degradation and polymerization of chemical components including flavonoids, phenylpropanoids, terpenoids and tannins in the MFHOL (Fig. 2, Table 1). These reactions result in alterations in the oral liquid's color, flavor, and precipitation, as well as a reduction in the content of bioactive compounds, and other manifestations of chemical instability, leading to a degradation in the oral liquid's quality.

At elevated temperatures, the anthocyanin within flavonoids exhibits instability and undergoes hydrolysis, leading to various chemical transformations. Initially, the C3 glycoside of anthocyanin is hydrolyzed, followed by hydration of the anthocyanin aglycones to form a pseudobase, which subsequently isomerizes into chalcone and its diketone isomer. Another possible pathway is that the pseudobase glucoside is formed first, and then the ring is opened to produce chalcone glycoside, and the glycoside is subsequently removed, and finally chalcone and its isomer dione are formed (Fig. 2A). Ultimately, these compounds further degrade into phenolic acids and aldehydes[20,21]. Phenylpropanoid chlorogenic acid is lactone synthesized through the polymerization of caffeic acid and quinic acid, both of which contain ester bonds. The ester hydrolysis will produce caffeic acid and quinic acid under high temperature conditions, reducing chlorogenic acid content[22].

1.3 Effect of HPSS on the bioactive factor of MFHOL

SMFH are usually rich in proteins, amino acids, enzymes and other bioactive factors. These bioactive factors play an important role in maintaining human health and promoting disease recovery. However, these active components may lose their activity under high temperature conditions, thus affecting the nutritional value and medicinal effect of the medical-food homologous substances.

Enzymes are a class of proteins with catalytic activity. They play a crucial role in the body of living organisms to promote the progress of various biochemical reactions. The activity of enzymes depends on their specific 3D structure, which is usually very fine and sensitive to environmental changes. When enzymes are exposed to high temperature steam sterilization, they undergo a series of structural and functional changes. In the process of sterilization, high temperatures and high pressures can destroy the three-dimensional structure of the enzyme, resulting in the reduction or loss of its catalytic activity. Enzymes, as biocatalysts, are highly sensitive to environmental conditions, with their activity and stability being readily influenced by factors including temperature, pressure, and pH (Table 2). The catalytic action of polyphenol oxidase (PPO) can have a significant impact on the quality of fruits and vegetables, causing alterations in color, flavor, texture, and nutritional value. Browning caused by this reaction can degrade the sensory quality of the food. Consequently, the food industry employs heat treatment to suppress enzyme activity during production and processing, but this will also cause the destruction of other thermal unstable ingredients and affect the

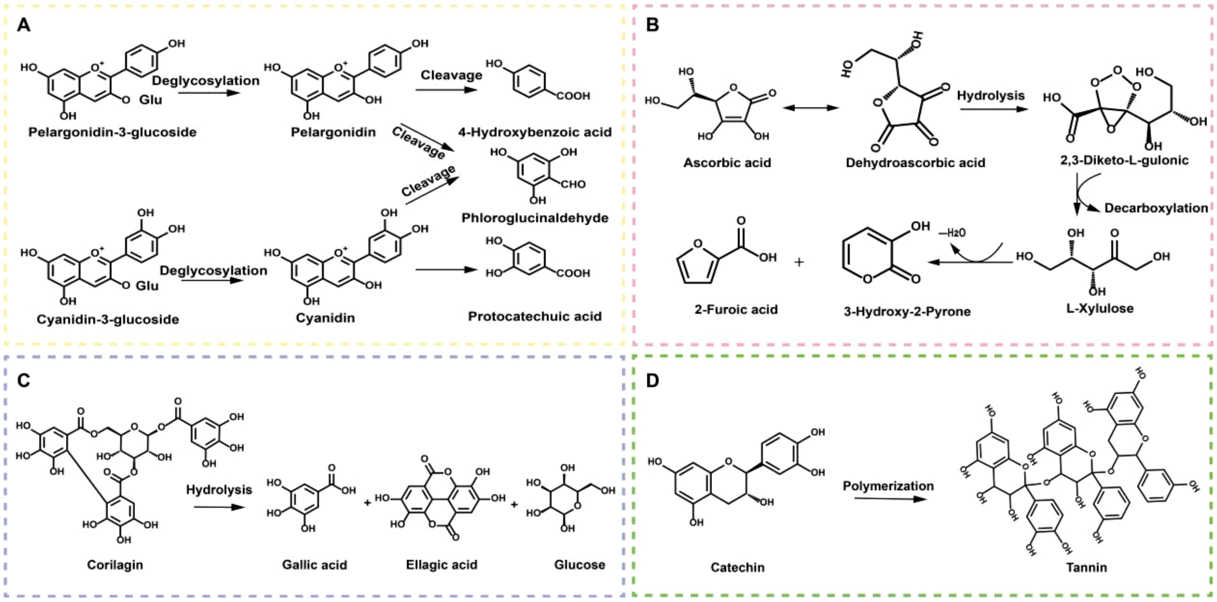

Figure 2 Biochemical reactions of different types of components under high temperatures: (A) Anthocyanin degradation, (B) Vitamin C oxidation, (C) Corragine hydrolysis, (D) Catechin condensation.

Table 1 Unstable components and their mechanisms at high temperatures.

