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Review

Molecular and technical aspects on the interaction of serum albumin with multifunctional food preservatives

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ABSTRACT

Synthetic food preservatives like sodium acetate (SA), sodium benzoate (SB), potassium sorbate (PS) and Butyl paraben (BP) have been widely used in food and pharmacy industries. One of the toxicological aspects of food additives is evaluation of their interaction with serum proteins such as albumin. These additives interaction with human serum albumin (HSA) can exert considerable effect on the absorption, distribution, metabolism and toxicity of chemical compounds. It should be noticed that the aforementioned food preservatives intake increase mainly in the presence of glucose may lead to complex formation of SA, SB, PS and BP with HSA and accelerate the development of variety disease such as cancer, diabetes, multiple sclerosis, brain damage, nausea and cardiac disease. Therefore, to understand the mechanisms of aforementioned food additives interaction and conformational changes of proteins, we aim to review various studies that investigated albumin interaction with these additives using several procedures.

1. Introduction

Chemical food additives such as sodium acetate (SA), sodium benzoate (SB), potassium sorbate (PS) and Butyl paraben (BP) have been widely used in food, cosmetic and pharmaceutical products as potential preservatives in many countries owing to their bacteriostatic and fungistatic properties during several years (Mohammadzadeh-Aghdash, Dolatabadi, Dehghan, Panahi-Azar, & Barzegar, 2017; Piper & Piper, 2017). Therefore, their use as safe food preservatives has been questionable and biological risks of these compounds to the human body still remain unclear. It must be noted that SA may be used as a natural preservative food additive substitute (Blaauboer et al., 2016; Mirza, Asema, & Kasim, 2017; Mohammadzadeh-Aghdash et al., 2018; Parke & Lewis, 1992; Zengin, Yüzbaşıoğlu, Ünal, Yılmaz, & Aksoy, 2011). To decrease their harmful effects on human health, natural preservatives could be substituted by synthetic compounds. The maximal permitted limit of these preservatives in bakery and meat products is around 0.1–0.4% and in various food products, they have been used according to good manufacturing practice (GMP) promulgated by the Food and Drug Administration (FDA) and usually is recognized as nontoxic when ingested in quantities below a specified limit. Therefore, the amount of any particular food additive ingested by various individuals cannot be predicted and the quantity ingested may differ according to different courses of additives (Blaauboer et al., 2016; Erickson & Doyle, 2017; Pisoschi et al., 2017). Fortunately, the growth and multiplication microorganisms are prevented by food additives. The aforementioned food additives are more effective at low pH values where solutions contain increased concentrations of undissociated acids forms. The mechanism of action of chemical preservatives is through rapid diffusion of their lipophilic acid (LA) molecules via the plasma membrane into the cytoplasm, dissociation of these molecules within cells and release of protons, which lead in acidifying of the cytoplasm and inhibition of respiration system and growth of microorganisms (Kouassl & Shelef, 1995; Marie Skirdal & Eklund, 1993; Membré & Dagnas, 2016; Ouattara et al., 2002).

The most common preservatives for dairy, bakery and meat products is SA and PS. But SB and BP are adequately stable to heat and are often used in cooked and meat products. The disadvantage of aforementioned food preservatives is their tendency to form precipitate in the presence of nitrite ions and formation of mutagenic compounds.

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Some preservatives, such as SB and PS are usually used in combination with apparent impressive synergistic effects. Synergistic effect of PS with SA has been reported as well (Liu, Antoniou, Li, Ma, & Zhong, 2015; Mendonca, Molins, Kraft, & Walker, 1989; Münzner, Guigas, & Renner, 1990; Preciado-Iñiga, Amador-Espejo, & Bárcenas, 2018).

The synthetic preservatives have been broadly assessed for their biological and toxicological activities. Therefore, when toxicity information of these additives becomes available, their application in food industry should be reviewed (Dehghan, Mohammadi, Mohammadzadeh-Aghdash, & Dolatabadi, 2018; Piper & Piper, 2017; Pongsavee, 2015; Schiffmann & Schlatter, 1992). The major stable products of these food additives upon interaction with biological macromolecules are 6-dihydro-2-pyridone, 6-dihydro-2-pyridone, *n*-methyl-6-methyl-3-oxoheptanoate, which is formed due to the reaction with different amine groups such as methylamine, ethylamine, propyl amine, butylamine and benzylamine. Also, cyto-genotoxicity of this compound was approved through the ames and deoxyribonucleic acid (DNA) damage tests using DNA plasmid and genomic DNA of human cervical cancer (HeLa) cells (Bauza et al., 1995; Ferrand, Marc, Fritsch, Cassand, and de Saint Blanquat, 2000a,b; Ferrand, Marc, Fritsch, & De Blanquat, 2000; Sohrabi, Mohammadzadeh-Aghdash, Baghbani, Dehghan, & Dolatabadi, 2018). The recent studies indicated that SB could bind to DNA and hydrophobic interactions and hydrogen bonds play a role in the binding process. Moreover, SB was able to quench the fluorescence of DNA through a static procedure. The observed quenching process was indicative of an intercalative mode of interaction between SB and DNA, which was supported by melting studies, viscosity measurements and CD analysis.

