Extraction, purification, food applications, and recent advances for enhancing the bioavailability of 6-gingerol from ginger – A review

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Abstract

6-Gingerol is the major pharmacologically active component of ginger (*Zingiber officinale)* rhizome widely used in the food, cosmetics, and pharmaceutical industries. Various extraction and purification methods have been developed to obtain highly purified 6-gingerol. 6-Gingerol can be extracted using conventional and nonconventional extraction techniques. Hydroalcoholic solutions and liquid CO_2 are the most suitable solvents for the extraction of 6-gingerol, while microwave-assisted extraction is the best extraction method. High-speed counter-current chromatography is the purification technique resulting in the highest purity of 6-gingerol. Despite the various biological properties of 6-gingerol, the low bioavailability of 6-gingerol is the main challenge that limits its application. Novel encapsulation and solubilization techniques, including nano-emulsion, complexation, micelles, and solid dispersion methods, have been introduced to enhance the bioavailability of 6-gingerol, overcoming its limitations. 6-Gingerol showed potential applications as a natural antioxidant, preservative, and flavor enhancer as well as demonstrated a synergistic effect with different ingredients for maintaining the quality and shelf-life of the food products. The current work provides a comprehensive review of the prevailing techniques applied for extraction and purification of 6-gingerol from the rhizome of ginger, current research on the application of 6-gingerol in the food industry, and novel advances for increasing its bioavailability.

Keywords: chromatography; conventional extraction; encapsulation; nonconventional extraction; solubilization; *Zingiber officinale*

Introduction

Ginger (*Zingiber officinale*), which belongs to the *Zingiberaceae* family, is a popular spice with a fresh aroma and pungent taste. It is also used as an herbal medicine having a wide range of medicinal properties (Ko *et al*., 2019). Gingerols are a set of phenolic ketones found in the rhizome of ginger, and they are the main constituents contributing to the pungency of ginger (Xu *et al*., 2016). 6-gingerol [5-hydroxy-1-(4-hydroxy-3methoxy phenyl) decan-3-one] is the most abundant type of gingerol in the fresh rhizome of ginger among other gingerols, including 4-gingerol, 8-gingerol, and 10-gingerol (Semwal *et al*., 2015). Furthermore, 6-gingerol demonstrates antioxidant, analgesic, and anti-inflammatory properties (Kawamoto *et al*., 2016; Wang *et al*., 2014; Young *et al*., 2005; Zahoor *et al*., 2020). In addition, *in vivo* and *in vitro* experiments prove the anticancer potential of 6-gingerol (Chakraborty *et al*., 2012). For example, 6-gingerol suppresses cell proliferation and induces apoptosis in

colorectal cancer cells (Md Yusof *et al*., 2015). The antioxidant potential of 6-gingerol is vital for its commercial application in various industries, such as food, agronomic, and pharmaceutics (Li *et al*., 2015).

6-Gingerol is thermally unstable, and it is converted to 6-shagol, the dehydrated form of 6-gingerol during thermal treatment and long-term storage (Figure 1) (Schwertner and Rios, 2007). 6-gingerol can be identified as a spicy, bitter, and white powder, and it is poorly soluble in water while it easily dissolves in organic solvents (Xu *et al*., 2016). The oral absorption of 6-gingerol is limited due to its poor solubility, and it is rapidly metabolized in the body (Jiang *et al*., 2008). Scientists have explored various techniques to increase the bioavailability and clinical applications of 6-gingerol (Xu *et al*., 2016).

Extraction is a critical step for isolating phytochemicals from plant materials, and the extraction methodology greatly influences the extract quality (Jeyaraj *et al*., 2021; Vidana Gamage *et al*., 2021). Traditionally, 6-gingerol is extracted by solvent extraction, Soxhlet extraction, and steam distillation (Said *et al*., 2015). 6-gingerol is also extracted from the rhizome of ginger by extraction technologies such as microwave-assisted extraction (MAE) (Teng *et al*., 2019), ultrasonic-assisted extraction (Said *et al*., 2015), subcritical water extraction (SWE) (Ko *et al*., 2019), and supercritical CO_2 fluid extraction (Sondari *et al*., 2017). Purification is crucial to obtain 6-gingerol with high purity, resulting in maximum health benefits to consumers by incorporating it into commercial food, and pharmaceutical and cosmetic products. Modern separation and purification techniques such as column chromatography (CC), semi-preparative high-performance liquid chromatography (Semi-prep HPLC), and high-speed counter-current chromatography (HSCCC) are applied to purify 6-gingerol. Several reviews have expertly summarized the pharmacological effects of 6-gingerol (Ahmed *et al*., 2021; Lima *et al*., 2018; Mughal, 2019; Wang *et al*., 2014). However, to the best of our knowledge, a review that comprehensively compares extraction and purification techniques, and discusses possible applications of 6-gingerol in the food industry has not yet been done. The present work addresses this gap. Recent strategies to overcome the low bioavailability of 6-gingerol are also discussed (Figure 2).

Extraction Methods

Developing effective and selective extraction methods to isolate bioactive compounds from plant materials has become urgent with the increasing demand for natural compounds. Conventional extraction methods, including Soxhlet extraction, infusion, solvent extraction, or maceration and digestion, have been used for decades to isolate bioactive compounds (Osorio-Tobón, 2020). In conventional techniques, the extraction efficiency mainly depends on the solvent and raw material properties, the extraction temperature, the solid-to-solvent ratio, and the extraction duration (Zhang *et al*., 2018). However, these conventional techniques usually need a large volume of organic solvents, require a long extraction duration, cause thermal degradation of target compounds, and have a negative environmental impact (Chaves *et al*., 2020). Nowadays, scientists have explored greener and economically feasible extraction techniques such as MAE, supercritical fluid extraction (SFE),

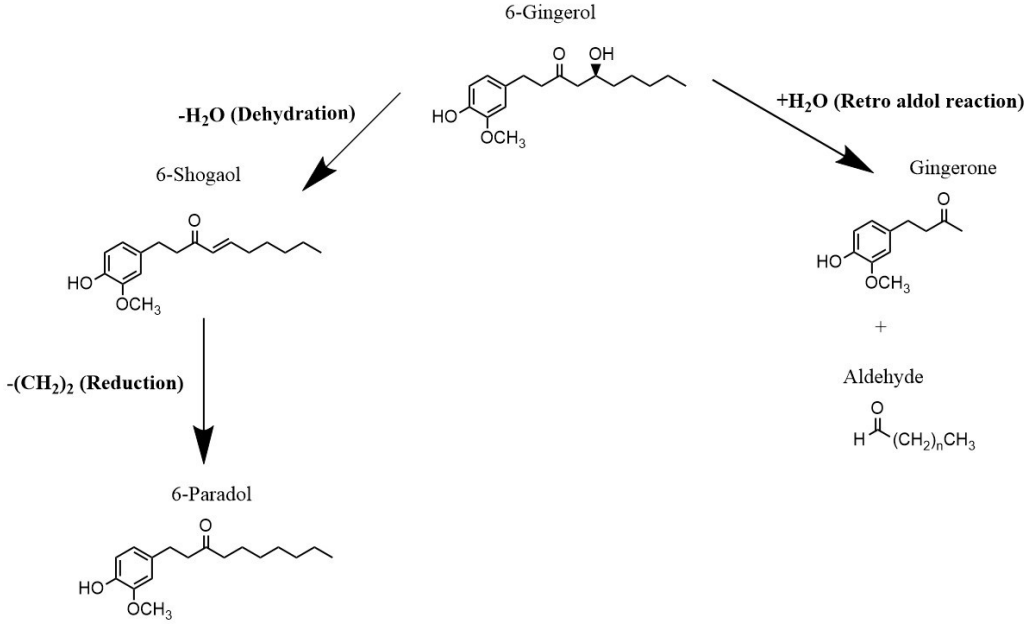

Figure 1. Conversion of 6-gingerol to 6-shogaol, 6-paradol and gingerone.