Type of ingredient	Representative ingredient	Source	The instability mechanism at high temperatures	Reference
Polysaccharide	Astragalus polysaccharide Lycium barbarum polysaccharides Angelica polysaccharide	*Astragalus* *Lycium barbarum* *Angelica sinensis*	Under the condition of high temperatures, the branch chain of sugar in polysaccharide is reduced, the structure of polysaccharide is destroyed, the polysaccharide molecules are easy to aggregate, and the activity is reduced.	[23-27]
Flavonoid	Anthocyanin Rutin	*Fructus, Mori, Lycium barbarum* *Ginkgo leaf, Hawthorn*	Flavonoid compounds mostly contain unstable double bonds, which are easy to react under the action of high temperatures, double bond breakage, degradation, oxidation, etc.	[22, 28, 29]
Phenylpropanoids	Chlorogenic acid	*Honeysuckle*	Chlorogenic acid molecules contain ester bonds, which can be hydrolyzed to produce caffeic acid and quinic acid under high temperature conditions, reducing the content of chlorogenic acid.	[30]
Saponins	Ginsenoside Gypenosides	*Ginseng, Notoginseng, American ginseng* *Gynostemma pentaphylla*	After high temperatures treatment, the saponins will undergo thermal hydrolysis, resulting in glycoside bond cleavage and side chain isomerization.	[31, 32]
Terpenoids	Volatile oil	*Amomum, Mint, Patchouli, Perilla*	Olyunsaturated bond, unsaturated bond fracture, epoxidation and dehydrogenation will occur at high temperatures, higher temperatures will also cause free radicals to form in the oxidation reaction initiation stage, accelerate the autoxidation reaction.	[33]
Polyphenols	Catechin Chebulagic acid, Corilatin	*Phyllanthus emblica* *Myrobalan*	Many unsaturated bonds, unsaturated bonds will be broken at high temperatures, hydrolysis, oxidation and other reactions.	[15, 34, 35]
Alkaloids	Dandelion alkaloids	*Dandelion*	According to the study, the extraction efficiency of dandelion alkaloid at 55 °C is reduced, which may be caused by the structure of the alkaloid being destroyed at high temperatures.	[36]

quality of food[37]. Superoxide Dismutase (SOD), a kind of antioxidant metal enzyme widely existing in living organisms, known for its antioxidant and anti-aging effects. High temperature treatment can reduce the content of vitamin C and SOD in kiwifruit juice, resulting in the weakening of the antioxidant capacity of the juice, which will have a greater impact on the color of the juice[38]. It was found that lipoxygenase (LOX), hydroperoxide lyase (HPL), Pectin methylesterase (PME) and ethanol dehydrogenase (ADH) were inhibited during the process of high temperature sterilization, which resulted in the reduction of the synthesis of C6 aldehyde volatile compounds, and the flavor of red raspberry juice was seriously reduced[39].

Wang[40] and Polis *et al.*[41] studied the changes in amino acid content of different dates during drying at different high temperatures, and the results showed that when the drying temperature was 140~150 °C, it showed a trend of first decreasing and then increasing with time, which was mainly related to the Maillard reaction occurring in the heating process and the pyolysis of the proteins in the dates[42], After the drying temperature reaches 140 °C, the essential, medicinal, umami, bitter and salty amino acid contents will rapidly increase with the extension of drying time. However, the content of sweet amino acids mainly showed a decreasing trend during the whole heating process, and the higher the drying temperatures, the faster the decreasing rate[43], flavor free amino acids are important substances to express food flavor. Different amino acids can express salty, bitter, sweet

Table 2 Effect of high pressure or high temperature treatment on biological stability (effects on enzyme activity)

Processing method	Process objects	Enzymes	Impact	Unstable results	Reference
Ultra high-pressure homogeneous sterilization (100MPa)	Carrot juice	PME	Pectin side chain exposure, and the gelling ability of pectin were enhanced	Protein aggregation, and juice viscosity increased	[45]
Ultra-high pressure and high temperature instant sterilization	Watermelon juice	PME, PPO	It acts on the carboxyl group of pectin galacturonic acid residue C6 and degrades pectin		[46]
Heat treatment (70 °C, 30 min)	Tea leaf	PPO	The enzyme activity is almost lost		[47]
Heat treatment (90 °C, 1min)	Sea buckthorn juice	PPO	PPO was inactivated and enzymatic Browning reaction was inhibited	The value of L* increased, the contents of total phenol, total flavone and vitamin C decreased. DPPH free radical scavenging ability decreased	[48]
Ultra-high pressure sterilization, pasteurization	Mulberry juice	α-glucosidase	Hot pasteurization inhibits α-glucosidase activity		[49]
Heat treatment	Apple juice	PPO	Promote the interaction between protein molecules, induce the aggregation of molecules to form large particles,and lead to the aggregation of small molecules and the depolymerization of large molecules	High temperatures cause the catalytic center to collapse, and protein aggregation results in the inactivation of PPO	[50]
Heat treatment	Orange juice	Peroxidase, PME	After treatment at ≥ 42 °C for 12S, peroxidase activity decreased to less than 4.3% in fresh orange juice. After heat treatment at 72 °C, PME was deactivated by more than 84% and even 90%		[51]
High pressure-thermal processing	Pear	Peroxidase, PME, PPO	It was almost completely inactivated after treatment at 100 °C for 3 min		[52]

and umami taste respectively. Therefore, high temperature sterilization will cause certain adverse effects on the flavor of jujube, or give it a unique flavor[44].

Therefore, in the production process of MFHOL, the conditions of HPSS must be considered comprehensively to balance the relationship between sterilization effect and oral liquid's bioactive factor protection.