Binding mechanisms between preservatives and various albumins such as human serum albumin (HSA) and bovine serum albumin (BSA) is of interest for researchers to understand its probable danger to human health. As it is shown in (Fig. 2) SA, SB, PS and BP can form covalent binding with HSA and result in conformational changes in this biological protein. Also, stimulation of extracellular and intracellular activators such as advanced glycation end products (AGE_S), oxidative stress, amyloid fibril formation of albumin upon interaction with them has been reported, which in turn led in human diseases such as obesity, diabetic and cancer. Therefore, in this article we will review the complex formation capability of these food preservatives with serum albumins. Serum albumin binding studies of these food additives were frequently evaluated by the several researchers in past two decades in order to estimate their mechanisms of action. Due to widespread usage of chemical preservatives, it is valuable to review the results of synthetic food additives interaction with albumin through various procedures to understand the mechanisms of their interaction and conformational changes of proteins.

2. Properties of synthetic food preservatives

2.1. Sodium acetate (SA)

2.1.1. Sources

SA is a hydrophilic organic compound, which is known as sodium ethanoate and can be generated via many methods but mainly it can be produced via reaction of acetic acid with sodium carbonate or sodium hydroxide. Also, it can be prepared via combination of vinegar and baking soda (Fig. 1). It is the derivative of carboxylic acid in which hydrogen atom is substituted with sodium group. It is soluble in alcohol, acetone and water (Abbas, Ahmed, Sulaiman, & AbdalLatif, 2017; Manju, Jose, Gopal, Ravishankar, & Lalitha, 2007).

2.1.2. Benefits

SA prevents microbial proliferations in various food products. As an acid, it acts as a neutralizing agent for alkaline foods and can also play as a buffer to retain a specific pH. It can be also used as foods flavor enhancer, acidic adjuvant, gelatin films and variety of meat and bakery products (Gómez-Estaca, Gómez-Guillén, Fernández-Martín, & Montero, 2011). Unlike other food additives, SA has no side effects and the use of SA in pickling is similar to its use as a more simple food additive. Its food preservation activity was due to the decrease of decadence caused by micro-organisms in pickling, SA can be used in high quantities and for longer periods of time. Mostly, pickled food such as a cucumber is soaked in a solution of SA. This imparts a very salty or sour taste. The salty taste was because of the Na ions, and the sour taste was due to the acetate ions and the ion of acetic acid (Feedap, 2005; Smith, Daifas, El-Khoury, Koukoutsis, & El-Khoury, 2004).

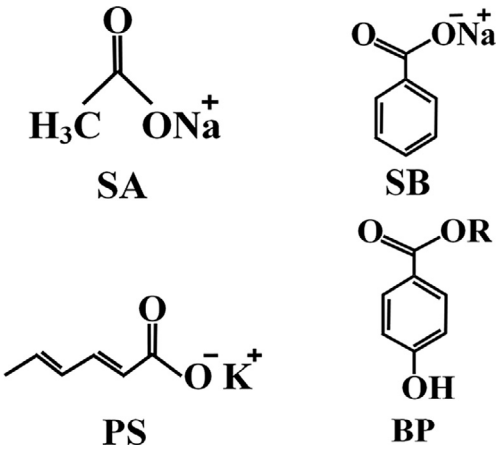

Fig. 1. Molecular structure of (a) SA, (b) SB, (c) PS and (d) BP.

2.1.3. Side effects

In vitro studies showed that SA up to 12.5 mM stimulated proliferation in human gastric adenocarcinoma epithelial cell line (AGS). Also, SA increased the levels of IL-1beta, IL-8, and tumor necrosis factor (TNF)-a protein and mRNAs. The effect of SA on the expression of these cytokines in cell culture was verified on lab animals *in vivo*. A number of studies have shown that high dose ingestion of SA via consuming foodstuffs may has cytotoxic and genotoxic effects. In this regard, as SA increased in urinary bicarbonate excretion infusion, it can decrease respiratory exchange ratio (RER) and led to a respiratory system disorders (Chioléro et al., 1993; Sun, Bi, Chi, Aoki, & Misumi, 2005).

However, its effect on numerous biological and physiological processes needs more investigation. Human being may be exposed to various compounds via several ways. Inhalation, skin and oral routes are examples of the main paths of exposing to various chemicals in human. Venous injection and aspiratory ways are most important and effective routes for substance entrance into the plasma. But, oral route is considered the most at the recent years (Deshpande, 2002; Gualdrón-Duarte & Allen, 2018).

2.1.4. Limitations

According with FDA, the acceptable daily intake (ADI) for SA is between 0 and 15 mg/kg of body weight. It is also used in different products at concentrations usually less than 3000 ppm (Feedap, 2005).

2.2. Sodium benzoate (SB)

2.2.1. Sources

SB ($NaC_7H_5O_2$) is the sodium salt of benzoic acid, which chemically can be produced through reaction of sodium hydroxide with benzoic acid (Fig. 1). It is a derivative of benzene in which one Hydrogen atoms substituted with an alkyl group. It is soluble in liquid ammonia, pyridine, ethanol but it dissolves in water very well (Ren et al., 2014).