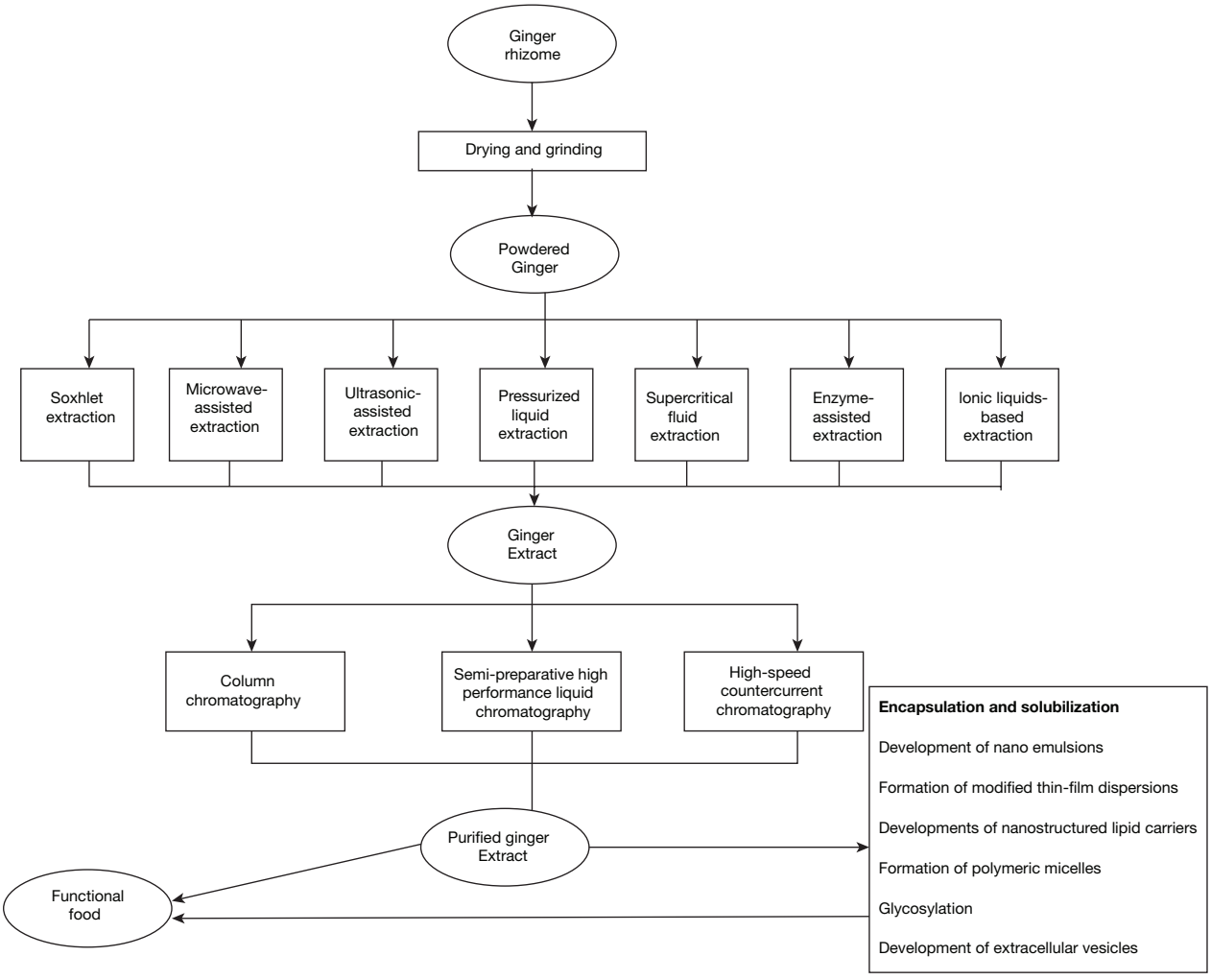

Figure 2. Techniques used for ginger processing to obtain the functional foods containing 6-gingerol.

pressurized liquid extraction (PLE), UAE, and enzyme--assisted extraction (EAE) to resolve the drawbacks of conventional extraction techniques (Ameer *et al*., 2017). Research studies have been carried out to evaluate the potential of various extraction techniques for the extraction of 6-gingerol from the rhizome of ginger (Table 1).

Conventional Extraction Methods of 6-gingerol

Solvent extraction or maceration is a widely used technique involved in soaking the sample in a solvent and allowing them to remain at room temperature for several days with frequent agitation. The type of compound extracted from a sample depends on the solvent used for extraction (Azwanida, 2015). Other critical factors are extracting power of solvents, applied heat, and degree of mixing (Azmir *et al*., 2013).

Soxhlet extraction is the standard solid–liquid extraction technique, and it is still commonly used in laboratories and industries (Chemat *et al*., 2020). Generally, the sample placed in the Soxhlet apparatus is repeatedly kept in contact with a condensed solvent. The siphon discharges the solvent back into the distillation flask at the overflow level. This solvent transport extracted solutes into the liquid in the distillation flask (Luque de Castro and Priego-Capote, 2010). According to Anisa *et al*. (2014), Soxhlet extraction with ethanol resulted in the highest yield of 6-gingerol (8.40 mg/g) at 78.1ºC for 8 h with a solvent to solid ratio of 4:1. In another research, Said *et al*. (2015) compared Soxhlet extraction with ultrasonic-assisted extraction for isolation of 6-gingerol under different solvents and temperatures. The study showed that the highest extraction yield of 6-gingerol (7.3% w/w) was obtained in Soxhlet extraction with methanol, followed by acetone, ethanol, and n-hexane at 64ºC. Furthermore, Salea *et al*. (2017) compared the extraction yields of 6-gingerol obtained from Soxhlet extraction with n-hexane (SE-n-hexane), high-pressure Soxhlet extraction with liquid carbon dioxide (HPSE-CO_2), percolation, and SFE. They found that the highest 6-gingerol

Table 1. Extraction methods of 6-gingerol from ginger.

