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A comprehensive review on Ginger (*Zingiber officinale*) as a potential source of nutraceuticals for food formulations: Towards the polishing of gingerol and other present biomolecules

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Abstract

Currently, ginger is one the most consumed plants when dealing with the treatments of various illnesses. So far, it is known that various biologically active molecules, such as gingerols, shogaols and zingerone, among others, are the main responsible for specific biological activities, opening a new window for its utilization as a nutraceutical in foods. In pioneering extraction processes, solvent extraction has been initially used for these applications; however, the drawbacks of this typical extraction method compared with other emergent separation techniques make it possible for the exploration of new extraction pathways, including microwave, ultrasound, supercritical, subcritical and pressurized-assisted extraction, along with three phase partitioning, high-speed counter current chromatography and magnetic solid phase extraction. To the best of our knowledge, *there is no report documenting the recent studies and cases of study in this field*. Here, we review the progress of the current research developments, focused on meaningful outcomes and strategies.

Keywords: *Ginger, metabolite purification, nutraceuticals, gingerol, shogaol.*

Abbreviations:

CO_2: carbon dioxide

GNs: Gingerols

HSCC: Subcritical water extraction

MAE: Microwave-assisted extraction

MSPE: Magnetic solid phase extraction

PLE: Pressurized liquid extraction

SCFE: Supercritical fluid extraction

SWE: Subcritical water extraction

TPP: Three phase partitioning

UAE: Ultrasonic-assisted extraction

1. Introduction

Nutraceuticals are natural biomolecules that do not require complex processes for its production; they are typically obtained from natural products whether they are plant, mineral or animal based. Often, they are utilized as a food supplement in the form of powder or pills without being considered pharmaceutical drugs, as they do not assure that the component is completely effective in dealing with a disease or condition. Mostly, they are used as an alternative to prevent specific conditions, which will require medication if the person consuming them does not take care of their health. Products, such as punicic acid and whey protein, are examples of these nutraceuticals as they have specific needs for their target audience (López Flores et al., 2016). Punicic acid, for instance, is a food supplement for diabetics as it can help express mechanisms that can reduce glucose levels, preventing the need for aggressive drugs like metformin. On the other hand, whey protein helps bodybuilders and athletes fulfill their protein intake after exercise to build muscle mass. Since nutraceuticals do not require medical intervention to be administered, there is a current need for searching different types of sources of these components. It is likely that ginger is one of the most used natural products by society due to its content of

phytochemicals, which could be used to extract a wide variety of nutraceuticals. Likewise, Ginger is one of the most investigated natural sources over the last decades; for instance, **Figure 1** evidences the continuous effort from the research community, as evidenced by the number of publications related to this natural source. As can be seen in **Figure 1**, this natural product may be strongly explored in recent years, which could be associated with the dietary supplements and nutraceuticals market growth due to the coronavirus pandemic. In this latter framework, many extracts and their related-bioactive substances are currently being investigated to face symptoms related to this virus.

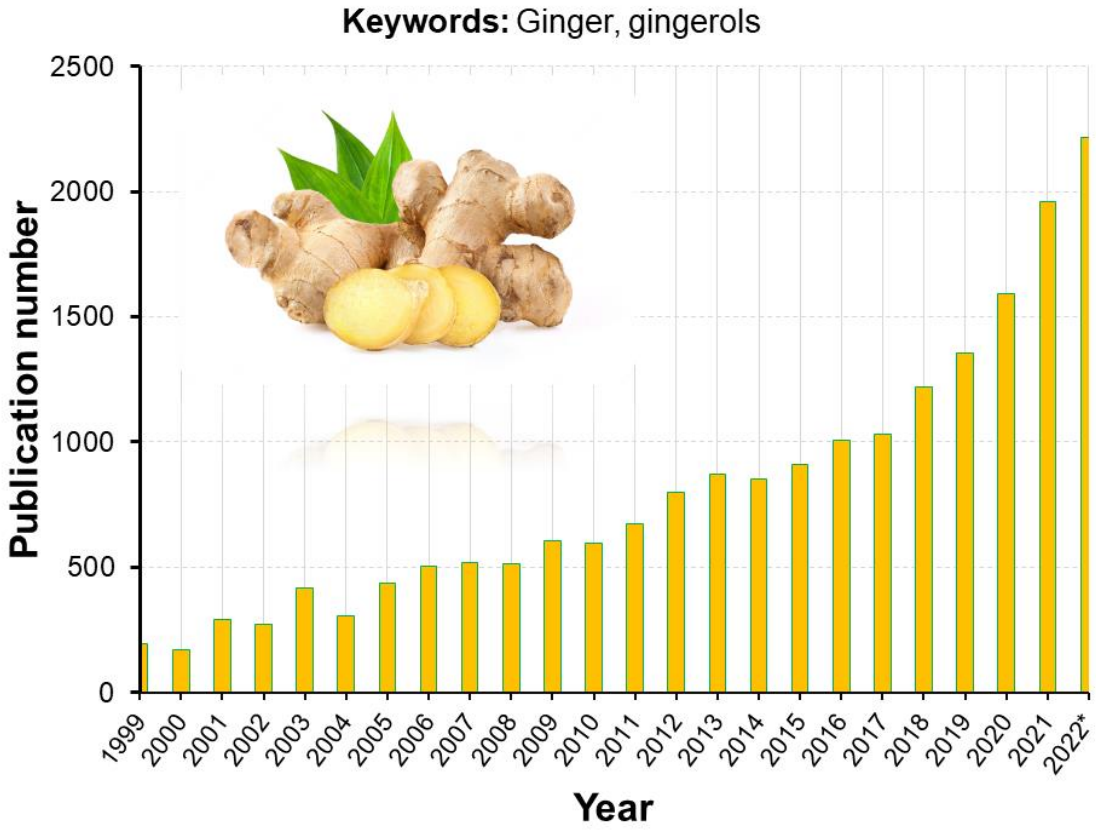


Figure 1. Documented publications associated with the research towards Ginger over the last two decades (until October 19th, 2022; source: Scopus). *Keywords*: Ginger, gingerols

Ginger is a plant indigenous to tropical Asia that is now cultivated across the world. There are records of this root being used for both culinary and medical applications as well as being noted by other cultures as a useful spice to combat nausea and stomach related illnesses. The use of ginger, whether in fresh or dried forms, allows for the treatment of different conditions related to pain. Most of the compounds tend to be processed to extract what is necessary for the treatment to produce nutraceuticals. Though, in ancient times, most of the ginger was used as a food additive for treatments (Semwal et al., 2015).

Although ginger is one of the most consumed spices in the world with at least 115 varieties between fresh and dried ginger, the geographical differences between varieties allows the creation of different compounds. For instance, Ginger contains gingerol, chemically known as [6]-gingerol, which displays a nutraceutical effect. This biomolecule is identified as a phenol phytochemical compound found in fresh ginger that activates spice receptors on the tongue. Gingerols are associated with the alleviation of nausea, arthritis, and pain; while some of these gingerols have a specific role helping in the treatment of diabetes and various tumours (Yulianto et al., 2020). While these properties are being studied in different cell lines rather than tested on humans, they set a precedent for investigating the ginger itself. Gingerol compounds are thermally labile and transform at high temperature into shogaols which serve to create biomarkers for ginger related products. Gingerols have a high commercial value that pushes the development of different ways to biosynthesize and extract them. Therefore, experimenting on different extraction methods seems to be the most friendly and efficient pathway of obtaining them from their natural source (Yulianto et al., 2020). In this review, we analyse the current

developments, ideas and methods for extracting gingerols and some other related biomolecules from ginger, paying attention to the most relevant outcomes and findings. Considering that most of the Ginger substances are nutraceuticals, a feedback on the main medicinal and biological activities of such compounds is also given.