2.2.2. Benefits

SB is a commonly used as fungistatic and bacteriostatic to prevent

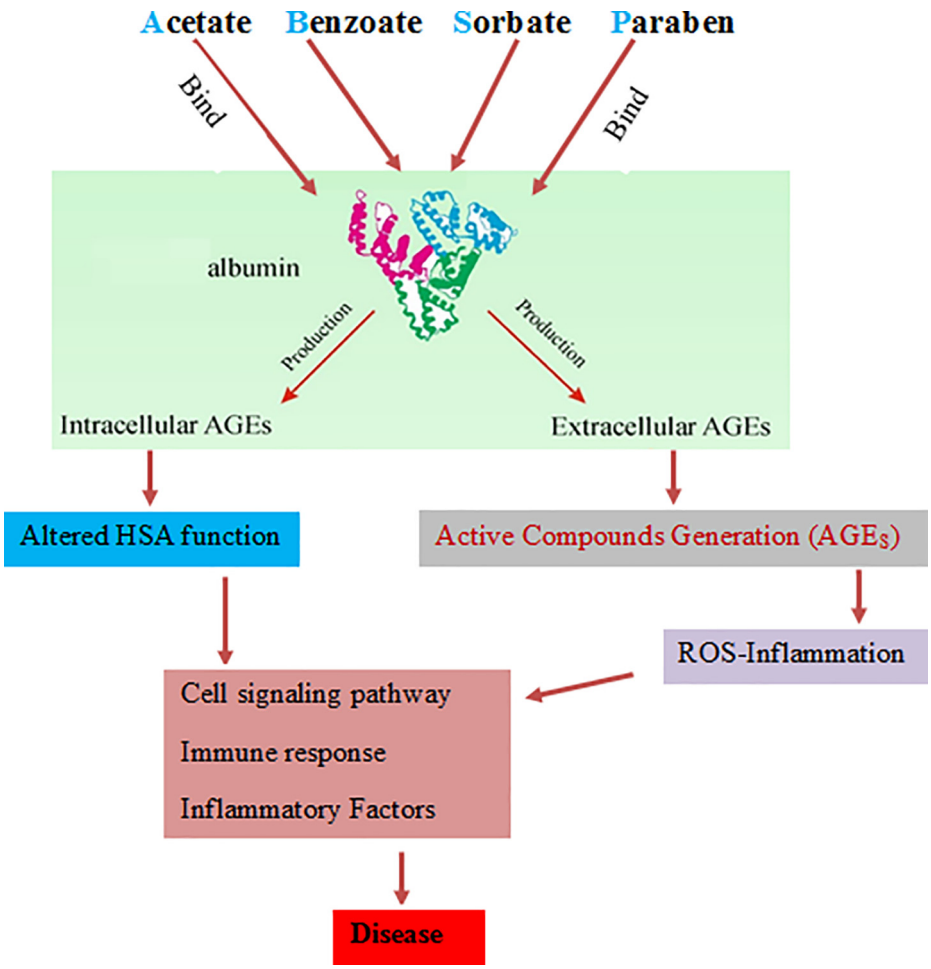

Fig. 2. Biological and toxicological effects of SA, SB, PS and BP on the albumin after absorption via gastrointestinal system.

deterioration caused by microorganisms during storage. It is stable in the presence of mildly acidic conditions and food processing operations (Ren et al., 2014). Because of its good stability and excellent solubility in water SB is extensively used in various food products including dairy, beverage, fermented foodstuffs and also its can act as therapeutic agent in some diseases comprising acute hyperammonemia. It is listed among the generally regarded as safe (GRAS) materials by FDA, and can be applied in food products at a concentration up to 0.1% (Lennerz et al., 2015). It is noteworthy to mention that SB is the main dietary source soft drinks (Tfouni & Toledo, 2002).

2.2.3. Side effects

SB with a hygroscopic shape and high water solubility contains a benzene ring with a carboxyl group that provides the powerful option for binding with small macromolecules (Krause, Thommes, & Breitkreutz, 2009). Toxic level of SB in plasma was 8 mM. *In vitro* studies showed that SB can be a potential inhibitor of kidney D-amino acid oxidase (Cyr & Tremblay, 1989). Suppression of T helper 1 (Th1)-type immune response in human peripheral blood mononuclear cells upon exposure to SB has been reported that could led to shift in the Th1–Th2-type immune balance towards cellular Th2-type immunity. (Maier et al., 2010). High doses of SB can result in metabolic complication such as a carnitine shortage due to enhancement in excretion of benzoyl-carnitine and hepatic ATP depletion in animals (Lennerz et al., 2015). Decreased leptin release during the consumption of dietary containing SB (at high doses) can decrease the circulating levels of leptin and consequently development of obesity (Ciardi et al., 2012).

2.2.4. Limitations

The estimated ADI for SB through various food products is between 0 and 5 mg/kg of body weight per day (Reddy, Aruna, Parameswari, Banu, & Reddy, 2015).