1.4 Effect of HPSS on the curative effect of MFHOL

HPSS is a widely used method to ensure the microbiological safety of pharmaceutical products, including oral liquids. This process involves the use of steam at high temperatures and pressures to achieve sterility, which is essential to prevent the spread of pathogens and ensure product safety. However, the application of high temperature steam sterilization of oral solutions can have a significant impact on their therapeutic efficacy. A considerable number of components in SMFH are sensitive to heat, such as volatile oil, easily oxidized components and enzymes. Steam causes degradation and volatilization of such components. At the same time, some SMFH will be changed under high temperatures, resulting in reduced efficacy and even toxic side effects[8]. For example, thermal instability components such as certain vitamins, proteins, and antioxidants may be adversely affected by the high temperatures used in the sterilization process, thereby reducing the overall efficacy of the oral solution. Chlorogenic acid is an effective component of a variety of SMFH, which has good antioxidant activity. The reduction of content will directly affect the efficacy of MFHOL, and the antioxidant activity of oral liquid containing chlorogenic acid will be reduced[16]. The sterilization process may also affect the solubility of some drugs and may reduce the absorption rate of the drug in the GI tract after administration, which may lead to pharmacokinetic changes of the drug affecting its absorption, distribution, metabolism, and excretion. To mitigate these effects, sterilization parameters such as temperature, pressure, and time often need to be optimized in the process to achieve a balance between ensuring microbiological safety and preserving the quality and efficacy of the oral solution. Although essential to ensure the sterility of oral liquid products, HPSS can have a profound impact on the efficacy of oral liquid products due to the potential degradation of heat-sensitive components. Therefore, understanding the thermodynamic properties of SMFH and optimizing sterilization conditions are essential to maintain the desired therapeutic effects of oral solutions.

2 Analysis the unstable factors of MFHOL caused by HPSS

MFHOL is a complex system, which not only refers to its complex phase system, but also contains complex chemical composition. Under the influence of HPSS, the physical and chemical changes in the system will affect the stability of MFHOL, and one of the influencing factors will affect the whole system (Fig. 3). The chemical changes of main components such as oxidation, thermal degradation and thermal hydrolysis are often associated with the processing of MFHOL, which is one of the important reasons for the differences in chemical composition and function of oral liquid.

2.1 Physical change

2.1.1 *Physical phase*

Some MFHOL contain colloidal macromolecules. Free alkaloids, fat-soluble pigments, oils, and organic macromolecules in crude drugs frequently aggregate in water, forming colloidal systems[53]. The second law of thermodynamics dictates that homologous oral liquids possess dynamic stability yet are thermodynamically unstable. As ambient temperatures decrease, the Brownian motion of particles diminishes, leading to colloidal particle aggregation and subsequent precipitation and flocculation.

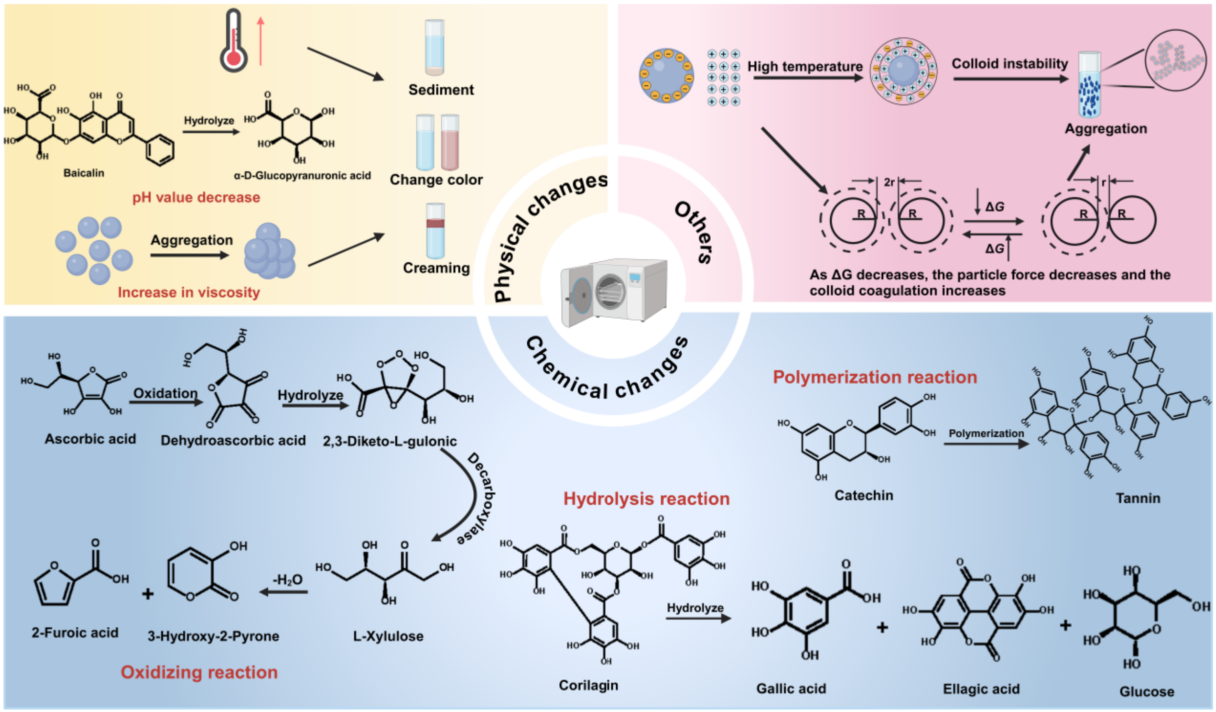

Figure 3 The instability mechanism of HPSS for MFHOL. "Created in BioRender.com".

This phenomenon is one reason for the precipitation observed in many oral liquids post-sterilization storage[54]. Colloids maintain stability over a specific duration and under defined conditions, related to osmotic pressure arising from the overlap of the electric double layers on colloidal particle surfaces within the same dispersion series, and the solvation of water molecules on the colloid surface, which prevents collisions and aggregation among colloidal molecules, as well as Brownian motion[55]. Due to the thermodynamic instability of colloidal solutions, particles tend to spontaneously aggregate into larger entities over time. At room temperature, colloidal particles struggle to overcome aggregation barriers, whereas high temperatures supply the necessary energy, leading to particle aggregation and precipitation. Colloidal dynamic stability arises from particle Brownian motion, with temperature increases accelerating this motion and promoting dispersion. However, intensified Brownian motion can also enhance particle collision and coalescence. If Brownian motion fails to counteract gravity, colloidal precipitation occurs[56,57].