2. An overview on medicinal and biological activities of Ginger extracts

Acquire the knowledge about ginger extracts and their impact in different fields of medicine is of utmost importance to provide a conscious about bioprocessing and biotechnology. This root has been used for different medical purposes, for example, ginger based infuses are commonly prepared worldwide to alleviate many ills like treat coughs, colds and flu. In some countries, this specie was mainly used to reduce fatigue, combat nauseas, prevent rheumatism (especially Indian thought) and improve digestion. As mentioned previously, ginger is an important source with a high nutraceutical value because of the variety of bioactive compounds, as shown in **Figure 2**. Several studies have demonstrated the importance of this root due to the presence of various biomolecules and their associated biological activity (Semwal et al., 2015). Specific compounds found in ginger are phenolic and terpene compounds, which are widely known as bioactive molecules that work as antioxidants, anti-inflammatory, antimicrobial and symptoms of cancer inhibitor activities. This latter characteristic is one of the most studied properties because it could be an opportunity to prevent cancer proliferation in any part of the body, however, it is also important to identify which compounds are the aim for achieving successful bio-products.

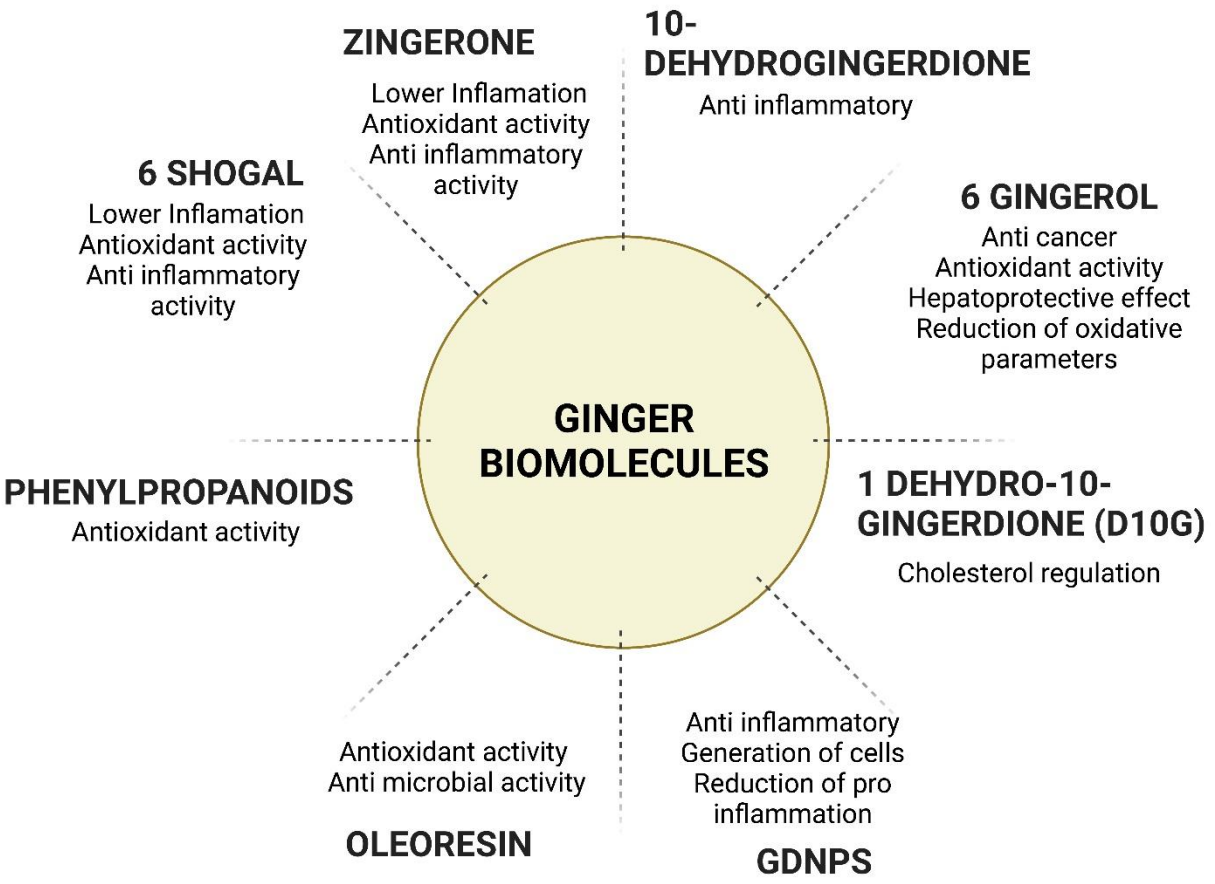


Figure 2. Importance and biological activities attributed to Ginger biomolecules.

Among phenolic compounds, there is a specific compound that increases the nutraceutical value of Ginger, such as gingerols (GNs). The typical chemical structure of GNs which display antioxidative properties and are studied for cancer prevention research (Mao et al., 2019).

To some extent, mechanism of action of these compounds are still unknown but with great potential to be discovered thanks to the evolution of high effective technologies in the pharmaceutical industries. For instance, Rahmani et al. reported that in the cancer

studies the compounds could give a biological modulation for some activities, such as antioxidant activity that prevent cell damage, anti-inflammatory which is an important activity for the modulation of genetic pathways (induction of apoptosis in endometrial cancer cells), antimicrobial properties against pathogens, among other activities towards critical diseases like obesity, cancer, diabetes, etc (Rahmani et al., 2014). However, the authors pointed out that deeper research is needed to recognize and understand each activity. In general, punctual biological activities have been attributed to the compounds contained in Ginger, as follows:

1. Antioxidative activity: The main role of ginger in the antioxidative activity is to balance free radicals' production and make a better defence system in humans. It is also used an *in vitro* evaluation via ferric-reducing antioxidant power aiming the break of phenolic compounds in the cell associated to phenolic contents after heated (Mao et al., 2019). Important compounds of ginger that work as an antioxidant factor are the flavonoids which are studied for reducing symptoms like vomit and nauseous in patients involved in chemotherapy sessions. This has been demonstrated by *in vitro* studies (Danwilai et al., 2017). Rahmani et al. reported that besides that ginger helps as a radical free production inhibitor, it also plays a role in reduction of lipid oxidation while acting as an important precursor for lipid oxidation to prevent gastrointestinal ills. Also, essential oils of ginger containing 6-dehydrogaol, 6-shogaol and 1-dehydro-6-gingerdione can bring antioxidative activities, which act as nitric oxide inhibitor and degrades macrophages (Rahmani et al., 2014).

2. Anti-inflammatory activity: There are several compounds that act as an anti-

inflammatory precursor for muscle contractions. Ginger oil has revealed such a characteristic, preventing the repression of paw associated with arthritis. For example, studies demonstrate that cytokines acquired in ginger, such as interleukin-1 (IL-1) and IL-8, are inhibitors in the pathway for inflammatory precursors. The main compounds are based on zingerone and gingerol related compounds (Rahmani et al., 2014). Additionally, ginger root has been used worldwide in plenty of countries to treat arthritis, muscular discomfort, and inflammation (Semwal et al., 2015).

3. Antimicrobial activity: It is known that some compounds formed in ginger root are precursors for inhibition the proliferation of bacteria, fungi, and viral infections, which may lead to chronic diseases or antimicrobial resistance. Specific lipophilic ginger compounds permit the disintegration of cell membrane thanks to the permeable phase

in which the compound attaches. In the case of viruses, ginger compounds block the attachment of viral organisms and then their inhibition (Mao et al., 2019). In a recent study, it was demonstrated that ginger rhizome is a great compound for microbial inhibition thanks to its constitution and related attachment to some bacterial cell membrane (Rahmani et al., 2014).

181 **Table 1.** Biomolecules present in Ginger and their related biological activities.