2.3. Potassium sorbate

2.3.1. Sources

PS is the potassium salt of sorbic acid with molecular formula of $C_6H_7KO_2$ that specified with potassium 2, 4-*hexa*-2, 4-dienoate in food industry (Fig. 1). PS is produced synthetically via neutralizing the sorbic acid with potassium hydroxide or a two-step process through the condensation of crotonaldehyde and ketene. This compound hardly dissolves in ethanol and acetone and easily dissolves in water and chloroform while it is insoluble in benzene. Moreover, its solubility is dependent to water temperature (Dehghan et al., 2018; Silva & Lidon, 2016; Yarramraju et al., 2007).

2.3.2. Benefits

PS as simple practical food preservative have been consumed in various industries all over the world. Besides, a high percentage of this compound is used in food industry. It is widely used to increase the shelf life of commercial products without affecting the organoleptic properties of the foodstuff. PS prevents growth of microorganisms in food products and can be used as substitute of parabens. Hence, the use of PS is not limited in foods with high and adequate acidity but not recommended in corrupted and alkaline foods. Therefore, PS is used as fungistatic and bacteriostatic in food products such as, pickles, sweets, soft and alcoholic drinks, vegetable products, sauces, salad dressing,

margarine, meat and bakery products (Gören et al., 2015; Mohammadzadeh-Aghdash et al., 2018).

2.3.3. Side effects

It should be noted that even though PS is used commonly in the various product, it might result in complications like allergy, chest pain, oral slot, eye irritation, asthma and urticarial when its intake be higher than the approved limits (Zamani Mazdeh et al., 2014). High doses of SB leads to chromosomal aberrations in human blood lymphocytes and induces cytotoxic, genotoxic and mutagenic effects in the human peripheral blood lymphocytes (HPBL) and formation of mutagenic products was due to reaction with nitrite in various products (Mamur, Yüzbaşıoğlu, Ünal, & Yılmaz, 2010). The possible genotoxicity assessment of PS using the sister chromatid exchanges and chromosomal breaks assays showed induction of DNA impairment in human lymphocytes after 48 h of treatment (Soares et al., 2015). Hence, it seems that cell cycle changes at high doses of PS was owing to the expression of NFκB, GADD45α, and MAPK8 gene (Ferrand et al., 2000).

2.3.4. Limitation

The joint FAO and WHO as the famous expert committees on food additives of the United Nations approved the ADI level of 0–25 mg/kg of PS per body weight per day.

2.4. Butyl paraben (BP)

2.4.1. Sources

BP or butyl p-hydroxybenzoate (Fig. 1) is an organic compound with the chemical formula of $C_{11}H_{14}O_3$. It is produced synthetically via the esterification of 4-hydroxybenzoic acid with butanol in the presence of sulfuric acid. It can be produced in some microorganisms like *Microbulbifer* as well. BP is slightly soluble in water but is easily dissolves in acetone, ethanol, chloroform, glycerin and propylene glycol (H. Yang & Rasmuson, 2010).

2.4.2. Benefits

BP is used as fungistatic and bacteriostatic preservative in foods, cosmetics, toiletries and pharmaceuticals. The popularity of BP in these products is because of their relatively lower toxicity in humans and its more effective antimicrobial activity. It had been reported that the antimicrobial properties of the BP seem to be increased through increasing of its chain length and also lower chains can limit its applications due to decreasing it solubility in water (Meeker, Yang, Ye, Calafat, & Hauser, 2011). This compound showed good stability over a broad pH, different temperature ranges and acceptable safety. Therefore, this preservative not only is used in numerous foodstuffs but also it is applied in more than 20,000 cosmetic products including eye shadow, facial moisturizer and solid medication suspensions and various drugs such as ibuprofen and acetaminophen (Oishi, 2002; Routledge, Parker, Odum, Ashby, & Sumpter, 1998).

2.4.3. Side effects

In vivo studies showed estrogenic activity of BP in increasing uterine weight, spermatogenesis and endocrine function of immature rats and mice (Kang et al., 2002). It has been shown that it can bind to the rodent uterine estrogen and human estrogen receptors. Also, many studies showed that BP decreased sperm counts in men and increased incidence of complication in the male reproductive tract and the secretion of testosterone (Routledge et al., 1998). Recent studies have showed that it may act as antiandrogens through decreasing estrogen level (Chen et al., 2007). It should be noted that BP through post-meiotic stage can led to DNA hyper-methylation in germ cells in adult rat testes (Park, Nah, Lee, Oh, & Gye, 2012). In addition, BP promoted the generation of intracellular reactive oxygen species (ROS), induced endoplasmic reticulum stress (IERS) and mitochondrial membrane depolarization, increased Ca^{2+} concentration in trophoblast cells (HTRC8), which in turn led to decrease of cellular normal physiological activity because of apoptosis and cell death occurring (C. Yang, Lim, Bazer, & Song, 2018).

2.4.4. Limitation

Based on several studies, use of BP is permitted in a range of various products with ADI of 0–10 mg/kg (Güzel Bayülken, Ayaz Tüylü, Sinan, & Sivas, 2017).