Polyphenols possess a chemical structure with both hydrophobic and hydrophilic segments. In aqueous solutions, polyphenols self-assemble into associative colloids, exhibiting reversible binding, thus rendering the polyphenol solution a miscible system comprising both true solution and associative colloids. Solubilization of the associative colloid enlarges micelles through the aggregation of polyphenol molecules, preventing the collision and aggregation of ellagic acid molecules within the solution, thereby preventing precipitation formation. However, it is found that in the case of higher temperature and pH value, hydrogen bonds are destroyed, colloid instability will be caused, resulting in precipitation of precipitation[16,58]. In addition, some SMFH will also be developed into emulsions, suspensions, etc., because these dosage forms have higher bioavailability and faster absorption than conventional dosage forms. However, in the process of sterilization, with the increase of temperature in the system, the droplet size increases, breaking the balance of the initial phase system, it is difficult to maintain the original interface stability, and demulsification, flocculation and complete stratification will occur[59].

2.1.2 pH

Post-sterilization, the pH of most oral liquids decreases, causing precipitation of certain components[60]. pH alterations can diminish the clarity, solubility of chemical constituents, and alter the appearance of the oral liquid. For instance, increased alkalinity in oral liquids reduces alkaloid solubility, promoting precipitation; heightened acidity increases saponin precipitation. Studies indicate that the stability of water-soluble curcumin rises within a specific pH range; it is most stable at pH 3~7, exhibiting a lemon yellow color. Below pH 2, yellow precipitates form, while pH ≥ 8, the solution turns orange-yellow or reddish-brown[61,62]. Cyanidin exhibits high sensitivity to pH fluctuations, being more stable in acidic, low pH conditions compared to alkaline, high pH environments[63]. Baicalin undergoes partial hydrolysis to glucuronic acid under high temperature and alkaline conditions, increasing solution acidity, and is prone to oxidation to quinones, which can impart a green color[64]. Polyphenol solutions are colloidal in nature. Decreasing the pH enhances colloidal aggregation, increasing the likelihood of precipitation. Elevating the pH decreases the chemical stability of polyphenols[65]. Catechin molecules gradually polymerize into dimers and higher polymers in acidic conditions, reducing their water solubility and leading to precipitation[58]. Xie[66] found in the study of Silverflower oral liquid that with the increase of pH, the clarity and stability of the solution increased, however, the content of the chlorogenic acid decreased.

2.1.3 Solution viscosity

During autoclaving, the oral liquid is exposed to high temperatures. This high-temperature environment may have an effect on some components in the oral liquid, such as causing degradation or denaturation of certain components, which will affect the viscosity of the oral liquid, as elevated temperatures enhance the thermal motion of molecules within the oral liquid, this leads to altered intermolecular forces and, consequently, viscosity changes. Typically, the viscosity of polysaccharide-rich oral liquids decreases at high temperatures, as the thermal motion of polysaccharide molecules intensifies, causing the disruption of hydrogen bonds and other weak intermolecular forces, resulting in reduced solution viscosity. The viscosity of the emulsion also changes at high temperatures, resulting in instability of the emulsion. For soybean emulsion, the shear rate of the emulsion will increase under high temperature conditions, resulting in a decrease in the viscosity of the emulsion, so that small droplets will aggregate between each other to form large droplets, resulting in a decrease in the stability of the emulsion[67]. The molecular weight of pectin in hawthorn juice increased significantly after high pressure treatment. The molecular weight change may be due to the aggregation of pectin chains or the inactivation of pectin lyase, which prevented the break of glucoside bond, led to the increase of apparent viscosity of juice, and made the sensory quality of hawthorn juice better. It may also be related to the improvement of methyl hydrophobic water cooperation induced by high pressure. After heat treatment, the pectin of hawthorn juice showed a variety of structures such as linear structure, spherical particles and rod-like chain segments, and the distance between molecules widened, resulting in a decrease in viscosity[68].

2.1.4 Entropy change of solution

Moist heat sterilization is the most widely used sterilization method at present, but high temperatures in the sterilization process will lead to a large loss of volatile and heat-sensitive components in oral liquid. According to the empirical law of VantHoff, the reaction rate increases about 2-4 times for every 10 °C increase in temperature.

Arrhenius exponential law:

$$K = Ae^{-E/RT}$$

Logarithmic form:

$$\text{lgk} = -\frac{E}{2.303RT} + \log A$$

Where k is the rate constant, A is the frequency factor, E is the activation energy, R is the gas constant, and T is the temperature.

It can be seen that high temperatures can accelerate the speed of hydrolysis, oxidation, polymerization and other reactions, and aggravate the instability phenomenon in oral liquid. At the same time, it should be noted that for some homology oral liquids containing polyoxyethylene non-ionic surfactants, when the sterilization temperature reaches the Tan point, the solubility of the surfactant decreases sharply, and the solution precipitates. When the temperature decreases below the Tan point, some solutions can recover clarity, while others are difficult to recover.

Entropy is used to measure the degree of order of the system. According to Boltzmann's expression, the entropy of the system is:

$$S = k_B \ln W$$

Where, k_B is the Boltzmann constant and W is the number of microscopic states corresponding to the macroscopic state. The higher the entropy, the higher the disorder of the system. According to the second law of thermodynamics, the internal energy of the system must be reduced to compensate for the loss of entropy caused by the transition from a disordered phase to an ordered phase[69].