Molecule	Concentration	Biological activity	Remark of the study:	References:
6-gingerol	5 mg per pill. 2 pills prior to chemotherapy	Antioxidant activity. Reduction in oxidative parameters.	Antioxidative parameters CuZn-SOD, CAT, GPx and GSH/GSSG increased, while xidant parameters MDA, NO2- /NO3- declined.	(Danwilai et al., 2017)
	N/A*	Anticancer activity	Cell death in mutant p53-expressing cells by apoptosis and cell cycle arrest.	(Park et al., 2006)
	(30 mg/kg) orally	Hepatoprotective effect	Lowering of AST, ALT, ALP and bilirubin (hepatic marker enzymes). Maintained hepatic malondialdehyde formation from elevating.	(Sabina et al., 2011)
6-Shogaol	100 mg/kg of 6-Shagol	Antioxidant potential where Nrf2 target genes were activated.	6-Shagol activates Nrf2 in colon epithelial cells (in vitro and in vivo) and can be used for colonic diseases.	(H. Chen & Wang, 2017)
	N/A	Anti-inflammatory activity due to nitric oxide inhibition in macrophages.	Inhibition of the NF-kB activation in macrophage demonstrated that activities are structure-dependent of ginger compounds.	(Li et al., 2011)
	N/A	Reduction of inflammation in the lungs and airway hyperresponsiveness.	Treatment for asthma due to inflammation reduction.	(Menon et al., 2021)
Oleoresin	2 mg/mL of Oleoresin	Antioxidant and antimicrobial activities. Due to its phenolic compounds.	Low concentrations of oleoresin are needed to obtain its antioxidant and antimicrobial activity. The phenolic compounds are responsible for its properties	(Bellik, 2014)

Phenylpropanoids	40 ug/mL of ginger phenylpropanoids.	Antioxidant activity increasing Nrf2 activity in BJ fibroblastic cells	Phenylpropanoids have an effect increasing the level of Nrf2 of BJ cells which demonstrate it could diminish oxidative stress regarding the human skin cells demonstrating they have chemoprotective activity.	(Schadich et al., 2016)
GDNPs	0.3 mg/mouse per day (oral)	Generation of intestinal epithelial cells. Reduction in pro-inflammatory cytokines Increase in anti-inflammatory cytokines in mouse colitis models.	In mouse colitis models there was enhancement of intestinal repair, prevention of inflammation of the intestines, reduction and prevention of colitis. GDNPs 2 were higher in non-starved mice. Potential usage for inflammatory bowel disease.	(Zhang et al., 2016)
Zingerone	N/A	Anti-Inflammatory properties, antioxidative. anti-cancer, antioxidative antidiarrheal, and growth enhancer.	Zingerone inhibits xanthine oxidase enzyme, degrades free radicals minimizing oxidation of lipids. Reduces mitochondrial injury. It also increases phagocytic activity, increases respiratory burst, fights pathogens by inhibiting enterotoxins, great for the conversion of energy due to its lipolytic activity and reduces inflammation and toxicity.	(Ahmad et al., 2015)
10-Dehydrogingerdione	N/A	Cholesterol regulating activity	Dyslipidemic rabbits that were fed 10-dehydrogingerdione had lower LDL cholesterol and higher HDL cholesterol due to the suppression of CETP. Potential treatment for cardiovascular diseases since it reduces oxidative risk and modulates inflammation.	(Elseweidy et al., 2013)
1 dehydro-10-gingerdione (D10G)	N/A	Anti-inflammatory activity.	D10G inhibits activity of IKKB by interacting with Cys bond which leads to the supressión of NFKB which is in charge of inflammatory genes (iNOS, COX-2 or IL-6). Potential use in autoimmune disorders.	(Lee et al., 2012)

*N/A: Not Available

2.1. Past, ongoing and future research towards Ginger

One of the first scientific reports documented on Ginger (*Zingiber officinale*) was in the year 1990 where Fischer-Rassmussen used 250 mg of powdered ginger to see its effect in nausea and vomiting in pregnant women (Anh et al., 2020). This study concluded that ginger was effective in preventing excessive nausea and vomiting in women who were in their first trimester (Fischer-Rasmussen et al., 1991). According to a study published by Anh and colleagues, the effect of ginger on human health has been mostly positive, proving effective in improving digestive function, anti-inflammatory effects, pain, metabolic syndrome, and symptoms. Currently ginger is being researched on its anticancer activity and chemotherapy effects. Furthermore, Kumar and colleagues reveal studies in the future related to inflammatory properties against anaemia disorders. It is proposed to develop an anti-inflammatory drug that is based on the activation of blocker agents that suppress the NF-kB cytokinin to prevent this symptom. For chemotherapy, drugs based on ginger bio compounds could represent a great opportunity to research and development and according to the same study made in 2013, natural products and their derivatives will represent a 50% of all drugs used in clinical cases. However, it also could represent some disadvantages, for example, with all the changes that the planet is suffering the quality and control of plants represent a lack of standardization and efficacy in drug development. It is also important to notice that some climate changing reasons could lead to plant extinction (Kumar et al., 2013).

On the other hand, some studies reported the potential of this root in medical and toxicological properties among the ones explained before in this study. This is shown, for example, in gynaecological surgery to reduce pain and nausea in a random study to 60

209 women. However, it is indeed a development in research because it is important to
210 consider doses implemented for drug testing (rat model only is required up to 50 mg/kg/d),
211 therefore, those dosages are still at research development (Rupasinghe & Gunathilake,
212 2015).
213 Among other properties of medical importance for ginger bioactive compounds, **Table 1**
214 reports some of the most studied cases in different fields of medicine, including
215 gastrointestinal diseases, cancer treatments and antimicrobial processes. It is important
216 to consider that the doses of each case for the prevention of cytotoxicity, which is typically
217 ascribed to high doses in the patient body. Considering the promising future of ginger
218 biomolecules in several health concerns, the research community is focused on different
219 pathways to either extract or purify target biomolecules from this specie. Therefore, the
220 following section is devoted to elucidating the advances towards the extraction and
221 purification of gingerols and many other bioactive substances.
222
223 **3. Up-to date strategies towards the extraction and purification of gingerols**
224 **and other bioactive substances from Ginger**
225 Knowing the extensive content of bioactive substances of Ginger, this natural source has
226 been subjected to distinct separation techniques for the extraction and purification of
227 particular GNs, including 6-gingerol, 6-Shogaol, 1-dehydro-10-gingerdione, 10-
228 Dehydrogingerdione, zingerone, and also other substances, such as phenylpropanoids,
229 oleoresins, etc. In this regard, various separation techniques have been proposed over
230 the recent years, being solvent extraction the pioneering option in this field. However, as
231 chemistry and chemical engineering evolute, emerging extraction techniques have been

developed and thus evaluated in the extraction of ginger molecules, as illustrated in **Figure 3**.

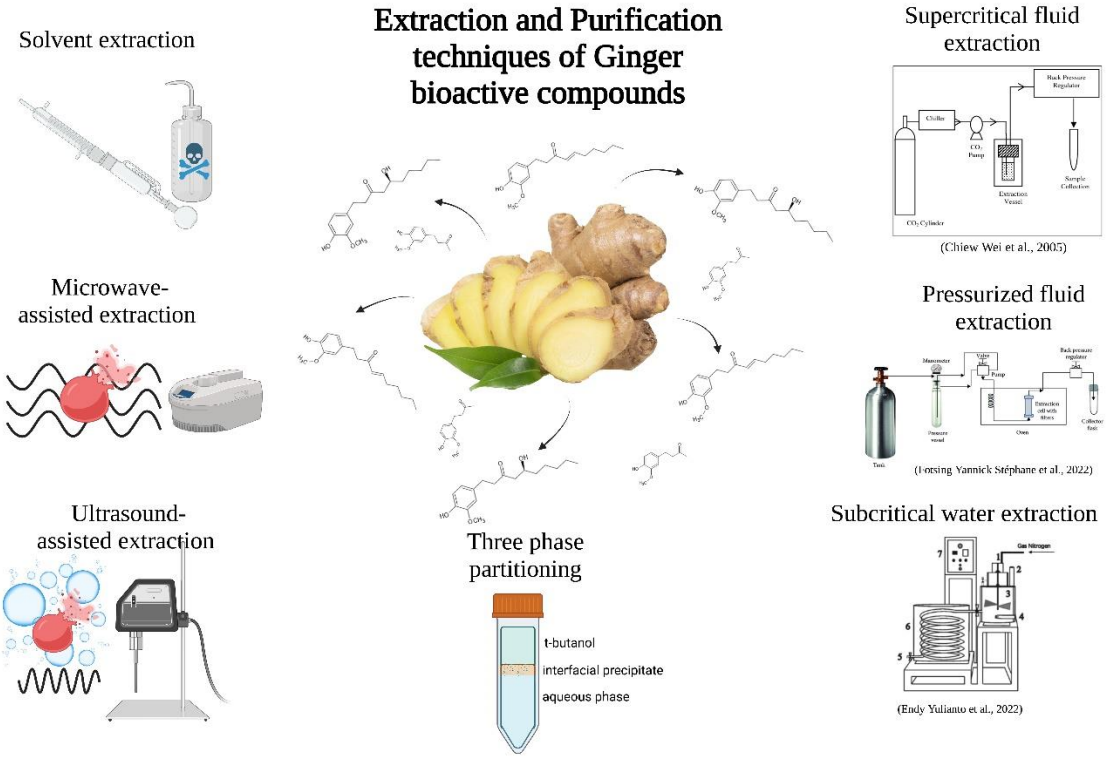


Figure 3. Classic and emerging extraction techniques used for the extraction and purification of Ginger biomolecules.