3. Synthetic food preservatives interaction with serum albumin

It is known that the absorption, distribution and metabolism of various chemicals are powerfully affected by additives–protein interactions in the blood stream and this type of interaction can also influence the additives stability and toxicity of them during the biotransformation process (Shahabadi, Hadidi, & Feizi, 2015). Recently, several studies results showed that the structure of different proteins such as albumin change because of binding to small molecules like food preservatives. Albumins as the most abundant soluble protein in the blood circulatory system of numerous organisms play an important role in the transport and distribution of a variety of exogenous and endogenous compounds and excretion of substances and have various physiological functions. For this reason, interaction of different chemical compounds with albumin can considerably affect the absorption, distribution, metabolism and toxicity of them. Thus, the surveys on the interaction of chemicals with albumin are of more interesting in food chemistry and industry, which can result in the conformational change of blood protein (Dolatabadi et al., 2014; Neault, Benkiran, Malonga, & Tajmir-Riahi, 2001).

3.1. Spectrophotometric studies on the interaction of food preservatives with albumin

To understand the structural changes and complex formation of chemical food additives with serum albumin, UV–vis absorption spectra experiments were performed in recent years. UV–vis spectroscopy refers to absorption spectroscopy or reflection spectroscopy in the UV spectral region. This means that it uses light in the visible and adjacent ranges. The absorption or reflectance in the visible range directly affects the perceived color of the chemicals compounds involved. In this region of the electromagnetic spectrum, atoms as well as molecules undergo electronic alterations. Absorption spectroscopy study is a preliminary test and complementary to fluorescence spectroscopy, in that fluorescence deals with transitions from the excited state to the ground state, while absorption measures transitions from the ground state to the excited state. UV-vis spectroscopy is usually used in analytical chemistry for the quantitative determination of diverse analysis, such as transition metal ions, synthetic chemicals, organic compounds and biological macromolecules. Spectroscopic analysis is frequently carried out in solutions but solids and gases may also be studied.

Spectroscopic technique can be used to investigate the structural changes of albumin and to explore albumin and ligand complex formation. Serum albumin has two absorption peaks at around 280 nm and 240 nm. The strong absorption peak at around 280 nm reflects the main structure of the albumin. It has been reported that absorption peak of albumin was due to the presence of aromatic amino acids like Tryptophan, Tyrosin, and Phenylalanine. It has been reported that peak decrease in the area of 240 nm is owing to the changes in the α-helix of biological albumin. It is noteworthy that interaction of food additives with albumin can lead to structural and conformational change of it.

The binding of SA to BSA using absorption spectroscopy was characterized. The spectroscopic experiments suggested that the BSA structure can be changed upon interaction with SA (Mohammadzadeh-Aghdash et al., 2017). The UV absorption spectra of HSA in the presence of BP (210 nm) were investigated as well. It is observed that HSA absorbance peak intensity decreases upon the addition of different

concentrations of BP (Wang, Zhang, Sun, Chen, & Chen, 2011). Meanwhile, the formation of the complex between BP and HSA led to wavelength shift. The recent facts clearly indicated that the binding between BP and HSA lead to change in structure of the biomacromolecule (Yue, Chen, Qin, & Yao, 2009).

3.2. Fluoremetry studies of food preservatives interaction with albumin

Binding of chemical compounds like food additives to albumin can be investigated via fluorescence spectroscopy. Usually, the fluorescence properties of biological protein were due to the presence of three intrinsic residues including Tyrosine, Phenylalanine and Tryptophan. Phenylalanine fluorescence is frequently very weak due to quenching and the Tyrosine fluorescence is almost entirely quenched (Sułkowska, 2002). Actually, Tryptophan plays the main role in intrinsic fluorescence of albumin. In other words, the change in intrinsic fluorescence of albumin is because of Tryptophan residue when small molecule are contact to it (Sułkowska, 2002). Fluorescence quenching refers to any process that lead to fluorescence intensity decreasing of an albumin due to interaction with various molecules. Quenching can occur by different mechanisms, which are usually classified as dynamic quenching and static quenching. Dynamic quenching refers to a process in which the fluorophore and the quencher come into connection during the temporary existence of the exited state. Static quenching refers to fluorophore and quencher complex formation. Generally, dynamic and static quenching by their differing dependency on temperature and excited state lifetime can be distinguished. But the fluorescence intensity is related to the concentration of the quencher. Consequently, the quenched fluorophore can be defined as an indicator for quenching agent. The fluorescence quenching data can be calculated through the Stern–Volmer equation (Sauer, Hofkens, & Enderlein, 2011).

$$F_0/F = 1 + k_{SV}[Q]$$

where, F and F_0 show the fluorescence intensity of albumin in the presence and absence of quencher (Q), respectively. K_{SV} is the Stern–-Volmer quenching constant, which is a measure of the quenching rate constant of biomolecule upon addition of Q (Dolatabadi & Kashanian, 2010).