Since most of the current sterilization methods of oral liquid will have a certain impact on the temperature of oral liquid, after sterilization, the temperature of oral liquid will increase, and then in the process of storage, the temperature will slowly decrease to room temperature. In the process of storage, it can be regarded as a constant pressure system with constant pressure, and the condition for the system to reach equilibrium is that the Gibbs free energy G reaches a minimum value.

$$G = H - TS$$

$$\Delta G = \Delta H - \Delta(TS)$$

H is the enthalpy of the system, and T is the temperature. In the storage process, the oral liquid is an exothermic process, $\Delta H < 0$, $\Delta T < 0$; The system will spontaneously proceed in the direction of the reduction of Gibbs free energy, so the entropy change of the system will be reduced, the degree of chaos will be reduced, and a large number of colloids will be coagulated[70].

2.2 Chemical change

2.2.1 Oxidation

Many bioactive components in SMFH are susceptible to oxidation, particularly in oral liquids with structural features like double bonds, hydroxyl groups, and aldehyde groups. These can easily cause precipitation or discoloration under heat or light exposure. Flavonoids, phenolic acids, alkaloids, saponins, polysaccharides and other chemical components contained in SMFH have certain antioxidant activities, and these components can react with oxygen to reduce the activity under the conditions of temperature and light[71]. For example, the quercetin contained in beans will lose 70% under the conditions of atmospheric boiling at 100 °C or pressurized boiling at 121 °C, and the quercetin contained in grapefruit juice will lose 17% under high temperature sterilization conditions. This degradation is likely due to quercetin's oxidation at high temperature, forming quercetin-quinones with one o-quinone and three methylene quinones, and reacting faster under alkaline conditions[72]. The color of oral liquids containing chlorogenic acid darkens due to oxidation during storage under heat and oxygen exposure. The physical and chemical properties of the volatile oil are unstable, and there are some disadvantages such as strong volatility, easy oxidation and degradation, resulting in the decrease of the activity of the volatile oil. The terpenoids contained in the volatile oil SMFH will undergo double bond breaking, epoxidation and dehydrogenation under the condition of high temperature. When the volatile oil reaches a certain temperature, the oxidation will also occur, which changes the structure of the volatile oil as well as causes the quality and content of the volatile oil to decline[33].

2.2.2 Hydrolysis

Glycosides, amides, esters and other compounds contained in the SMFH are susceptible to hydrolysis under acidic or alkaline conditions, with hydrolysis rates accelerating under elevated temperatures, leading to a degradation in quality. Ester-based drugs are readily hydrolyzed in aqueous solutions, causing a frequent decrease in solution pH post-hydrolysis, with the hydrolysis reaction further catalyzed by H^+, OH^-, or generalized acid-base reactions. Alterations in pH can also precipitate other chemical reactions. Esters exhibit greater stability and reduce hydrolysis at higher pH values, while glycosides are particularly prone to hydrolysis under acidic conditions, when the pH of amides is increased, the hydrolysis is accelerated[73]. Precipitation in Sanlejiang oral liquid was primarily attributed to the polymerization and hydrolysis of catechins and tannins, yielding ellagic acid and tannin precipitates, with precipitation levels increased as temperature rose, due to the accelerated hydrolysis rate of tannins at higher temperatures[16]. When ginsenosides are heat-treated, it is found that the major ginsenosides (Rb1, Re, and Rg1) contained in ginseng are gradually converted to secondary ginsenosides. In addition, no organic acids are detectable in unheated crude ginsenosides, but if they are heated, organic acids, including citric acid, acetic acid, and malonic acid, which are produced by malonylginsenosides through a decarboxylation reaction during heating, are detected in crude saponins. Under the action of organic acid generation, ginsenoside Rb1 will be hydrolyzed to form deglycosylated ginsenosides and dehydrate ginsenosides under the heating condition of 130 °C, while ginsenosides without acid still maintain good stability[31].

2.2.3 *Polymerization*

Elevated temperatures accelerate polymerization reactions within oral liquids, as increased temperatures enhance molecular thermal motion, raising the quantity of active centers and the likelihood of chain initiation and propagation. Catechins in Sanlejiang oral liquid are susceptible to oxidative polymerization, resulting in tannin deposits over time. Catechins are abundant in Sanlejiang oral liquid. At high temperature, catechins are oxidized and polymerized to form condensed tannins, which form insoluble polymers under the action of oxygen or metal ions in the solution, and finally produce tanning red precipitates. And as the temperature rises, the amount of precipitation will increase[58].

The Maillard reaction is a condensation, polymerization, and degradation reaction between amino groups on proteins, peptides, and amino acids, and carbonyl compounds, which ultimately produces brown or black pigmented macromolecules, commonly termed the browning reaction. Polyphenols, including flavan-3-ols, hydroxycinnamic acids, flavonoids, and tannins, exert various effects in the Maillard reaction. These effects encompass binding with amino acids and sugars, sequestering dicarbonyl compounds, inhibiting Amadori rearrangement products (ARPs), and diminishing acrylamide and 5-hydroxymethylfurfural (5-HMF) levels, significantly influencing food flavor and texture[74].