To date, microwave, supercritical & subcritical, pressurized fluid and ultrasound assisted techniques are among the main emerging tools used within the strategies for the extraction of bioactive substances. The following sub-sections reveal an update on applying such techniques in Ginger extracts.

3.1. Solvent extraction

Since ancient times, organic solvents have been used for the recovery of bioactive compounds from plants, which have been used in traditional medicine. Solvent extraction technique is based on the transference of analytes (compounds) from one solvent to another, ascribed to the difference in solubility or distribution coefficient (H. Chen & Wang, 2017). This method offers high selectivity, low energy consumption and continuous operation. However, the utilization of organic solvents can lead to the degradation of the target compounds, while the extraction times are relatively long, requiring large volumes and high purity reagents; in addition to this, organic solvents exhibit high toxicity for human beings while provoking environmental issues.

Many authors use solvent extraction techniques for many purposes according to different needs, such as desired product, shortening of the extraction time, slurry to solvent ratio, temperature, etc (Castro-Muñoz, Gontarek-Castro, et al., 2022). **Table 2** enlists the current studies reporting the successful extraction of distinct biomolecules from ginger, such as gingerol, zingerone, zingiberene, flavonoids, among many others. In a recent study provided by Keosaeng and co-workers, they compared different solvents to extract gingerols and shogaols from ginger rhizome. As part of the main outcomes, hexane achieved the highest recovery yield of ginger extract. The isolated bioactive compounds, such as 8-shogaol and 10-shogaol, were utilized as insecticidal against *Spodoptera spp*. larvae, obtaining a LD_{50} of 9.92 and 8.40 µg/larva after 24 and 48 h, respectively (Keosaeng et al., 2022). Interestingly, 8-shogaol and 10-shogaol displayed the highest mortality towards the assayed insect, which did not vary significantly after 24 h assay, as illustrated in **Figure 4**.

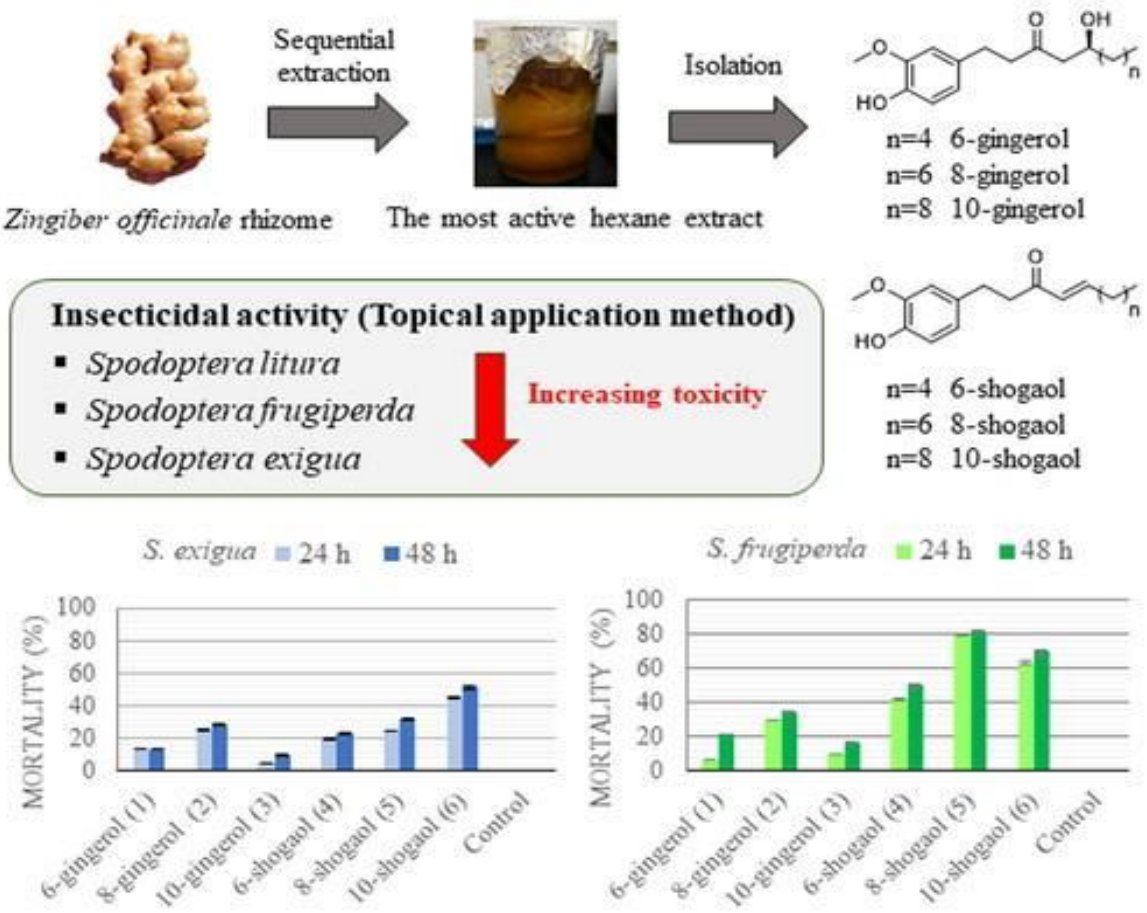
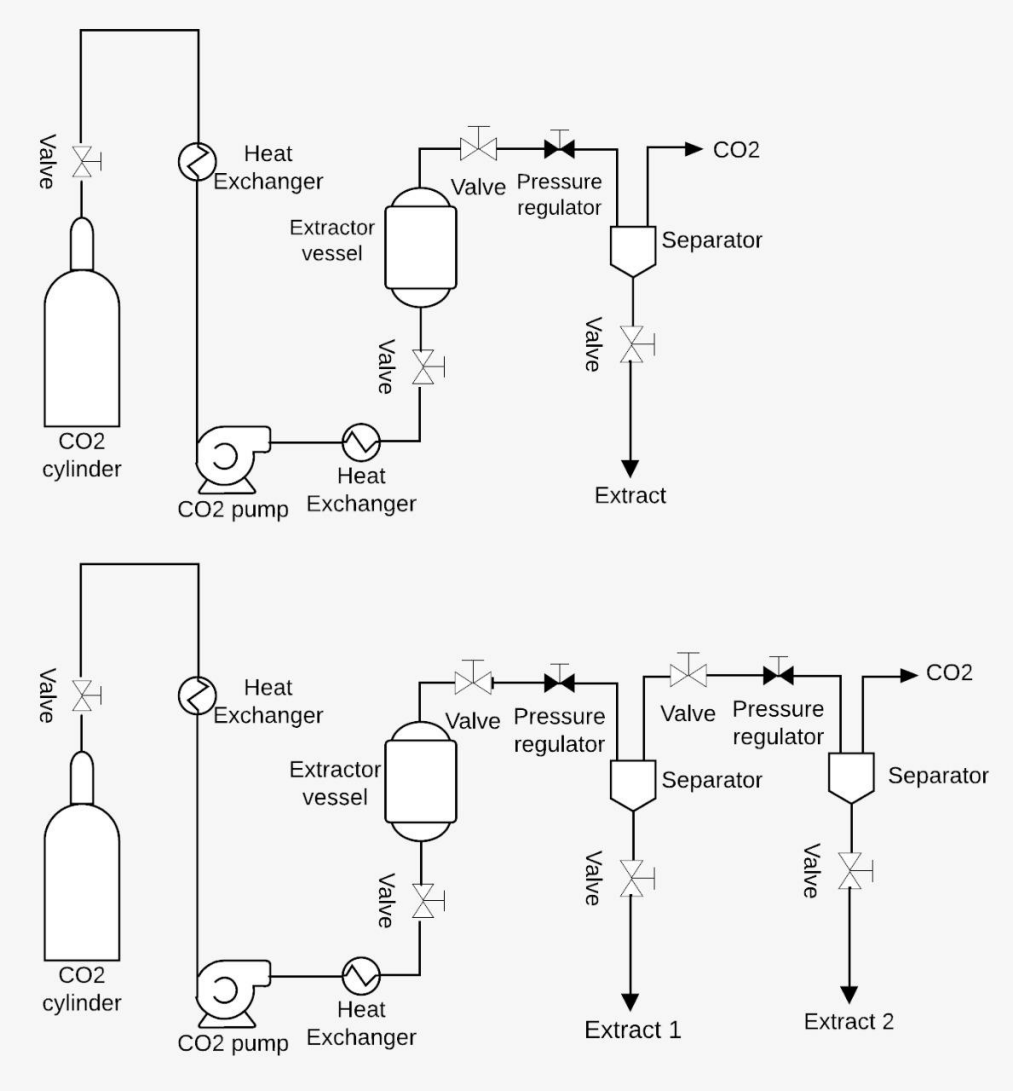