Fluorescence intensities experiments of SA binding with BSA was carried out and the fluorescence emission intensity of BSA decreased by increasing the amount of SA as a quencher, which indicated that intrinsic fluorescence of BSA was quenched due to interaction with SA (Fig. 3). Mohammadzadeh-Aghdash et al demonstrated that the temperature rising led to the increasing of Ksv, which is indicative of dynamic quenching mechanism happening.

Fluorescence spectroscopic study of SB binding with HSA was carried out and the emission intensity of HSA decreased upon increasing the amount of SB, which is shown in Fig. 3 (Taghavi et al., 2014). They concluded that partial unfolding of HSA incubated with SB occurred in the presence or absence of glucose, while maximum partial unfolding happened in HSA incubated with glucose.

It has been reported that HSA has a strong fluorescence emission band at 335 nm. Fig. 3 shows that the interaction of BP with HSA led to a significant decrease in the fluorescence intensity with a slight shift of emission spectra to a shorter wavelength. Wang et al showed (Table 1) that the quenching mechanism of HSA upon addition of BP at four various temperatures (313, 308, 303 and 298° K) was static due to the decrease of Ksv by rising temperature (Wang et al., 2011).

It has been shown that PS had a quite strong ability to quench the fluorescence intensity of BSA. Hu et al reported that PS interact with BSA through electrostatic interactions and the apparent binding constants between them were 2.23×10^3 and 2.74×10^3 at 288 K and 293 K, respectively. Besides, they concluded that the binding process of PS to BSA was a spontaneous in which Gibbs free energy change was negative (Hu, Fu, Chen, Yang, & Zhang, 2009).

3.3. Circular dichroism studies of food preservatives interaction with albumin

To achieve further information on the interaction of food additives to serum albumin, circular dichroism (CD) spectroscopy was used to study the structural modification of albumin. The CD is a sensitive technique for monitoring of the conformational change of biological protein. Two negative bands in the ultraviolet area at 208 and 222 nm obtained for CD spectrum of albumin that is characteristic of α- helical structure of albumin. The CD spectra of serum albumin in the absence and presence of SB shows a significant CD change of HSA upon interaction with this additive in the presence and absence of glucose after 0 and 35 days. Analysis of CD spectra data demonstrated that α-helix amount in HSA was significantly increased (71.51%) upon incubation with SB after 35 days and other secondary elements like β-sheet were diminished compared with untreated HSA. Whereas the amount of α-helix structure in HSA was decreased (62.97%) and the other secondary elements were increased due to interaction with glucose. Most notably, HSA interaction with SB in the presence of glucose showed almost the same amount of α-helix structure as untreated HSA (Taghavi et al., 2014). Also, the CD spectra of the HSA upon treatment with PS in the presence and absence of glucose were compared with that of HSA treatment with glucose at pH 7.4 and the minimum ellipticity observed for HSA modified with glucose + PS after 35 days of incubation that shown in Fig. 4a (Taghavi et al., 2013). The CD spectra change of HSA owing to the complex formation with BP has been reported as well (Fig. 4b). The binding of BP to HSA caused an increase in band-intensity without any significant shift in the CD peaks, which is indicative of a rise in the α-helix content in the HSA (Wang et al., 2011). Therefore, it can be deduced that the interaction of aforementioned preservatives with HSA led to a conformational change in the biological protein.

Overall, the binding of these food preservatives to serum albumin is greatly important in food chemistry and industry, which finally can lead in the conformational change of biological albumin.

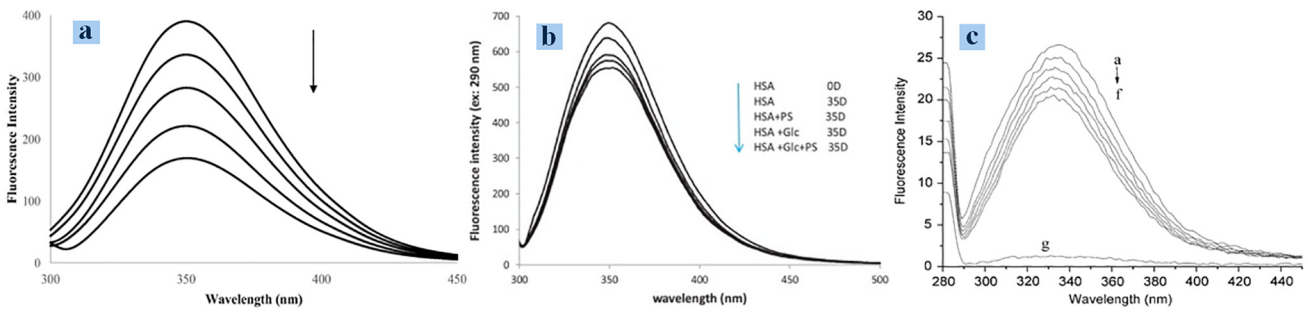

Fig. 3. The fluorescence spectra result of albumin modified with SA, PS and BP. Republished with permission from the following references: a) Mohammadzadeh-Aghdash et al. (2017), b) Taghavi et al. (2013) & c) Wang et al. (2011).