Treatment conditions	Extraction conditions	Extraction yield (% of 6-gingerol in dried ginger)	References
Water extraction			
Hydro-distillation			
	50°C, 90 min, solid to solvent ratio 1:20 (w/v)	0.24%	(Awang *et al*., 2014)
Pressurized liquid extraction (PLE)			
	130°C, 10 MPa, 25 min	0.06%	(Ko *et al*., 2019)
	130°C, 3.5 MPa, 30 min, hot compressed water	0.17%	(Md Sarip *et al*., 2014)
Soxhlet extraction			
	Ethanol, 78.1°C, 8 h, solid to solvent ratio 1:4 (w/v)	0.84%	(Anisa *et al*., 2014)
	Food grade liquid CO_2, 35–45°C, 4–5 MPa, 6 h	14.79% (6-gingerol content in ginger oil extract)	(Salea *et al*., 2017)
	n-hexane, 69°C, 6 h, atmospheric pressure, solid to solvent ratio 1:12 (w/v)	4.59% (6-gingerol content in ginger oil extract)	(Salea *et al*., 2017)
Ultrasonic-assisted extraction (UAE)			
	Ethanol (80%), 65°C, 1 h, 250 W, 40 kHz, solvent to solid ratio of 65:1 mL/g	1.33%	(Liu *et al*., 2014)
	Methanol, 50°C, 1 h, solvent to solid ratio of 10:1 mL/g	1.27%	(Foudah *et al*., 2020)
Microwave-assisted extraction (MAE)			
	Ethanol (78%), 31 s, 528 W microwave power, solvent to sample ratio of 26:1 mL/g,	1.53%	(Liu *et al*., 2014)
	Ethanol (70%), 10 min, 180 W microwave power, solvent to solid ratio of 20:1 mL/g	0.28%	(Teng *et al*., 2019)
Pressurized liquid extraction (PLE)			
	70% bioethanol, 100°C, 1500 psi, 20 min	1.41%	(Hu *et al*., 2011)
Supercritical fluid extraction (SFE)			
	40°C, 280 bar, commercial extraction plant of capacity 2 × 200 L, followed by purification using silica gel column chromatography (CC)	25.97% (6-gingerol content in ginger extract)	(Swapna and Kadimi, 2014)
	35°C, 15 MPa, CO_2 flow rate of 15 g/min, 60 min static time, 160 dynamic time	20.69% (6-gingerol content in ginger extract)	(Salea *et al*., 2017)
Enzyme-assisted extraction (EAE)			
	Stargen (a blend of α-amylase and glucoamylase) and accellerase (blend of cellulose and glucosidase), 1 h incubation period, 50°C temperature, three-phase partitioning	0.047%	(Varakumar *et al*., 2017)
Ionic liquids-based extraction (ILE)			
	75°C, 30 min, 0.8 M [C10MIM]Br concentration, 0.1:10 g/mL solid to solvent ratio, 400 W power	0.334%	(Guo *et al*., 2017)

content resulted from SFE (20.6%) compared to other conventional methods. 6-gingerol content of HPSE-CO_2, SE-n-hexane, and percolation was 14.7, 4.59, and 6.26%, respectively. Although conventional extraction methods resulted in higher yields than SFE, thermal degradation occurs at high temperatures in conventional methods and 6-gingerol content decreases because 6-gingerol contains a thermolabile β-hydroxy keto functional group. Time is one of the key factors in the extraction because the extraction duration affects thermal liable bio-actives and the cost-effectiveness of the process (Aris and Morad, 2014). Azian *et al*. (2014) investigated the concentrations of 6-gingerol with different extraction times by Soxhlet extraction using ethanol as the solvent. The concentration of 6-gingerol was low in the first 2 h, but the rate of extraction increased within the next 6 h because the 6-gingerol, which saturated the ginger matrix, diffused to the solvent in the later 6 h of extraction. The maximum concentration of 6-gingerol (13.4 mg/g) was observed at 8 h in the extraction process. 6-Gingerol content was higher than other bioactive compounds (8-gingerol, 10-gingerol, 6-shagoal) found in the extract because 6-gingerol is more available in the ginger matrix while possessing lower molar volume and more polarity than other considered compounds (8-gingerol 10 gingerol, 6-shagoal). However, the major drawbacks of Soxhlet

extraction are poor extraction efficiency, long extraction time, and the requirement of a large amount of solvents (Zhang *et al*., 2020). High-temperature conditions in Soxhlet extraction may degrade thermolabile compounds and produce hazardous solvent waste (Azian *et al*., 2014).

Hydro-distillation is the most commonly applied technique for extracting plant essential oils and bioactive compounds. In hydro-distillation, heat is applied to a sample by steam or placed in boiling water, resulting in the bursting and breaking down of cell structures of plant materials. Thus, phytochemicals and essential oils are released from the sample (Tongnuanchan and Benjakul, 2014). Hydro-distillation can be categorized into three types of distillations. They are direct steam distillation, steam and water distillation, and water distillation (Azmir *et al*., 2013). Awang *et al*. (2014) investigated the application of hydro-distillation to extract ginger essential oil. Maximum ginger essential oil yield and 6-gingerol content from the extraction were 7.02% (w/w) and 35.3 mg/L, respectively, under optimum conditions; 50°C drying temperature, 90 min extraction time, and solid to solvent ratio of 1:20.

Nonconventional Extraction Methods of 6-gingerol

Microwave-assisted extraction

The microwave heating accelerates the mass and heat transfer while disrupting cells and tissues which enhances the release of bioactive compounds from cells to the surrounding medium (Garavand *et al*., 2019). This mechanism results in higher extraction yields under low extraction duration and quantity of solvents than conventional extraction techniques (Mena-García *et al*., 2019). Microwave power, radiation time and the number of extraction cycles, physicochemical properties of samples, type and concentration of solvent, and temperature and pressure are the main variables that affect the efficiency of MAE (Zhang *et al*., 2011).

The application of MAE for the extraction of 6-gingerol has been investigated. Liu *et al*. (2014) carried out single factor experiments to determine the optimal MAE conditions. The optimum conditions for MAE were: 528 W microwave power, 26 mL/g solvent to solid ratio, 31 s extraction duration, and 78% ethanol proportion. The 6-gingerol content (15.3 ± 0.85 mg/g) obtained by MAE under optimum conditions was higher compared to results obtained by stirring extraction, maceration, heat reflux extraction, and UAE. Furthermore, the yield of 6-gingerol increased with increasing ethanol concentrations. It reached a maximum at the ethanol concentration of 80% (v/v) because the polarity of ethanol for the high dielectric constant of water varies with its concentration, resulting in differences in solubility of 6-gingerol in ginger on the different concentrations of ethanol (Liu *et al*., 2014).

The effect of microwave radiation on the extraction yield of 6-gingerol and 6-shogaol from ginger was compared by Teng *et al*. (2019). In that study, 30.0% of 6-gingerol and 87.8% of 6-shogaol were obtained under optimized conditions: 70% ethanol concentration, 180W microwave power, and 10 min extraction duration (Teng *et al*., 2019). Accordingly, MAE proved efficient extraction efficiency of 6-gingerol with lower extraction time than other conventional extraction methods. Recently, Utama-ang *et al*. (2021) found that the yield of 6-gingerol decreased on high microwave power and long extraction time. This was because high microwave power and temperature accelerate the dehydration, reduction, and retro aldol reactions leading to the synthesis of 6-shogaol, paradol, and zingerone compounds from 6-gingerol. The microwave power of 400 W and extraction time of 1 min was the optimal conditions for MAE, resulting in 71.5 ± 3.6 mg/g of 6-gingerol.