Figure 4. Isolation of gingerols and shogaols from ginger using solvent extraction (Keosaeng et al., 2022).

3.2. Supercritical fluid extraction

Supercritical fluid extraction (SCFE) is one of the available techniques that may potentially replace the traditional organic solvent extraction technique, due to the achievement of a homogeneous phase after evaporation of the gas phase and separation of the liquids beyond their critical point (Mesomo et al., 2012). The supercritical phase helps the transformation of the fluid into a super solvent, which increases the extraction efficiency.

In the extraction process, the diffusion coefficients of lipids and waxes in supercritical fluids are much higher compared to liquids, shortening the extraction time. In addition, supercritical viscosity values and diffusion coefficients are between liquids and gases, so there is low surface tension and increased mass transfer rates (Salea et al., 2017). It also eliminates the use of organic solvents, which reduces storage, disposal, and environmental concerns. For instance, some supercritical fluids currently being explored for extraction are ethylene, carbon dioxide (CO_2), ethane, methanol, ethanol, benzene, toluene, and water. In a successful application of this technology, Shukla et al. optimized the fluid extraction conditions using CO_2 as a supercritical fluid. Interestingly, two extractors were operated at lab scale and one commercial, as schematized in **Figure 5**. Finally, the optimal supercritical CO_2 fractionation conditions resulted in a yield of 5.95% oleoresin, which had a purity of 96.15% and 51.2 wt.% in separator 1 operating at 175 bar and 40 °C. In the second scenario, a 2.71% yield of volatile oil with a purity of 95.94% was recovered at 40 bar and 40 °C (Shukla et al., 2019). R. Swapna et al. carried out a study for the characterization and extraction of the active components of ginger, in which supercritical CO_2 at 280 bar and 40°C were found as optimal conditions. Substances, such as 4-,6-,10-gingerols, were extracted with a yield of 4.54, 75.92, and 13.15%, respectively, and a total yield of 34.5% for 6- shogaols was reported. Also, oleoresin was extracted with a yield of 4.8 % (Swapna Sonale & Kadimi, 2014).



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295 **Figure 5**. Laboratory scale (top) and commercial (bottom) SCFE plant (Shukla et al.,

296 2019).

297 In a study conducted by Said and co-workers, two different methods of oleoresin

298 supercritical CO_2 extraction were compared, the first one assisted with ultrasound

299 operated at 35 °C and 250 bar, resulting in a yield of 8.15%, while the second one, in

300 which only supercritical CO_2 was used at conditions of 40 °C, 250 bar and 15 g/min of

301 CO_2 flow rate, revealed a yield of 6.87% (Said et al., 2015). It can be assumed that the

combination of two extraction methods assisted with supercritical fluids can improve the extraction of active compounds from ginger. In 2017, Salea et al. conducted an experiment on ginger oil extraction. The 6-gingerol content in ginger oil was investigated with operating values in the range of 10-15 MPa, 35-45°C, and 10-20 g/min. The highest oil yield of 3.10%, along with the highest 6-gingerol content in ginger oil extract with a yield of 20.69%, were achieved at 15 MPa, 35 °C, and 15 g/min. Under optimum conditions, the SCFE of ginger oil increased with the highest oil yield of 3.83% while giving the lowest 6-gingerol content of approximately 18% (Salea et al., 2017).

3.3. Microwave-assisted extraction

Microwave-assisted extraction (MAE) is a novel extraction technique commonly proposed due to its effectiveness and simplicity when separating compounds from natural sources (Castro-Muñoz, Díaz-Montes, et al., 2022) . It uses microwave radiation along with distinct solvents, such as water, methanol, and ionic liquids, to evaporate residual water from the material. The heat and the solvents that are in contact with the solid or liquid samples promote the partitioning of the compounds of interest from the sample into the solvent (Bener et al., 2022). One of its main advantages compared with the conventional methods is the reduction of time and solvent quantity needed for the extraction; surprisingly, it is possible to perform MAE without adding solvents (Routray & Orsat, 2019). MAE can be used to extract pigments, lipids, and bioactive molecules from plants, spices, seaweeds, microalgae, and oils (Juin et al., 2015). In a study made by Guo et al. in which a MAE method assisted by ionic liquids was developed to extract 6-, 8-, 10-gingerols and 6-, 8-, and 10-shogaols from ginger. The results indicated that among the investigated ionic liquids, (C_{10}MIM)Br was found as the optimal. The selected conditions for ionic liquid MAE

were at a concentration of 0.80 M (C_{10}MIM)Br, with an extraction temperature of 75 °C, irradiation time of 30 min, and irradiation power of 400 W. The overall yield was reported as 0.716 % (Guo et al., 2017). Another study performed by Teng et al. showed the MAE method at different concentrations of solvent, irradiation time, and power to extract 6-gingerol and 6-shogaol in ginger rhizomes. This resulted in a maximum yield recovery of 28.4% with ethanol 50%, 9 min of irradiation, and 180 W of irradiation power, which permitted to obtain 3,149 mg/g of 6-gingerol and 1,662 mg/g of 6-shoganol (Teng et al., 2019). As enlisted in **Table 2**, Liu et al. used MAE to obtain 6-gingerol with optimum conditions as follows: 528 W of power, ethanol proportion of 78%, and extraction time of 31 seconds with a yield of 15.35 mg/g. Alternatively, MAE was compared with maceration, ultrasound-assisted extraction, stirring extraction and heat reflux extraction with yields of 7.49 mg/g, 13.38 mg/g and 7.49 mg/g, respectively (Liu et al., 2014).

342 **Table 2.** Current research and separation techniques aimed for the extraction and purification of bioactive compounds

343 from Ginger.