2.3 Bioactive factors change

The stability of enzymes, proteins and amino acids in oral liquid has a direct impact on the stability and efficacy of MFHOL. As sterilization temperatures rise, amino compounds (amino acids and proteins) undergo Maillard reactions, damaging proteins structures and reducing bioactivity (Table 3). UHT can significantly reduce the content of protein and amino acid, which is due to the Maillard reaction occurring in protein and the high temperature accelerates the deamination of amino acid, thus affecting the appearance and flavor of food[75]. Cu, Zn SOD are usually composed of 152~154 amino acid units. Kumar *et al.*[76] studied Cu and Zn SODs in Honeycoae japonicae and found that sterilization at 121 °C would mutate the amino acid sequence of the side chain of SOD, reduce the catalytic activity of SOD, and produce geometric shapes that are not conducive to protein structure. Naringinase in grapefruit juice is composed of *α-L*-rhamnosidase and *β-D*-glucosidase. *α-L*-rhamnosidase can hydrolyze naringin to prunin and rhamnose, reducing the bitterness, while *β-D*-glucosidase can hydrolyze prunin to non-bitter naringin and glucose. During the sterilization of grapefruit juice, the color and flavor of the juice were changed. This phenomenon was due to the decrease of naringin activity and the decrease of the ability to catalyze naringin decomposition, which resulted in the increase of bitter taste of grapefruit juice[77].

3 Effect of HPSS on the stability of novel oral liquid preparations

3.1 Pickering emulsion

Pickering emulsion is an emulsion system stabilized by inorganic or organic solid particles. Compared with emulsions stabilized by Tween, Span and other small molecule surfactants, pickering emulsions stabilized by particles have many advantages, such as strong stability, resistance to Austenostil aging and good safety[59]. Emulsion systems are typically stabilized by the adsorption of amphiphilic surfactant molecules at the oil-water interface, reducing interfacial tension. Pickering emulsions are stabilized by solid colloidal particles at the interface, altering steric hindrance and the fluidity between the interface and the continuous phase. The solid particles at the interface are interconnected via capillary action, forming a tightly ordered structure, thereby endowing the interface film with properties akin to elastic solids, protecting against droplet aggregation, enhancing the interface film's rheological and shear properties, and significantly enhancing emulsion stability[78]. An additional stabilizing mechanism in Pickering emulsions may involve a three-dimensional viscoelastic particle network, where particle interactions create this network structure, which results in increased continuous phase viscosity and reduced migration rates and degrees of emulsion droplets, thereby preventing droplet agglomeration and enhancing emulsion stability[79]. Du *et al.* prepared the pickering emulsion with agar-gelatin as stabilizer, and the SEM characterization results showed that the stability of the emulsion mainly depended on the weak gel network formed during the emulsification process and the filling of gelatin in the pores[80]. Pickering emulsions are inherently thermodynamically unstable, exhibiting a spontaneous tendency toward oil-water separation, but separation requires overcoming a specific activation energy (ΔG); the greater the activation energy, the more stable the emulsion. Temperature fluctuations commonly influence the stability of Pickering emulsions, particularly for temperature-sensitive systems. For certain temperature-sensitive Pickering emulsions, demulsification occurs upon reaching a specific temperature threshold. Conversely, when the temperature is lowered to a specific value, the emulsion can disperse evenly and re-emulsify. Moreover, certain temperature-sensitive Pickering emulsions display greater stability at elevated temperatures and diminished stability at lower temperatures. Thus, temperature control facilitates reversible emulsification and demulsification[59]. In Gong and Dai's research, pickering emulsion still maintains its original properties at the initial temperature rise, but when the temperature rises to 60 °C or the high temperature is prolonged, from the microscopic point of view, droplets will aggregate, become larger and larger, and finally break, and Pickering emulsion will not be able to maintain its original properties, resulting in flocculation[81,82]. This is because of increasing temperature reduces the solid particles' ability to sustain interface stability in Pickering emulsions, leading to stratification, demulsification, and flocculation.

3.2 Nanoemulsion and microemulsion

Nanoemulsion (NE) and microemulsion (ME) also belong to emulsion systems, and there are also unstable phenomena such as flocculation, aggregation and demulsibility, which will be exacerbated under high temperature conditions. Research indicates that elevated temperatures lead to intensification of lipid oxidation reactions within NEs and MEs, resulting in the production of hydrocarbons including aldehydes, ketones, acids, and esters, and consequent degradation of emulsion quality[83]. Within a certain temperature range, the microemulsion system containing non-ionic surfactants will lead to the mutual transformation between structures with the change of temperature. When the temperature is low, the interface layer is close to the oil, forming O/ W-type microemulsion, and when the temperature is high, the W/ O-type microemulsion will be formed. When the temperature is too high, beyond the range that the system can bear, demulsification phenomenon will occur[84].

3.3 Liposome

Liposomes are thermodynamically unstable formulations composed of phospholipids and cholesterol. The majority of phospholipids in liposomes possess unsaturated acyl chains, making them susceptible to hydrolysis and oxidation. Oxidation reactions generate peroxides and malondialdehyde, which can further hydrolyze to produce free fatty acids and lyso-phospholipids, posing a risk to human health. Elevated temperatures accelerate the oxidation and hydrolysis of phospholipids, further diminishing the stability of liposomes. Furthermore, high-temperature conditions can induce liposome aggregation and drug leakage, resulting in a decline in liposome quality[85].

4 Select reasonable sterilization parameters or methods

4.1 Select the appropriate methods

Currently, HPSS is the primary method for sterilizing MFHOL. However, the high pressures and temperatures may result in the degradation of volatile and thermolabile components within the oral liquid, or induce a range of hydrolytic, oxidative, and polymerization reactions, leading to alterations in the solubility of certain components and potential precipitation, which can adversely affect the appearance and flavor of the oral liquid. This can also significantly impair the therapeutic efficacy of the oral liquid. Given that MFHOL are complex systems comprising numerous substances and bioactive ingredients, it is imperative to tailor the sterilization parameters of the oral liquid accordingly. Sterilization parameters should be judiciously selected based on the primary bioactive constituents and their physicochemical properties, including the determination of sterilization temperature, duration, and whether additional ingredients should be added. While ensuring effective sterilization, minimizing input costs, maintaining minimal clarity alterations, and limiting efficacy changes, to enhance consumer adherence to medicinal and food homologous oral liquids. Table 3 outlines the principles and characteristics of diverse sterilization methods.