Ultrasound-assisted extraction

UAE is extensively used to recover phytochemicals from plant materials. Ultrasound generates intense pressure, high shear stress, shock waves, and macro-turbulences resulting in cavitation (Supardan *et al*., 2012). UAE facilitates the release of extractable compounds from plant samples by speeding up the diffusion and solvent contact to the target compounds under accelerated mass and heat transfer through the cell walls of a plant matrix (Garavand *et al*., 2019).

Pandotra *et al*. (2013) examined the effect of different solvents on the extraction of 6-gingerol from fresh ginger rhizomes in India using the UAE. According to the mass yield data and liquid chromatography analysis, methanol was the best solvent compared with the other solvents (ethanol, ethyl acetate, acetone, and chloroform) used for extracting 6-gingerol. The 6-gingerol content of methanolic extracts obtained from the UAE was between 0.20 and 0.51% (Pandotra *et al*., 2013). In another study, UAE of polyphenols from ginger was optimized by response surface methodology (Murphy *et al*., 2020). Maximum polyphenols were extracted by 1200 mg of ginger in 86% ethanol under 11 min extraction time and 65°C temperature. The total phenolic content of the ginger extract was 1039.6 mg gallic acid equivalent (GAE)/g. Murphy *et al*. (2020) revealed that UAE increased the polyphenol yield and further showed the potential of ginger extract as a natural food preservative. According to Foudah *et al*. (2020), 6-gingerol content of ginger extract obtained from UAE and traditional extraction were 12.7 and 10.2 mg/g, respectively. Sasikala *et al*. (2018) found that the concentration of polyphenols from ginger increased by up to 1 min and decreased with further sonication time due to the degradation of polyphenols in the ginger sample.

Pressurized liquid extraction

PLE is a green technology that operates under high temperature and pressure, accelerating the mass transfer between the substrate and the solvent (Mustafa and Turner, 2011). As a result, PLE offers a higher extraction yield with low solvent consumption and a faster extraction than conventional extraction techniques (Alvarez-Rivera *et al*., 2020). When water is the solvent, PLE is called superheated water extraction (SHE), pressurized hot water extraction (PWE), or SWE (Gbashi *et al*., 2017).

Hu *et al*. (2011) conducted PLE of 6-gingerol with bioethanol/water as solvents. PLE operated at 1500 psi and 100°C for 20 min (static extraction time: 5 min) with 70% bioethanol as the optimum extraction conditions, achieving a 6-gingerol content of 14.106 ± 0.34 mg/g of dried ginger which was higher than the 6-gingerol content (13.203 ± 0.38 mg/g of dried ginger) obtained using Soxhlet extraction for 8 h. Furthermore, bioethanol was more efficient in extracting gingerol-related compounds using PLE than ethyl acetate, methanol, chloroform, and hexane. In another study, Ko *et al.* (2019) investigated optimum PLE conditions for extracting 6-gingerol and 6-shogaol obtained from ginger pulp and peel. The highest yield of 6-gingerol from the ginger pulp (0.68 ± 0.08 mg/g) was extracted at 130°C/25 min and the highest yield of 6-shogaol from the ginger pulp (0.39 ± 0.03 mg/g) was extracted at 190°C/15 min. In addition, 6-shogaol content increased with increasing temperature and time. This is due to the conversion of 6-gingerol to 6-shogaol by thermal cracking (Ko *et al*., 2019). The extraction yield increases at high temperatures due to the changes happening in water at elevated temperatures. For example, the constant dielectric declines at high temperatures making the polarity of water closer to that of nonpolar compounds by weakening hydrogen bonds. This phenomenon increases the solubility of less-polar compounds in water, facilitating extraction from different matrices (Teo *et al*., 2010). Several studies investigated the influence of temperature, extraction time, particle size, and the presence of a co-solvent on the extraction yield of SWE. Md Sarip *et al*. (2014) investigated the effect of extraction temperature and time on the extraction of 6-gingerol using SWE. The highest percentage recovery of 6-gingerol (20.71%) was obtained at 130°C and 30 min. Nourbakhsh Amiri *et al*. (2018) found that a pretreatment with α-amylase before SWE increased the concentration of total gingerols and shogaol by 2.22 folds. Furthermore, 2% ethanol as a co-solvent increased the 6-gingerol and 6-shogoal content in the ginger extract. The optimum conditions were 2% ethanol as co-solvent, 1 mm particle size of ginger, 130°C temperature, 20 bars pressure, and 30 min extraction time. The gingerols and shogaols, and polyphenol contents of the extract were 1346 μg bioactive/g dried ginger and 1.895 mg GAE/g dried ginger, respectively. Co-solvents improve the solubility and modify the interactions of solute with water (Nourbakhsh Amiri *et al*., 2018).

Supercritical fluid extraction

SFE is a sustainable, clean, and green extraction technology that resolved many limitations in other extraction methodologies (Da Silva *et al*., 2016). The solubilization of the compounds in a supercritical solvent and separation of extracted compounds from the supercritical solvent are the main steps in the SFE process. Supercritical fluids exhibit desirable transport properties such as low viscosity and high diffusivity. Quick diffusion through solid materials makes the extraction fast (Da Silva *et al*., 2016). The selection of SFE operating conditions such as temperature and pressure depend on the target compounds (Pereira and Meireles, 2010). Supercritical carbon dioxide is the commonly used solvent in SFE because it is nontoxic, economical, chemically inactive, and environmentally friendly. Supercritical carbon dioxide is generally recognized as a safe (GRAS) solvent (Uwineza and Waśkiewicz, 2020). In addition, the low critical temperature and pressure of CO_2 make it suitable for extracting thermally unstable and easily oxidized compounds (Khaw *et al*., 2017). SFE is used at the laboratory level as an analytical tool and at the industrial level in the food, cosmetic, and pharmaceutical industries due to its high efficiency (Uwineza and Waśkiewicz, 2020).

Swapna and Kadimi (2014) extracted gingerols from ginger using supercritical CO_2 and obtained a 6-gingerol content of 25.97% of the crude extract at a pressure of 280 bar, the temperature of 40°C in a commercial SFE plant capacity of 2 × 200L. The 6-gingerol content of the purified ginger extract was 75.9%. Salea *et al*. (2017) conducted SFE of ginger oil and achieved the highest 6-gingerol content (20.6%) at 15 MPa, 35°C, and CO_2 flow rate of 15 g/min. However, scaling up to a commercial scale plant reduced the 6-gingerol content (18.0%) of ginger oil. This indicated that the performance of SFE could be restricted by factors such as dimensions of the extractor, channeling, and aggregation (Salea *et al*., 2017). Temperature beyond 40°C causes dehydration of 6-gingerol to 6-shagoal. Therefore, previous SFE methods have been conducted around 40°C.