Molecule type:	Technique used	Operating conditions:	%recovery Or concentration	Remark of the study:	References:
6- gingerol 8- gingerol 10-gingerol 6-shogaol 8-shogaol 10-shogaol	Microwave-assisted extraction	0.80M (C10MIM)Br concentration, extraction temperature, 75 °C, irradiation time, 30 min, and irradiation power, 400 W	6-G:0.334 % 8-G:0.086 % 10-G:0.134 % 6-S:0.066 % 8-S:0.036 % 10-S:0.060 %	Microwave extraction was performed in combination with different ionic liquids.	(Guo et al., 2017)
6-gingerol 6-shogaol	Microwave-assisted extraction	Ethanol 50%, irradiation time 9 min and 180 W of irradiation power	Total yield of 28.4% 6-G: 3.149 mg/g 6-S: 1.662 mg/g	The experiment was run at different concentrations of solvent, irradiation time and power.	(Teng et al., 2019)
6- gingerol 8- gingerol 10-gingerol 6-shogaol	Pressurized liquid extraction	70% bioethanol operated at 1500 psi and 100 ◦C for 20 min	Total yield: 368.8 m'pp'g/g 6-G:14.106 mg/g 8-G:2.627 mg/g 10-G:3.336 mg/g 6-S:0.789 mg/g	PLE is compared to other extraction techniques such as ultrasonic and soxhlet and the results show a significant increase in yield compared with those methods.	(Hu et al., 2011)
6-gingerol	Supercritical fluid extraction	CO_2, 15 MPa, 35°C and 15 g/min	Total yield of 3.3 % with 22.30 % content of 6-G	It provides a comparison with other extraction methods such as soxhlet and percolation. The supercritical extraction had less yield but a higher 6-G content.	(Salea et al., 2017)

8-shogaol 10-shogaol	Solvent extraction	Solvents: hexane, dichloromethane, ethyl acetate and methanol. 7 L of each solvent, 7 day batch extraction. Filtration and rotary evaporator at 40 °C for removal of solvents.	Extraction yields (wt./wt.) of Hexane 2.12%, Dichloromethane 1.88%, Ethyl acetate 1.17%, and Methanol 1.56%.	Isolated shogaols from ginger rhizome extracts exhibited high toxicity against *Spodoptera spp*. larvae.	(Keosaeng et al., 2022)
Polyphenols: gallic acid, vanillic acid, ferulic acid; and Flavonoids: quercetin, kaempferol, isorhamnetin, rutin, catechin, caffeic acid	Ultrasound-assisted extraction	Extraction with ethanol, ethyl acetate, acetone and water overnight. Ultrasonication: 15 min, 60 Hz, pulses of 5s on and 3s off, temperature below 35 °C.	15.27% extraction efficiency found in aqueous extract	The ultrasonication method significantly increased the recovery of polyphenols with water as solvent; however, the antioxidant properties require extraction with ethyl acetate or ethanol for better results.	(Jan et al., 2022)
6-gingerol 8-gingerol 10-gingerol	Magnetic solid phase extraction	Graphene oxide/magnetite nanocomposite as sorbent for 8 mL of sample under magnetic stirring.	6-gingerol: 4.0 µg/mg from ginger extract. 8-gingerol: 0.64 µg/mg from tea leaves. 10-gingerol: 0.46 µg/mg from tea leaves.	GO-Fe_3O_4 nanocomposite was efficiently used for extraction of gingerols from ginger-containing products, achieving high selectivity and accuracy.	(Akamine et al., 2021)
Polysaccharides	Multifrequency ultrasound-assisted extraction	200 W of power, 10 s on with 2 s pause.	Double frequency: 9.74 ± 0.3% Triple frequency: 10.50 ± 0.2%	Dual and triple frequency ultrasound had a significant effect on the yield of polysaccharides extraction. Polysaccharides exhibited functional properties that can be used in the food industry.	(X. Chen et al., 2021)

Flavonoids: rutin, tangeretin, vitexin, isoquercitrin, myricetin-3–glucopyranoside	High speed counter current chromatography (HSCCC)	*n*-hexane-ethyl acetate-methanol-water (1:5:1:5 v/v/v/v) at 5 mL/min and *n*-hexane-ethyl acetate-methanol-water (4:5:4:5 v/v/v/v) at 5 mL/min. Previously purified by a macroreticular adsorption resin.	Rutin 16.6%, tangeretin 13.1%, vitexin 18.37%, myricetin-3-O-glucopyranoside 3.3%, and isoquercitrin 15.2%.	HSCCC could separate five different compounds from a purified sample of flavonoids and achieving; nonetheless two steps were required for an efficient separation.	(L. xia Wang et al., 2022)
Ginger oleoresin: 6-gingerol 8-gingerol 10-gingerol 6-shogaol	Ultrasound-assisted three phase partitioning	10% (w/v) ammonium sulphate, 1:2 *t*-butanol: slurry, pH 5 and 5% (w/v) solid loading in the slurry. 40% duty cycle, 36 W of power output and 5 minutes.	64 g/kg of oleoresin yield	Pretreatment with enzymes or ultrasound can greatly improve the recovery of 6-shogaol. The time required for TPP is much less compared to traditional Soxhlet extraction.	(Varakumar et al., 2017)
	Enzyme-assisted three phase partitioning	10% (w/v) ammonium sulphate, 1:2 *t*-butanol: slurry, ph 5 and 5% (w/v) solid loading in the slurry. 0.5% of accellerase loading.	69 g/kg of oleoresin yield		
Zingibain	Three phase partitioning	50% of $(NH_4)_2SO_4$ saturation, 1:1 ratio of crude extract and t-butanol; and pH 7	14.91-fold of purification, and 215% recovery	A milk-clotting enzyme was purified from crude ginger extract, obtained from the aqueous phase of a TPP system. This method exhibited high selectivity and purification.	(Gagaoua et al., 2015)

Zingerone 6-gingerol 8-gingerol 10-gingerol 8-shogaol	Ultrasonic-assisted micellar extraction (UAME)	100 mM of hyodeoxycholic acid sodium (biosurfactant), 10 min, and 100 W of ultrasonic power	N/A	MAME extraction proved to be an efficient technique due to its short times and high yields. Biosurfactants facilitate extraction, providing a green alternative against organic solvents.	(Peng et al., 2017)
	Microwave-assisted micellar extraction (MAME)	100 mM of hyodeoxycholic acid sodium (biosurfactant), irradiation time of 10s and 60°C.	88.66% zingerone 90.12% 6-gingerol 93.55% 8-gingerol 97.36% 6-shogaol 90.89% 10-gingerol		
Zingiberene, Geranial, ß-sesquiphellandrene, Geranyl acetate, Endo-Borneol, etc.	Subcritical water extraction	Hydrothermal extractor. 5000-15000 mL of subcritical water, 10-30 min, 120°C-140°C	2.03 g of bioactive compounds mixture. Variables: 130°C, 37 min, 10 L of subcritical water.	Extraction of bioactive compounds from ginger wastes was achieved with a greener method of extraction.	(Endy Yulianto et al., 2022)
6-gingerol	Sonic assisted water extraction (SAWE)	Mean particle size 0.89-1.77 mm, 45 min, 40 W of applied power, 1:30 sample to solvent ratio (w/v), 45°C, 15% ethanol as entrainer. 28 kHz (low) 800 kHz (high).	38.95 ± 0.02 % recovery and 16.14 ± 0.02 mg/g for low frequency. 46.81 ± 0.49 % recovery and 19.40 ± 0.49 mg/g for high frequency.	High frequency SAWE achieved recoveries and concentrations 2.69-fold higher than low frequency SAWE. Applied power was statistically proven to be the most significant factor for 6-gingerol extraction.	(Syed Jaapar et al., 2017)
Zingibain	Ultrasound-assisted liquid-liquid microextraction with deep eutectic solvents.	NADES concentration of 25%, source concentration of 15%, 35°C of ultrasound temperature and 10 min. of sonication.	75% of yield and 24- fold of purification	Ultrasound extraction combined with deep eutectic solvents yielded more protease extraction in the NADES enriched top phase.	(Balaraman & Rathnasamy, 2019)