When sterilizing oral liquids that primarily contain heat-sensitive components such as polyphenols, volatile oils, and amino acids, thermal sterilization methods should be circumvented whenever possible. We can opt for non-thermal sterilization techniques such as microwave and high-voltage pulsed electric field processes to prevent volatilization and oxidation. Radiation sterilization is a non-thermal sterilization method, for oral liquid, and the free radicals generated by radiation sterilization can be moved because of the continuous phase of water, which significantly enhances the irradiation sterilization effect, but it is easy to promote the oxidation of some active ingredients[86]. Radiation sterilization may induce alterations in the chemical constituents and bioactivity of traditional Chinese medicines, particularly the oxidation of anthraquinone components. Therefore, oral liquids containing anthraquinones should circumvent radiation sterilization where possible[87].

High voltage pulsed electric field sterilization (PEF) is also a new type of cold sterilization method developed in recent years, which has good sterilization effect. Compared with traditional sterilization methods, PEF has the advantages of short sterilization time, low sterilization temperature and small energy consumption, and will basically not cause a great impact on the appearance and flavor of food[88]. Studies have shown that processing fruit and vegetable juices with PEF performs better in terms of retaining nutrients compared to hot processed fruit and vegetable juices. PEF preserves more vitamins, carotenoids, anthocyanins and other nutrients in processed fruit and vegetable juice. In addition, the sensory characteristics of fruit and vegetable juices such as appearance and flavor and physicochemical properties were not affected[89]. This suggests that PEF may be a potential sterilization method for MFHOL in the future, but further experimental studies are needed to confirm its efficacy. In the case of the same microbial and enzyme inactivation, the shelf life of the sample after PEF is slightly longer than that of heat treatment, and the loss of volatile compounds is lower than that of heat sterilization, which better ensures the sample quality[90].

4.2 Select reasonable parameters

Since the oral liquid of the same medicine and food is a mixed system composed of a variety of substances and effective components, it is necessary to modify the corresponding parameters of the sterilization method of the oral liquid. The appropriate sterilization parameters should be selected according to the main active components in the oral liquid and their physical and chemical properties, such as determining the sterilization temperature, sterilization time or whether other components need to be added. On the basis of ensuring efficient sterilization, it should try to achieve low input cost, small change of clarity, and small effect on efficacy, so as to improve the compliance of consumers to the oral liquid with the same source of medicine and food.

PEF has a good bactericidal effect on E. coli, but the sterilization effect is affected by the field strength, pulse width, frequency and sterilization time. Liu *et al.*[91] studied the influence of different parameters on the PEF sterilization effect. The results showed that the larger the field strength and pulse width, the greater the influence on the permeability of bacterial cell membrane and the more obvious the shock effect on the cell membrane. The number of pulses is the key factor influencing sterilization effectiveness. The more the number of pulses, the more obvious the shock effect and the better the sterilization effect.

Low temperature plasma sterilization (LTPS) is a sterilization method based on ionized gas composed of ions, electrons and active molecules, which has been applied to pharmaceutical preparations, medical equipment, wound disinfection and other fields[92, 93]. Setting different working gas and working voltage can achieve different functions, but also have a positive or negative impact. Amini[94] studied the effect of LTP on saffron compounds. They found that when the working gas was argon and the voltage

Table 3 Principles and characteristics of different sterilization methods

Sterilization method	Principle of sterilization	Advantage	Shortcoming	Reference
Ultra-high temperature instant sterilization	The fluid is heated to 125-150 °C and maintained at this temperature for 4~20 S, thus achieving rapid sterilization	Shorter sterilization time allows better retention of volatile and heat-sensitive components	The high temperatures cause some chemical reactions and changes the phase state of the solution	[46]
Microwave-assisted thermal sterilizsation	The polarization of non-polar molecules oscillates with the change of the direction of the alternating electric field. The intense movement of polar molecules generates a lot of heat.	Strong penetration, energy saving, high work efficiency	Not suitable for heat-sensitive components	[96]
Ultra-high pressure sterilization	Using water as a medium to apply 400, 600 mpa pressure to the flexible packaging liquid, killing almost all bacteria, molds and yeasts, destroying hydrogen bonds, ionic bonds and hydrophobic bonds in the protein, denaturating the protein.	The processing time is short and continuous process can be carried out	The cost is high, the enzyme can be denaturated and deactivated, and the protein structure can be changed.	[97]
High voltage pulsed electric field sterilization	Under applied electric field, the cell membrane perforated and polarized, which destroyed the biological function of the cell membrane and the biological activity in the membrane.	Sustainable, environmentally friendly non-heat treatment	The killing effect of yeast is not good, and the equipment investment cost is high	[98]
Low temperature plasma sterilization	By using various active particles in the plasma and various physical and chemical reactions occurring in bacterial cells, it can effectively destroy bacteria, viruses and heat-causing substances	Killed microorganisms and residues can be carried away through a gas circulation system and are suitable for preparations containing heat-sensitive ingredients.	The cost is high and it is not suitable for preparations where the active ingredient is protein.	[99, 100]
Radiation sterilization	The use of high-frequency rays generated by radiation sources to oxidise substances or produce free radicals, and further damage microbial DNA, proteins and enzymes, damage and change the structure of biological macromolecules	Thorough sterilization does not affect the heat-sensitive ingredients.	There is no relevant regulation on the irradiation dose, and there is a serious problem of excessive irradiation	[88]
Microfiltration sterilization	Use the principle that bacteria cannot pass through the dense porous filter material to remove microorganisms in the liquid (generally ≤ 0.22 um)	It does not destroy heat-sensitive substances, and is Suitable for heat-sensitive components.	It takes a long time and the filter membrane needs to be replaced regularly.	[101]
Ultrasonic sterilization	By inducing cavitation to produce bubbles, the resulting implosive shock wave destroys cell membranes and produces free radicals resulting in microbial inactivation	Strong penetration, fast sterilization speed, suitable for the effective substance for protein, heat sensitive components of the preparation	The sterilization effect of ultrasonic wave alone is not complete, and the sterilization effect is general for spores and fungi with strong antibacterial properties.	[102]