Shukla *et al.* (2019) developed single-step SFE processes combined with fractionation of dry ginger for the separation of oleoresin enriched with gingerols. They found that powdered ginger having a particle size between 355 μm and 1000 μm resulted in the highest yield of 7.5% because the large surface area of fine ginger particles facilitates the mass transfer between solid matrix and solvent whereas

finer ginger particles (having particle size lower than 355 μm) decrease solvent diffusivity by increasing packing density. 6-Gingerol content of ginger extract obtained from SFE was 2.26% and it was higher than the 6-gingerol content (2.21%) obtained from the Soxhlet method with 95% ethanol as the solvent. Furthermore, SFE extraction combined with fractionation showed high selectivity for 6-gingerol and increased the 6-gingerol content in oleoresin by 37.38 wt % (Shukla *et al*., 2019).

Enzyme-assisted extraction

In recent years, an interest in EAE has increased because it is eco-friendly, sustainable, and efficient extraction technology. EAE involves using hydrolytic enzymes to disrupt the plant cell walls, consisting of cellulose, hemicellulose, lignin, and pectin, thereby accelerating the release of intracellular compounds (Boulila *et al*., 2015). In addition, EAE facilitates the extraction of anchored bio-actives within vacuoles and plant cell walls (Gligor *et al*., 2019). Therefore, it is essential to understand factors such as mode of action and catalytic property of the enzymes, appropriate enzyme combination, extraction duration, solvent system, temperature, substrate availability, and pH condition for efficient extraction (Nadar *et al*., 2018).

Nagendra Chari *et al*. (2013) conducted EAE using α-amylase, protease, cellulase, pectinase, and viscozyme to determine the effect of enzymes on the yield of oleoresin and 6-gingerol content of ginger. The yield of oleoresin and 6-gingerol for enzyme pretreated ginger (α-amylase or viscozyme) were 20 ± 0.5 and 12.2 ± 0.4%, respectively, which were higher compared to the control sample (15 ± 0.6% oleoresin, 6.4 ± 0.4% 6-gingerol). In another study, Varakumar *et al*. (2017) determined the effect of enzymatic pretreatment and extraction (three-phase partitioning) of 6-gingerol from the fresh ginger rhizome. Enzyme-assisted three-phase partitioning was conducted using stargen and accellerase. Stargen consists of α-amylase and glucoamylase, while accellerase is a mixture of cellulose and glucosidase. Accellerase pretreatment increased the 6-gingerol content by 64.10%, whereas stargen pretreatment increased the yield of 6-gingerol by 58.39%. Mainly cellulose and glucosidase mixture synergically contribute to cell wall degradation and recovery of 6-gingerol. The pH value of the medium plays a role as acidic pH influences hydrogen bond destabilization on cell walls and catalytic activity of enzymes (Gligor *et al*., 2019).

Ionic liquids-based extraction

Ionic liquid-based extraction (ILE) is widely applied for chemical and engineering purposes due to the excellent properties of ionic liquids such as environmental friendliness, thermal stability, low melting point, low vapor pressure, high viscosity, and favorable solvating properties for nonpolar and polar chemical compounds (Yang and Dionysiou, 2004). Furthermore, ionic liquids can interact with electromagnetic fields due to their ionic character and ionic liquid-based MAE or ionic liquid-based UAE have been studied as preferable alternative methods due to higher extraction efficiency with low extraction time (Ventura *et al*., 2017).

Guo *et al*. (2017) investigated the MAE of gingerols from ginger with different ionic liquids as solvents. They found that 1-decyl-3-methylimidazolium bromide-[C10MIM]Br was the best ionic liquid as compared to other ionic liquids such as 1-hexyl-3-methylimidazolium bromide ([C6MIM]Br), 1-decyl-3-methylimidazolium toluenesulfonate ([C10MIM]ToS), 1-decyl-3-methylimidazolium chloride ([C10MIM]Cl), and 1-octyl-3-methylimidazolium bromide ([C8MIM]Br). The yield of 6-gingerol obtained in MAE with [C10MIM]Br as the solvent (0.334%) was higher than that with methanol-marinated extraction (0.299%) and methanol-based MAE (0.314%) at extraction conditions: 0.8M [C10MIM] Br, 75°C temperature, 0.1:10 g/mL solid to solvent ratio, 30 min extraction time, and 400 W irradiation power. Absorption ability and flow of microwave energy in ionic liquids increase with enhancing the concentration of ionic liquids but the excess increase of the concentration of ionic liquid leads to lower penetration of solvent into the sample with enhanced viscosity (Guo *et al*., 2017).

Kou *et al*. (2018) extracted 6-gingerol from ginger using the ionic liquid-based ultrasonic-assisted extraction (ILUAE) in a one-step process. ILUAE significantly increased the extraction efficiency of 6-gingerol than traditional extraction methods. The extraction yield of gingerols was 12.21 mg/g under the optimized conditions. The concentration of butyl-3-methylimidazolium tetrafluoroborate ($[C_4mim]BF4$), temperature, extraction time, irradiation power, and solid to solvent ratio were 1.5 M, 25°C, 10 min, 200 W, and 1:20 g/mL, respectively. The length of the alkyl chain affects the yield of total gingerol under the same anion while the butyl alkyl chain exhibits the best solvation for gingerol.

According to the studies discussed above, water is not a suitable solvent for extracting 6-gingerol due to its poor solubility in water. Hydroalcoholic solutions and liquid CO_2 are the best solvents for the extraction of 6-gingerol (Table 1). Considering all the conventional and novel extraction techniques, MAE seems to be the most promising extraction method giving high extraction yields of 6-gingerol (Table 1). The MAE method has provided the maximum 6-gingerol yield at 1.5%. However, as outlined in previous studies, the yields of 6-gingerol are also

highly dependent on cultivation conditions (Kizhakkayil and Sasikumar, 2011), maturity stage of ginger (Kiran *et al*., 2013), and extraction process parameters (Awang *et al*., 2014). Therefore, it limits the direct comparison of the extraction yields of 6-gingerol obtained from different extraction studies (Table 1). Although MAE exhibits high extraction yield, low extraction duration, and low solvent consumption compared to other extraction methods, the efficiency of the MAE depends on the particle size, molecular size, and covalent attachment in the ginger matrix (Bagade and Patil, 2021). Extraction conditions of MAE including microwave power, extraction temperature, and extraction time should be controlled properly to prevent the conversion of 6-gingerol into 6-shogaol, paradol, or zingerone, and the MAE method can be modified further for the extraction of thermally sensitive compounds (Wang *et al*., 2018). Further studies are needed on the combination of efficient extraction methods which can increase the extraction of 6-gingerol from the rhizome of ginger.

Other nonconventional extraction methods of 6-gingerol

Techniques such as high voltage electric field (HVFD), pulse electric field (PEF), high-pressure processing (HPP), high-pressure homogenization (HPH), and ohmic heating (OH) are also studied alone or combined with other extraction techniques to increase the extraction efficiency of bioactive compounds from plant materials (Nguyen *et al*., 2021). HVED is based on the electrical breakdown in a liquid phase, resulting in cavitation, intense shock waves, strong UV radiation, and turbulence, leading to cell disruption and efficient extraction of bioactive compounds (Xi *et al*., 2017). The PEF technique is based on applying high voltage electrical pulses within a short time, resulting in the electroporation phenomenon. PEF enhances the permeability and conductivity of the cell membrane and increases the release of intracellular compounds (Mohseni *et al*., 2020). HPP shows great potential in the extraction of bioactive compounds. HPP technology works under high-pressure conditions, increasing cell permeability and diffusion of intracellular compounds with enhanced mass transfer rate (Agcam *et al*., 2021). HPH is a technique that works on the application of mechanical stress by forcing the liquid through a narrow gap using a displacement pump. The shear stress, cavitation, and turbulence resulting from the HPH process cause disruption of cell walls and cell membranes, resulting in the efficient release of bioactive compounds (Xing *et al*., 2019). In OH, the food sample acts as an electrical current conductor and internal heat is generated due to the electrical resistance of the food material. As a result, OH technology effectively extracts bioactive compounds becoming an alternative to conventional extraction methods (Hilphy *et al*., 2020). Although the extraction efficiency of bioactive compounds from plant material using these nonconventional extraction techniques has been proved by research studies, its applicability to the extraction of 6-gingerol from ginger has not gained much attention. In further studies, researchers can consider these methods to determine the efficient extraction method of 6-gingerol.