Table 1
Thermodynamic parameters and Stern–Volmer quenching constant (Ksv) of complex formation between food preservatives and albumin at various temperatures.

Food preservatives	T (°K)	ΔG° (kJ mol-1)	ΔH° (kJ mol^{-1})	ΔS° (J mol^{-1} K^{-1})	K_{sv} (M^{-1})	Ref
SA	288	−1.436	39.955	188.594	2.08×10^4	Mohammadzadeh-Aghdash et al. (2017)
	293	−1.530	39.955	188.594	2.22×10^4	
	298	−1.624	39.955	188.594	2.30×10^4	
	303	−1.719	39.955	188.594	2.54×10^4	
	310	−1.851	39.955	188.594	2.83×10^4	
SB	337	3.6 ± 0.3	183.3 ± 8.8	_	_	Taghavi et al. (2014)
PS	340	−11.5 ± 2.1	111.5 ± 3.5	0.34 ± 0.7	_	Taghavi et al. (2013)
BP	298	−22.30	−29.52	−24.23	0.815×10^4	Wang et al. (2011)
	303	−22.18	−29.52	−24.23	0.664×10^4	
	308	−22.06	−29.52	−24.23	0.544×10^4	
	313	−21.94	−29.52	−24.23	0.462×10^4	

3.4. Thermodynamic parameters of food preservatives interaction with albumin

To have a better understanding of albumin interaction with food preservatives thermodynamics parameters should be considered. The binding between chemical ingredients and biomolecule such as albumin may occur via electrostatic interactions, hydrophobic forces, hydrogen bonds and van der Waals, which can be estimated through values of enthalpy (ΔH) and entropy (ΔS) (Fathi, Mohammadzadeh-Aghdash, Sohrabi, Dehghan, & Dolatabadi, 2018; Sohrabi, Panahi-Azar, Barzegar, Dolatabadi, & Dehghan, 2017). The positive values of ΔH and ΔS showed that hydrophobic binding plays crucial roles in the interaction of chemical compounds like food preservatives with albumin; negative ΔH and ΔS values is demonstrative of van der Waals forces and hydrogen bonds occurring in the binding process, while negative value of ΔH and positive value of ΔS indicates that electrostatic interactions between albumin and food preservatives happened. Besides, the negative value of free energy ΔG confirms that interaction process between chemical compounds and albumin was spontaneous (Dolatabadi et al., 2014; Fathi et al., 2018).

Assessment of the complexation constant for the food preservative and HSA complex at various temperatures allows calculation of the thermodynamic parameters through Van't Hoff equation. The ΔG, ΔH and ΔS values of food preservative interaction with albumin are listed in Table 1, which showed that SA bind to protein via hydrophobic forces (Dolatabadi et al., 2014; Mohammadzadeh-Aghdash et al., 2017). The thermodynamic parameters of the BP interaction with HSA showed that Vander Waals force and hydrogen bonds are predominant forces in stabilizing of BP–HSA complex formation. Moreover, the calculated negative ΔG showed that BP binds to HSA spontaneously. After 35 days of the albumin incubation with SB in the presence and absence of glucose, protein structure changed according to Taghavi et al study. Calculated thermodynamic parameters of SB-albumin complex formation showed that stability of albumin modified and its enthalpy decreased compared with the untreated protein. Also, thermodynamic parameters for PS and albumin interaction showed that the enthalpy of PS-HSA combination was decreased compared with the untreated albumin. In this regard the main binding mode between SB and serum albumin seems to be due to the hydrophobic interaction but PS binds to albumin via electrostatic interaction.

3.5. Molecular docking studies of food preservatives interaction with albumin

Molecular docking procedure is a valuable method to estimate binding between the ligand and albumin which can confirm previous experimental results. Also, the docking programs can be utilized for experiments screening and may decrease labor and cost needed for the development of biological macromolecules interaction with effective chemicals compounds. It can also be used for better understanding of binding mechanisms of chemicals to albumin after experimental screening. Albumin protein has multiple binding sites that are known as subdomains IA, IIA, IIIA, IB, IIB and IIIB and have capacity for binding to chemical compounds. Therefore, various chemicals can bind to each of this binding site based on their hydrophobicity or hydrophilicity.

There is a binding site for the SB in the subdomain IIIA of HSA that is illustrated in Fig. 5. This finding was in agreement with the introduced site for aromatic and heterocyclic ligands within two hydrophobic subdomains of IIA and IIIA. The HSA hydrophobic residues (Cys-461, Glu-465, Cys-477, Thr-478, and Thr-474) were involved in interaction with SA, which showed in the Fig. 5. According to the docking results, IIA and IIIA subdomains of HSA with non-covalent property