6-gingerol, 8-gingerol, 10-gingerol	High speed counter current chromatography	Two phase solvent system of 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).	132 mg of 6-gingerol with 98.7% purity, 31 mg of 8-gingerol with 99.3% purity and 61 mg of 10-gingerol with 98.5% purity.	HSCCC was proven to be an efficient method for gingerol purification.	(X. Wang et al., 2011)
6-gingerol, 8-gingerol, 10-gingerol, 6-shogaol	Subcritical water extraction	130°C, 20 bars, 2% ethanol (as co-solvent), particle size 1mm, 0.5 h	16% of bioactives concentration. 1346 µg bioactives/g dried ginger.	Subcritical water extraction coupled with enzymatic pretreatment achieved higher levels of bioactives recovery than subcritical water extraction with sonication pretreatment.	(Nourbakhsh Amiri et al., 2018)
	Ultrasonic-assisted subcritical water extraction	130°C, 20 bars, 2% ethanol (as co-solvent), particle size 1mm, 1 h. Sonication pre-treatment of 50/60 Hz, 280 W and 40°C for 30 min.	16.7% of bioactives concentration. 1393.5 µg bioactives/g dried ginger.		
	Enzyme-assisted subcritical water extraction	130°C, 20 bars, 2% ethanol (as co-solvent), particle size 1mm, 1.5 h. Enzymatic pretreatment: 25 mg α-amylase at 6 U/mg, pH 4.5-5 at 50°C for 30 min.	35.8% of bioactives concentration. 2990.5 µg bioactives/g dried ginger.		
6-gingerol, 6-shogaol	Subcritical water extraction	130°C for 25 min for 6-gingerol. 190°C for 15 min for 6-shogaol.	6-gingerol 0.68 ± 0.08 mg/g and 6-shogaol 0.39 ±0 .03 mg/g.	6-gingerol can suffer from thermal cracking and be transformed into 6-shogaol during subcritical water extraction.	(Ko et al., 2019)

344

3.4. Pressurized Liquid Extraction

Pressurized liquid extraction (PLE) is a technique that employs solvents at high temperatures and pressures below their critical points, in which the solvent remains liquid throughout the extraction process. The result of using these conditions is a change in the physicochemical properties of the solvent, increasing mass transfer and solubility of the analytes, while the surface tension and viscosity of the solvent decrease (Carabias-Martínez et al., 2005). This allows the solvent to flow more easily and deeper into the matrix that is being extracted. As a result, higher extraction yields are obtained compared to conventional extractions, while decreasing the solvent consumption. The most important factors that influence the extraction process in this technique are the temperature, pressure, matrix, solvent flow rate, and extraction time (Alvarez-Rivera et al., 2020).

In an experiment performed by Hu et al., PLE was employed to obtain 6-, 8-, 10-gingerols, and 6-shogaol under different operating conditions. The highest total yield was obtained as high as 346.8 mg/g with an operating time of 20 min and 41 mL of ethanol at 70%. Additionally, in the experiments, different extraction techniques were carried out and compared with PFE showing lower yield concentrations (Hu et al., 2011). PLE offered relative yields of approximately 106.8%, 109.3%, and 108.0% yield for 6-, 8- and 10-gingerol, respectively.

3.5. Ultrasonic-assisted extraction

Ultrasonic-assisted extraction (UAE) is a technique where ultrasound waves are applied to the sample in a process called sonication. This process results in cavitation; when the ultrasound waves create small vacuum bubbles, they implode and create high temperatures and pressures (4500°C, 5000 MPa) that leads to the disruption of the cells (Weggler et al., 2020). This technique serves well as a pre-treatment for the extraction of intracellular products. Some advantages of UAE are the short extraction times, effective mass transfer, easy scale-up and simplicity. Furthermore, it can be coupled with other techniques, such as microwave-assisted extraction, enzymes, biosurfactants, solvents, etc (Yi et al., 2021).

Peng and collaborators utilized ultrasonics coupled with micellar extraction, resulting in the recuperation of 5 different target analytes: Zingerone, 6-gingerol, 8-gingerol, 6-shogaol and 10-gingerol. For micellar based extractions, surfactants are used to solubilize solutes in water and facilitate its separation process. In this experiment, hyodeoxycholic acid sodium was very efficient because the hydroxyl groups in the biosurfactant ring can form hydrogen and electrostatic interactions with the target molecules and increase mass transfer. Other parameters tested for an optimal extraction process were sonication time and ultrasonic power. Moreover, dual and triple frequency ultrasonication can positively affect the extraction yields of other compounds from ginger. This has the advantage of uniform energy distribution and ease of resonance within the extract; as well as better antioxidant and rheological properties (Peng et al., 2017). In the experiments carried out by Xuhui Chen and coworkers, polysaccharides were obtained from leaves and stems utilizing double and triple frequency ultrasonics. Yields of 10.50 ± 0.2% and 9.74 ± 0.3% resulted from this process using triple frequency and double frequency, respectively. The

composition of the polysaccharides extracts comprises neutral sugars, uronic acid, sulfate radicals and monosaccharides (X. Chen et al., 2021).

Jan and collaborators utilized ultrasonication to extract polyphenols from freeze dried samples of ginger and licorice. The extraction efficiency of phenols from the aqueous phase was estimated as 15.27%. Nonetheless, it was found that ethyl acetate or ethanol are required to obtain extracts with better antioxidant properties. In this work, several kinds of phytoconstituents were found in the ginger extract, such as alkaloids, glycosides, tannins, phenols, flavonoids, proteins and carbohydrates (Jan et al., 2022).

3.6. Three phase partitioning

Three phase partitioning (TPP) is a single-step technique which is mainly used for protein concentration and purification. It was first described by Denisson and Lovrien, but it has its precedent in the works of Tan and Lovrien from 1987, who described how enzyme activity is maintained, and even improved, in alcohol-water mixtures. In principle, this technique relies on the separation of phases when ammonium sulphate is added to a mixture of *t*-butanol and water, which would be completely miscible. If there is protein present in the sample, it will form a third phase between the alcohol and the aqueous phase (Dennison & Lovrien, 1997). Even though this technique is mainly used for protein purification, there are several studies that utilize it for other metabolites extraction. Varakumar and co-workers have used TPP for the recovery of ginger oleoresin by collecting the *t*-butanol phase and removing the solvent with evaporation under reduced pressure. They also tested two pre-treatments to the slurry prior to TPP: enzymatic, with 0.5% loading of accellerase; and ultrasonic with 40% duty cycle and 36 W power output.

These pre-treatments achieved yields of 69 and 64 g/kg (oleoresin/slurry) with enzyme and ultrasound, respectively, while significantly improved the concentration of 6-shogaol from 1758.6 ± 124 µg/g in TPP to 2752.3 ± 102 and 2623.4 ± 128 µg/g in enzyme-assisted TPP and ultrasonic-assisted TPP, respectively. Furthermore, TPP has also been used for zingibain extraction, a milk-clotting protein present in ginger rhizomes. In this study, parameters, such as $(NH_4)_2SO_4$ saturation, *t*-butanol concentration, pH, were optimized, obtaining a purification fold of 14.91, recovery of 215% and milk-clotting activity of 339 U/mL (Varakumar et al., 2017).

3.7. Novel extraction methods

Novel techniques for extraction and purification of metabolites have emerged to achieve higher yields with less time, power consumption and causing less environmental hazard (Castro-Muñoz et al., 2016). High Speed Counter Current Chromatography (HSCCC), Subcritical Water Extraction (SWE), and Magnetic Solid Phase Extraction (MSPE) are other reported techniques in the last few years that aim to overcome such limitations, including extraction time, purity, and utilization of hazardous solvents.

3.7.1 High speed counter current chromatography

High speed counter current chromatography (HSCCC) is a separation technique with a wide application range, large preparation volumes and flexible operation. It consists of a two-phase solvent system that establishes a unidirectional hydrodynamic equilibrium in a high–speed rotating tube. One phase act as a stationary phase while the other acts as a mobile phase; and then, a large number of stationary phases are retained during elution (Khan & Liu, 2018). Wang et al. (2021) utilized this chromatographic technique to

separate flavonoid compounds from the remaining ginger powder of a ginger oil extraction process. Five fractions of flavonoids were obtained utilizing n-hexane-ethyl-acetate-methanol-water (4:5:4:5 v/v/v/v) and n-hexane-ethyl-acetate-methanol-water (1:5:1:5 v/v/v/v) as the two solvent phases. This led to the extraction of rutin (16.6%), tangeretin (13.1%), vitexin (18.37%) myricetin-3-O-glucopyranoside (3.3%) and isoquercitrin (15.2%). Gingerol has also been purified in the works of Wang et al. (2011), where they utilized 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) as the two-solvent system; obtaining purities of 6-gingerol, 8-gingerol and 10-gingerol higher than 98%. From 360 mg of the pre-purified sample, 132 mg of 6-gingerol, 31 mg of 8-gingerol and 61 mg of 10-gingerol were obtained. The utilization of HSCCC permits a process without irretrievable sample adsorption; that is why it can separate high amounts of the desired analytes (X. Chen et al., 2021).