6-Gingerol purification techniques

Purification is an essential step after the extraction process for commercial applications of bioactive compounds. Different purification techniques are applied to purify 6-gingerol from ginger extracts or commercial crude gingerols. Recent research studies have utilized CC, Semi-prep HPLC, and HSCCC to purify 6-gingerol (Table 2).

Column chromatography

CC is a technology that offers separate bioactive compounds according to the distribution coefficients of the components in the stationary and mobile phases. CC technologies such as silica gel chromatography, flash chromatography, and vacuum chromatography were applied to isolate bioactive components from ginger (Wen *et al*., 2019; Zarate *et al*., 1992). The selection of stationary and mobile phases is vital for obtaining the maximum amount of target compounds because the separation efficiency in CC depends on the adsorption properties of the target compound (Ren *et al*., 2013). CC using silica gel is a common, simple, and low-cost technique broadly used to separate natural compounds (Zhang *et al*., 2018). Wang *et al*. (2017) applied the silica gel–based adsorption chromatography method with petroleum ether and ethyl acetate as the mobile phase for separating 6-gingerol from ginger. In this method, the purity of 6-gingerol was 98.1%. Swapna Sonale and Kadimi (2014) studied the composition of column chromatographic fraction of SFE-CO_2 purified ginger extract on a silica gel column using n-hexane and diethyl ether as the mobile phase. The 6-gingerol content of the SFE-CO_2 was 75.9%. Accordingly, petroleum ether and ethyl acetate could be considered a better mobile phase for the purification of 6-gingerol using silica gel–based CC.

Semi-preparative high-performance liquid chromatography

Semi-prep HPLC is a rapid and versatile technique to purify natural components (Latif and Sarker, 2012). The term preparative refers to the operation of an high-performance liquid chromatography (HPLC) system in a large column at high flow rates to purify compounds in large quantities (Mahato *et al*., 2019). Several studies

Table 2. Purification methods of 6-gingerol.

Samples	Material conditions	Operation conditions	Purity	References
Column chromatography (CC)				
Ethyl acetate extract	Silica gel column, petroleum ether/ethyl acetate as the mobile phase	Gradient elution consisting of petroleum ether and ethyl acetate (5:1, 4:1, 3:1, 2:1, and 5:3) with 500 mL of each mixture	98.15%	(Wang *et al*., 2017)
SFE extract	Silica gel column, n-hexane: diethyl ether as the mobile phase	Successive elution consists of n-hexane and diethyl ether with different proportions (80:20), (50:50), (40:60), (20:80)	75.92%	(Swapna and Kadimi, 2014)
Semi-preparative high-performance liquid chromatography (semi-prep HPLC)				
Ethanol extract	Luna C18 column (300 × 10 mm, 10 μm); methanol-water (75:25 v/v) as mobile phase	Flow rate at 6 mL/min, injection volume of 0.425 mg/μL	94.4%	(Silva *et al*., 2012)
Methanolic extract	C18-AR-II column Cosmosil (250 × 10 mm, 5 μm); acetonitrile-water (gradient method) as mobile phase	Flow rate at 3 mL/min, injection volume of 50 μL	98.3%	(Gawel *et al*., 2021)
High-speed counter-current chromatography (HSCCC)				
Ethanol extract	CCC TBE-300A instrument equipped with three polytetrafluoroethylene multilayer coils and UV absorbance measurement	Two-phase solvent system: light petroleum/ethyl acetate/methanol/water (5/5/6.5/3.5, v/v)	99%	(Zhan *et al*., 2011)
Ether extract	Preparative HSCCC with e multilayer coiled column and UV absorbance measurement	Two-phase solvent system: petroleum ether/ethyl acetate/methanol/water (1/0.2/0.5/0.7, v/v) and petroleum ether/ethyl acetate/methanol/water (1/0.2/0.7/0.5, v/v) in a stepwise elution	99.9%	(Wang *et al*., 2011)
SFE extract	Preparative HSCCC with e multilayer coiled column and UV absorbance measurement	Two-phase solvent systems: n-hexane/ethyl acetate/methanol/water (7/3/5/5, v/v), n-hexane/methanol/water (3/2/1, v/v) and n-hexane/chloroform/acetonitrile (6/2/5, v/v)	98.6%	(Wang et al., 2020)
SFE extract	Preparative HSCCC with e multilayer coiled column and UV absorbance measurement	Two-phase solvent system: n-hexane/ethyl acetate/methanol/water (10/2/5/7, v/v/v/v)	99.6%	(Gan *et al*., 2016)

suggested that the semi-prep HPLC method effectively purifies 6-gingerol as considerable amounts of 6-gingerol with high purity can be achieved quickly. Silva *et al.* (2012) conducted semi-prep HPLC to separate the 6-gingerol using a C18 column, and methanol/H_2O (75:25, v/v) was the best mobile phase. 6-Gingerol with high purity (94.4%) was obtained in a 30-min chromatographic run with a 6 mL/min flow rate and 400 μL injection volume. Gawel *et al.* (2021) isolated 6-gingerol from a methanolic ginger extract using a semi-preparative column. A purity of 98.3% of was obtained using a flow rate of 3 mL/min.

High-speed counter-current chromatography

HSCCC is a partition chromatography technique based on the separation of compounds using two immiscible liquid phases, whereby the stationary phase is a liquid (Wang *et al*., 2020). HSCCC has been extensively used to isolate and purify active compounds from natural products (Chen *et al*., 2018). In the HSCCC technique, the liquid stationary phase is retained in the column using the centrifugal force while the liquid mobile phase is pushed through it. Each compound is distributed between the stationary and mobile phases based on the component's distribution coefficient (Abdel Ghafar *et al*., 2009). It is an economically viable alternative for purification procedures because it displays rapid and effective recovery, easy scaling-up potential, and low solvent consumption (Khan and Liu, 2018).