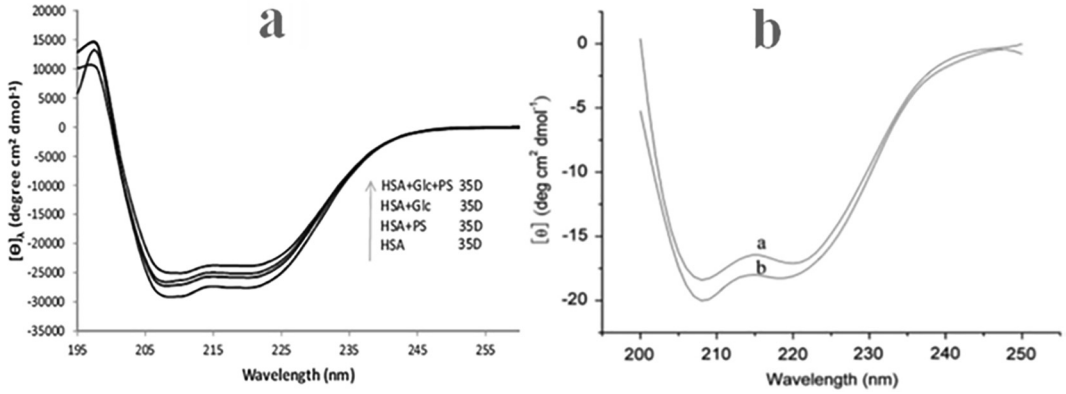

Fig. 4. CD spectra of the PS and BP interaction to albumin. Republished with permission from the following references: a) Taghavi et al. (2013) & b) Wang et al. (2011).

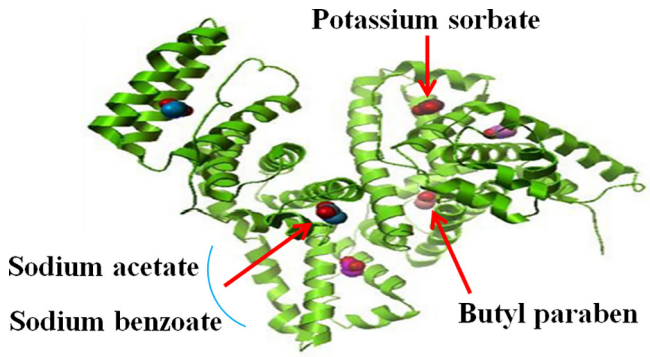

Fig. 5. Docking results of HSA complex with SA, SB, PS and BP. Aforementioned Preservatives and HSA interaction site is shown by an arrow.

proposed as binding sites for SB (Fig. 5). This site is near the single Trp-214 residue and the binding energy of −185 kcal/mol was estimated for this binding (Taghavi et al., 2014). Moreover, according to attained results from molecular docking (Fig. 5) the A binding sites play the crucial role in interaction of SA to BSA, where these sites have lowest binding energy and highest H-Bond in comparisons with B sites (Mohammadzadeh-Aghdash et al., 2017). The docking studies indicated that probable binding sites for the PS-HSA interaction are IA and IB subdomains. It demonstrates that both hydrophobic and hydrophilic binding sites are involved in PS and HSA interaction, which is demonstrated in the Fig. 5. It has been reported that the Lys residues of HSA are involved in PS and HSA complex formation.

Possible HSA binding site for the PS were subdomains IA and IB, which shows that two interactions are involved in HSA–PS physical binding: (1) hydrophobic interaction between PS and HSA residues (His-146, Arg-145, Pro-110) and (2) hydrogen bound between PS and the Asn-111 of HSA. It should be noted that PS has a stimulatory effect on glycation and fibrillation of HSA with or without glucose and could accelerate various diseases such as mellitus diabetes (Taghavi et al., 2013).

Application of molecular modeling has been also employed to improve the understanding of the binding between BP and HSA. It should be noted that BP not only can bind to hydrophobic hollow of HSA but also can form two hydrogen bonds with the amino acid residues of HSA through donating of the H at 3-H substituent of BP to O of the isoleucine residue (IIe290) (Wang et al., 2011).

4. Conclusions

Acetate, benzoate, sorbate and paraben possess multifunctional and high antibacterial properties and are extensively used in food, cosmetics and pharmaceutical industries. Therefore, study of their interaction with biological macromolecules like albumin can be valuable. SA, SB, PS and BP can be metabolized in the human digestive tract and may directly enter into biological process via consumption of drugs and various food products and result in nutritional deficiency and many diseases. The side effects of aforementioned food preservatives have been confirmed on human health at high amounts. Previously several researchers have shown successful incorporation of synthetic food additives with numerous objectives in food products. But, additional studies about application of this synthetic additive in the food industry are mandatory. In this regard, numerous researches may be necessary and it can be valuable for altering the attitude of industries toward the use of SA, SB, PS and BP as harmless preservatives. This review revealed that aforementioned preservatives can have side effects on human health through interaction with albumin and result in activation of inflammatory paths, accelerated of diabetes and trigger of the gradual development of various diseases such as cancers. This overview showed that binding mode between SA and SB with serum albumin seems to be due to the hydrophobic interaction but the electrostatic interaction play the major role in the PS binding to albumin and Vander Waals force and hydrogen bonds are predominant forces in stabilizing of BP–HSA complex formation. Therefore, we highlight that SA, SB, PS and BP food preservatives intake in the human dietary through gastrointestinal tract should be reduced.

Declaration of Competing Interest

The authors declare that they have no conflict of interests.

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