was 8kV, LTP could decrease the content of safranin ester and safranin, and increase the content of isophorone and 4-ketoisophoroneAmini. In another study, Hosseini replaced the working gas with oxygen at a power of 60 W, which did not significantly reduce the content of safranin ester, safranin and other components and antioxidant activity of safflower, and could completely kill Aspergillus, but it would have a certain impact on the cell wall and accelerate the release of color[95].

Therefore, after selecting the appropriate sterilization method, it is also necessary to select the appropriate and optimal sterilization parameters within the range of maximum sterilization effect and minimum production cost through experiments.

5 Future prospect

HPSS usually requires high temperatures and pressures, which may affect the activity of some heat-sensitive components and bioactive factors, or change the physical and chemical properties of the solution, resulting in a series of unstable phenomena, which greatly affects the quality and safety of oral liquid. In the production process, HPSS requires the use of specific equipment, and the sterilization process needs to accurately control the temperatures, pressure and time and other parameters, for the final sterilization effect also needs to be verified by specific methods to ensure the sterilization effect, which leads to an increase in the input cost of human and material resources in the actual production. And a single sterilization method is not once and for all for the complex system in MFHOL, and will more or less have a certain impact on a certain index. Therefore, it may be possible to try a variety of sterilization methods combined with technology in the future. PEF or pasteutization alone significantly reduced the a* value of orange juice, but the a* value of orange juice treated with 16 kV/cm electric field intensity and 100 kJ/L specific energy was not significantly different from that of the control group[103]. It had little effect on the spore activity in apple juice, but when combined with pressure and heat treatment, it had obvious spore killing effect[104]. Although many new sterilization technologies have been developed in recent years, such as microwave sterilization, high voltage pulse electric field sterilization, low temperature plasma sterilization, etc., all have good sterilization effect, but also can better retain the effective active ingredients in oral liquid. However, the use of these new methods is still relatively scattered, has not formed a relatively systematic system, has not been widely used in the sterilization of oral liquid with the same source of medicine and food, so it needs to be further studied. As the global demand for MFHOL continues to grow, systematic studies of sterilization methods must be urgently improved.

First, a variety of sterilization methods can be considered. For example, it has been reported that the combination of pulsed electric field sterilization and pasteurization can accelerate the deactivation of spores in the beverage, better preserve the antioxidant capacity and ascorbic acid concentration of the juice, and have minimal impact on the pH value and quality changes of the juice when sterilizing citrus drinks[103, 105]. In the study on the inhibition of Bacillus acid spores in apple juice, it was found that pressure alone had little effect on spore activity, but when combined with pressure and heating, it had obvious spore killing effect[104]. As the treatment temperature increases, the pH of the juice decreases. The study found that ohmic heating sterilization at lower pH conditions can produce effective sterilization at relatively mild sterilization temperatures, and this combined treatment can interfere with the homeostasis of pathogens while affecting different targets such as cell membranes, DNA, enzyme systems, pH, and water activity within microbial cells[106].

Secondly, the systematic research of low-temperature sterilization technology should be improved. The development of low-temperature sterilization technology provides more potential for the development of oral solution with homologous medicine and food. It can achieve good sterilization effect under low temperature conditions, and is friendly to the thermo-unstable components and phase states in the oral solution, and improve the stability of the oral solution with homologous medicine and food. In addition, combined with the online detection technology, the continuous sterilization production and intelligent control of the oral liquid with the same source of medicine and food were realized[107]. Through the detection of key quality attributes (content of active ingredients, pH, solid content, oral liquid color, etc.) in the sterilization process, and intelligent control of key process parameters (sterilization temperature, time, intensity, etc.) in the sterilization process, the dynamic situation of MFHOL sterilization process can be monitored in real time. At the same time, it can also select and determine the range of controllable parameters according to the characteristics of the product through the intelligent control system, establish a fully automatic sterilization monitoring system, reduce the investment of human and material resources and improve the safety of the product[108, 109]. Personalized sterilization programs are developed for different oral liquids to maximize the protection of the effective ingredients, while ensuring the sterilization effect and achieving environmentally friendly sterilization.

6 Conclusion

Based on the instability caused by HPSS, this paper analyzed the internal and external factors of the unstable behavior of the MFHOL under the conditions of HPSS, thus finding the mechanism of action leading to the instability and proposing potential solutions. In order to provide the corresponding theoretical basis for the rational and efficient sterilization of the MFHOL, while ensuring the sterilization effect, preserve its due efficacy, and promote the further development of the homologous oral liquid of medicine and food.

Conflicts of interest

The authors declare that there are no conflicts of interest in this work.

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Credit author statement

Xiaorong Wei and Jun Tang: Writing-original draft, Writing-review and editing. Guotao Xue, Fangyu Xiang and Dingkun Zhang: Data curation and Formal analysis. Mengqi Li, Sanhu Fan and Taigang Mo: Conceptualization and Validation, Junzhi Lin, Haozhou Huang and Li Han: Funding acquisition, Project administration, Supervision, Writing- Reviewing and Editing.

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