HSCCC is a novel method that successfully isolates and purifies gingerols from the ginger extract. Zhan *et al*. (2011) employed HSCCC to purify gingerols from ginger using a solvents system composed of light petroleum/ethyl acetate/methanol/water (5/5/6.5/3.5 v/v/v/v). The yield of 6-gingerol, 8-gingerol, and 10-gingerol from 200 mg of crude extract in one-step separation were 30.2 mg, 40.5 mg, and 50.5 mg with the purity of 99.9, 99.9, and 99.2%, respectively. HSCCC combined with better extraction, and the pre-purification method is an effective way to separate and purify gingerols from ginger extract (Wang *et al*., 2011). Accordingly, the gingerols were successfully separated with petroleum ether/ethyl acetate/methanol/water (1/0.2/0.5/0.7, v/v/v/v) and petroleum ether/ethyl acetate/methanol/

water (1/0.2/0.7/0.5, v/v/v/v). The yield of 6-gingerol, 8-gingerol, and 10 gingerol from 360 mg of pre-purified samples were 132 mg (purity; 98.7%), 31 mg (purity; 99.3%), and 61 mg (purity; 98.5%), respectively (Wang *et al*., 2011). Wang *et al*. (2020) performed HSCCC using different two-phase solvent systems at a flow rate of 2 mL/min and 35 mg of 6-gingerol was obtained with 98.6% purity. In another study, Gan *et al*. (2016) found that a two-phase solvent system composed of n-hexane/ethyl acetate/methanol/water (10/2/5/7, v/v/v/v) was optimal for the isolation of 6-gingerol by HSCCC. A total of 90.38 mg 6-gingerol with a purity of 99.6% was isolated from 600 mg of ginger oleoresin using supercritical extraction and molecular distillation. Therefore, HSCCC methods can be considered as the promising alternative method for the isolation of 6-gingerol.

Comparing the purification techniques in Table 2, HSCCC results in 6-gingerol with higher purity compared to other purification methods. However, more studies should be conducted to explore other purification techniques such as preparative supercritical fluid chromatography and crystallization. Apart from the purity of 6-gingerol, the practicability, effectiveness, and the feasibility of industrial adaptation of each purification method should be considered in selecting the proper purification method. Conventional purification methods including CC methods are less effective, time-consuming, tedious, and require multiple chromatographic steps (Wen *et al*., 2019). Using a semi-prep HPLC technique, Silva *et al*. (2012) isolated 94 mg of 6-gingerol with high purity (94.4%) in 30 min. Currently, automated prep-HPLC systems allow user-friendly purification of valuable compounds within a relatively short duration (Mahato *et al*., 2019). According to previous reviews, the HSCCC method having a liquid stationary phase is faster and an economically viable alternative for purification and it can be easily adapted and scaled up for industrial application (Khan and Liu, 2018). In the study conducted by Zhan *et al.* (2011), 30.2 mg of 6-gingerol with a purity of 99.9% was obtained using HSCCC, starting from 200 mg of crude ginger extract. However, the period of the chromatographic run was extensive (240 min). Some researchers have combined CC with HSCCC for the separation of 6-gingerol. Wang *et al*. (2011) used HSCCC to obtain 132 mg of 6-gingerol with 98.7% purity in 360 min, starting from 360 mg of ginger extract which had been subjected to initial purification on a silica column.

Current research on the application of 6-gingerol in the food industry

Increasing awareness regarding the health benefits of natural bioactive compounds containing products has elevated the demand and market size of such high-value products. Over the past three decades, extensive research and preclinical studies have been conducted indicating the potential application of 6-gingerol in the pharmaceutical industry against many human diseases. In addition, there is increased utilization of 6-gingerol in the food and cosmetic industries.

Researchers have paid attention to expanding the application of 6-gingerol in the food industry by introducing various technologies. 6-Gingerol possesses antioxidant properties, thus demonstrating potential application as a natural antioxidant in processed food products. Si *et al*. (2018) stated that 6-gingerol inhibits the oxidation of canola oil. The effect of 6-gingerol on properties of grass carp surimi fortified with perilla oil was investigated by Mi *et al*. (2017). It was found that 6-gingerol preserves grass carp surimi, preventing microbial growth as well as protein and lipid oxidation during refrigerated storage. Also, 6-gingerol combined with perilla oil improved the physical properties of surimi, including gel strength, water-holding capacity, and textural quality. Moreover, 6-gingerol can retard lipid oxidation and hydrolysis and maintain edible quality such as color and sensory properties in red drum muscle (Mi *et al*., 2016).

Table 3. Application of 6-gingerol in the food industry.

Applications	Results	Reference
Addition of 6-gingerol to canola oil	6-gingerol inhibited the oxidation of fat in canola oil	(Si *et al*., 2018)
Application of 6-gingerol to grass carp surimi fortified with perilla oil	6-gingerol prevented the microbial growth of perilla oil fortified surimi during refrigerated storage and inhibited the lipid and protein oxidation	(Mi *et al*., 2017)
Treatment on shrimp paste with tea polyphenol and 6-gingerol	The shrimp paste treated with tea polyphenol and 6-gingerol maintained the color, sensory quality, and total amino acid. Furthermore, it resulted in low microbial count and biogenic amines content	(Li, 2015)
Use of 6-gingerol-enriched sodium alginate coating on red sea bream fillets	Alginate coating combined with 6-gingerol retarded the lipid oxidation, protein degradation, and extended the shelf-life of red sea bream	(Cai *et al*., 2015)
Development of a nanoscale delivery system for gingerol- enriched oleoresin and incorporation in candied mango products	The delivery system developed for gingerols-enriched oleoresin worked as a food flavor, shelf-life stabilizer, and nutraceutical agent	(Shukla *et al*., 2020)

6-Gingerol can extend the shelf-life of food by acting as a natural preservative. Tea polyphenols and 6-gingerol demonstrate a synergistic effect for maintaining the quality of fish products and increasing their shelf-life. Li (2015) reported that shrimp paste treated with tea polyphenols and 6-gingerol maintained satisfied paste appearance and sensory quality. Also, it demonstrated low microbial count and inhibition of oxidation of protein and lipids. Furthermore, 6-gingerol demonstrated a significant antibacterial effect by extending the shelf-life of refrigerated red sea bream combined with alginate coating to 20 days (Cai *et al*., 2015). It has been experimentally proven that 6-gingerol reduced *Pseudomonas aeruginosa* biofilm formation, which is vital to enhance antibiotic effectiveness and reduce the pathogenicity of *Pseudomonas aeruginosa* (Kim *et al*., 2015).

Numerous research studies have explored the application of 6-gingerol as a food flavor and nutraceutical agent, demonstrating potential in commercial food applications (Kubra and Rao, 2012). Shukla *et al*. (2020) developed a formulation for nanoscale delivery of gingerol-enriched oleoresin in the candied mango product. Its nutraceutical profile and flavor were improved during 90 days of shelf-life at 25°C. In addition, 6-gingerol acts as a natural inhibitor of fungal alpha-amylase, which can inhibit *Aspergillus flavus* which is responsible for producing toxic aflatoxin (Tintu *et al*., 2012). Utama-ang *et al*. (2021) developed an edible Thai rice film fortified with ginger extract. According to their study, rice film showed significant antimicrobial properties by incorporating 3.2% (w/v) ginger extract while 6-gingerol is the main bioactive compound present in the ginger extract.

Although 6-gingerol possesses a wide range of potential benefits in the food industry, its processing conditions have to be controlled properly. Because 6-gingerol contains thermally liable β-hydroxy keto group and 6-gingerol could be converted to 6-shogaol at high temperature conditions (Awang *et al*., 2014). Furthermore, the low bioavailability of 6-gingerol limits its application in the food industry. Therefore, novel formulations for improving the bioavailability have to be discovered for the effective incorporation of 6-gingerol into food products (Wang *et al*., 2017). The studies which have explored the contribution of 6-gingerol in the food industry are limited; thus, more research can be conducted in the future.

Recent advances for the improvement of the bioavailability of 6-gingerol

Applications of 6-gingerol in industries are strongly limited because of the low water solubility, which severely reduces its oral bioavailability. Therefore, several encapsulations and solubilization techniques, including nanoparticles, complexation, micelles, nano-emulsion, and solid dispersion, are explored to solve the physicochemical challenges of 6-gingerol and enhance its application spectrum (Shukla *et al*., 2020). One strategy was the modification of a micro-emulsifying drug delivery system that can increase the plasma concentration of 6-gingerol and novel drug development (Xu *et al*., 2016). The self-micro emulsifying drug delivery system (SMEDDS) was made with oils, surfactants, and co-surfactants. The mean droplet size, zeta potential, and encapsulation efficiency were 73.06 ± 0.49 nm, -2.45 ± 0.41, and 89.40 ± 1.11%, respectively. Accordingly, 6-gingerol-SMEDDS demonstrated stable physicochemical properties with spherical and homogenous nanoparticles.

Modifying 6-gingerol proliposomes using the thin-film dispersion method was another technique for overcoming the low bioavailability of 6-gingerol (Wang *et al*., 2017). 6-Gingerol proliposomes showed physical stability demonstrating narrow particle size distribution. Furthermore, 6-gingerol-loaded proliposome exhibited a significantly higher in vitro release rate, and 6-gingerol concentration in the bloodstream was five times higher than the free 6-gingerol. Wei *et al*. (2018) developed a nanostructured drug delivery system through HPH, and the optimum formulation of these nano lipid carriers significantly increased the water solubility and the bioavailability of 6-gingerol. Nanostructured lipid carriers loaded with 6-gingerol displayed a stable, spherical, and homogeneous formulation with a mean particle size of 63.59 ± 5.54 nm and zeta potential of -12.18 ± 1.06 mV.

The polymeric micelle system formed with amphiphilic polymeric molecules is an effective nano-drug carrier (Ghezzi *et al*., 2021). Zhen *et al.* (2020) prepared a polymeric micelle of 6-gingerol via solvent injection method. 6-Gingerol-based polymeric micelle drug delivery system showed a homogenous and spherical morphology with even particle distribution, thereby increasing the solubility and bioavailability of 6-gingerol. Glycosylation is another valuable technique based on the synthesis of glycosides in the presence of biocatalysts for producing water-soluble and stable chemical compounds (Ojima *et al*., 2012). Matsumoto *et al.* (2016) investigated the microbial glucosylation of 6-gingerol, and 5-O-α-glucosylgingerol was produced in the presence of *Ensifer* sp. M-26 using the mixture of maltose and 6-gingerol. They also suggested that the biological properties of 5-O-α-glucosylgingerol should be further investigated to determine the possibility of application of 5-O-α-glucosylgingerol in functional food.

Recently, extracellular vesicles have received more attention as a new natural nanoscale drug carrier in drug delivery systems and clinical studies due to their ability to encapsulate and transport necessary active biomolecules such as proteins, lipids, and nucleic acids (Elsharkasy

et al., 2020). Man *et al*. (2021) studied the loading potential and absorption characteristics of ginger-derived extracellular vesicles (GDEV) as drug carriers in the small intestine of rats. The content of 6-gingerol was 10.21-fold of those in ginger slices under the same mass, revealing a better loading capacity of the GDEV nanocarrier system.

Encapsulation of bioactive compounds using electrospinning has gained attention in the food industry as any extreme conditions of temperature, pressure, or hazardous chemicals are not used in this method. In the electrospinning technique, bioactive compounds are encapsulated into fiber by applying an electric field (Wen *et al*., 2017). Mendes *et al*. (2016) developed nanofibers using the electrospinning method to increase the bioavailability of curcumin. Research can be explored on applying encapsulation of 6-gingerol to commercial food products using the electrospinning technique alone or combined with other technologies. Furthermore, protein-polysaccharide conjugates based on the Maillard reaction is a novel approach in the food industry for encapsulation and delivery of bioactive compounds. This delivery system shows stability over pH values and temperature and good solubility and emulsifying capacity. Protein-polysaccharide conjugates–based food emulsions have high stability and improve the bioavailability of lipophilic bioactive compounds (Nooshkam and Varidi, 2020). More research can be continued on this delivery system for encapsulation of 6-gingerol in food products.

These novel techniques improving the bioavailability of 6-gingerol mainly focus on developing drug delivery systems in the pharmaceutical industry. However, it is worth carrying out further studies on 6-gingerol to determine the possibility of applying the above novel techniques in the food industry as functional ingredients to promote human health and well-being. Specifically, techniques such as encapsulation by electrospinning and protein-polysaccharide conjugates have the potential for the application of 6-gingerol in the food industry.

Conclusion and Future Perspective

6-Gingerol possesses a variety of biological activities, which are influential for the extensive application of 6-gingerol in the food, cosmetic, and pharmaceutical industries. Various techniques for the extraction and purification of 6-gingerol have been reported. Conventional extraction techniques, including solvent extraction, Soxhlet extraction, maceration, and steam distillation usually require a large amount of solvents, resulting in a negative environmental impact. Thermal degradation of 6-gingerol to 6-shagoal occurs due to high temperature and long extraction duration. Therefore, maintaining proper temperature conditions and duration in the extraction process is critical for obtaining a maximum yield of 6-gingerol. Recently, researchers have explored more green and sustainable extraction techniques such as SFE, UAE, MAE, PLE, EAE as alternatives to resolve the drawbacks of conventional extraction methods. Researchers can focus on combining different extraction methods, which may further increase the recovery of 6-gingerol. In addition to the above methods, other nonconventional extraction techniques such as HVFE, PEF, HPP, HPH, and OH can be considered for future research to determine the effect of these methods on the efficient extraction of 6-gingerol from ginger. Purification is a vital step in the recovery of 6-gingerol with high purity. Out of the purification techniques discussed in this review, HSCCC is the best purification technique for recovering highly purified 6-gingerol. Further studies on the purification of 6-gingerol using different methods such as preparative supercritical fluid chromatography and crystallization can be conducted to evaluate their effectiveness. Scale-up and feasibility studies on extraction and purification of 6-gingerol are very important for establishing efficient industrial production of commercial products. Optimum conditions identified for recovery of 6-gingerol in laboratory studies can be considered for scaling up studies. Reduced bioavailability of 6-gingerol due to its poor solubility in water strongly limits its applications in the food industry. Recent studies have revealed many strategies, including producing nanoparticles, complexation, micelles, nano-emulsion, and solid dispersion to overcome poor bioavailability and broaden its utilization. Studies have proved the potential applications of 6-gingerol as a natural antioxidant, preservative, and flavor enhancer. However, further exploration is needed, especially in developing functional food enriched with 6-gingerol having high bioavailability to deliver the maximum health benefits to consumers.

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