3.7.2 Subcritical water extraction

Subcritical water extraction (SWE) allows the recovery of less-polar compounds. In this technique, water is maintained in a liquid state under high pressures and high temperatures ranging from 100 to 374°C. The extraction times are as short as 30 min; and the dielectric constant of the water is lower, weakening the hydrogen bonds and changing the polarity of water (Ko et al., 2020). At subcritical conditions, the viscosity and surface tension of water decreases, promoting the mass transfer rate and adsorption into the particle-matrix that is being worked on. Another advantage of this technique is the zero toxicity that water represents to the final product. Endy Yulianto et al. studied this technique for the recovery of bioactive compounds from ginger dregs, utilizing statistical

methods for optimization. The optimal conditions were determined as 120°C, 10 L of solvent (water) and 30 min. Among the isolated compounds, it was found zingiberene, geranial, ß-sesquiphellandrene, geranyl acetate, endo-borneol, etc (Endy Yulianto et al., 2022).

Amiri et al. (2018) utilized subcritical water extraction as well to purify bioactive compounds from dried ginger. Apart from the SWE, they compared sonication and enzymatic pre-treatment. For the SWE, optimal conditions were studied, obtaining 130°C, 20 bars, 2% ethanol (as co-solvent), particle size 1mm, 0.5 h. Between the two pre-treatments, enzymatic pre-treatment turned out to have higher extraction efficiency than sonication and SWE alone. While SWE and -ultrasonication-assisted SWE reached 16% and 16.7%, respectively, during the recovery of bioactive. In comparison to traditional Soxhlet extraction, Enzymatic-SWE reached higher recovery of ca. 35.8%. This means that more than double extraction efficiency can be achieved by using enzymes. α-amylase is an enzyme that disrupts the cell wall; hence, its utilization coupled with the particle size of dried ginger utilized, helped to release a great number of intracellular products (Nourbakhsh Amiri et al., 2018).

3.7.3 Magnetic solid phase extraction

Magnetic solid phase extraction (MSPE) is a new technique that utilizes a magnetic adsorbent to a solution containing a certain analyte. The analyte is adsorbed into the magnetic sorbent and then separated magnetically. Finally, the analyte eluted from the recovered adsorbent. This procedure has been used for the isolation and preconcentration of specific analytes surpassing the long times of conventional solid-

phase and liquid-phase extractions (Šafaříková & Šafařík, 1999). To the best of our knowledge, the pioneering work documented by Akamine et al. (2021) is the only experimental attempt where a magnetic nanocomposite has been used as a sorbent for the extraction of GNs, as graphically represented in **Figure 6**. Herein, a magnetic nanocomposite GO-Fe_3O_4 was employed for the analysis of GNs in different food samples. The highest yields were 6-gingerol: 4.0 µg/mg from ginger extract, 8-gingerol: 0.64 µg/mg from tea leaves, 10-gingerol: 0.46 µg/mg from tea leaves (Akamine et al., 2021).

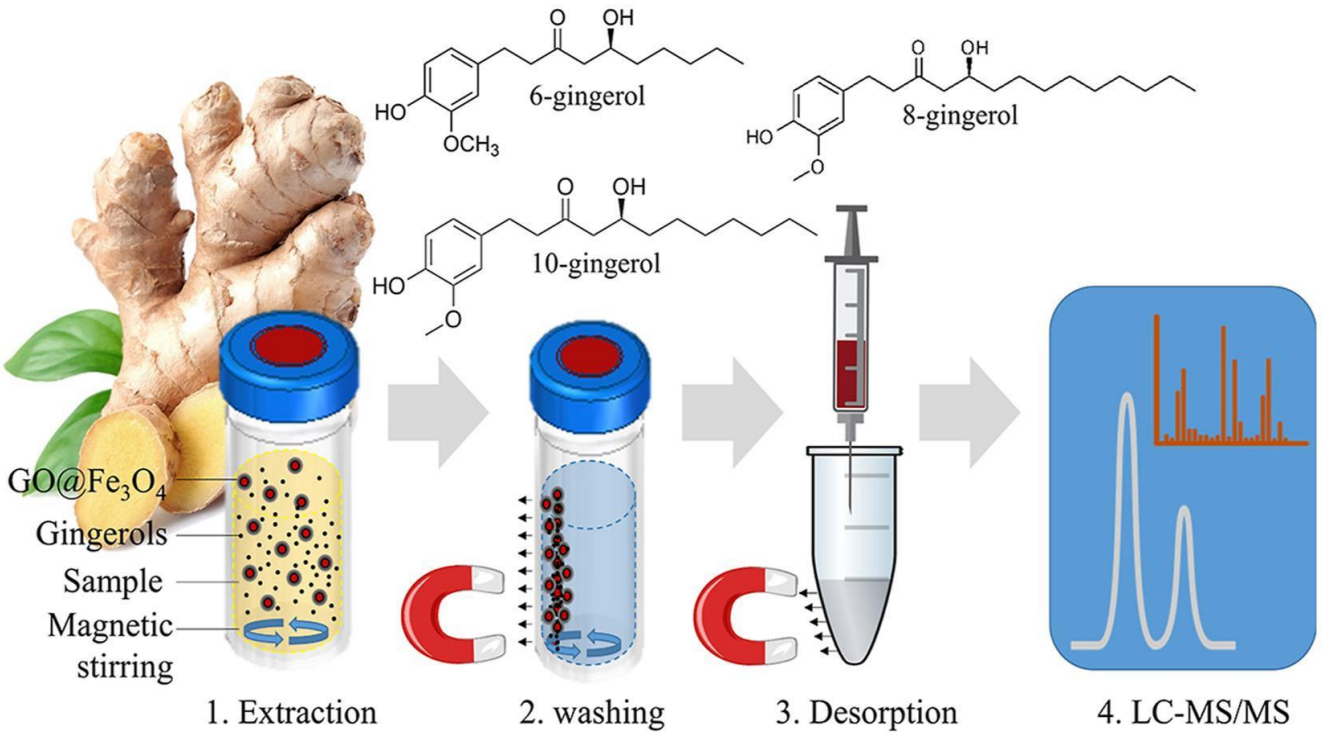

Figure 6. Magnetic Solid Phase Extraction of gingerols using a GO-Fe_3O_4 nanocomposite (Akamine et al., 2021).

6. Concluding remarks and perspectives

Ginger biomolecules have proven to show interesting medicinal properties, such as anti-inflammatory, anti-cancerous, anti-oxidative, anti-microbial activities as well as reducing oxidative parameters. Thanks to research community, *gingerols, shogaols* and *zingerone* have been identified and recognized as the main bioactive substances contained in Ginger extracts, which could potentially be used in new food and pharmaceutical formulations; unfortunately, the extraction and purification of such bioactive still remains as a challenge since there is still no artificial pathway for producing them; therefore, extraction and purification processes seem to be the most friendly and efficient way to obtaining them from their natural source. In this review, we declare the efforts of the research community on extracting ginger biomolecules (mainly gingerols), in which solvent extraction has been observed as the pioneering technique in this task. Even if solvent extraction is seen as a classic separation method, the advent of developing new solvents, such as ionic liquid and deep eutectic solvents, still makes it functional and versatile as starting point of extraction. This latter statement is supported by the current need of producing more healthy food enriched with nutraceutical substances to alleviate symptoms of endemic and unprecedented epidemics (e.g., coronavirus).

In addition to solvent extraction, other techniques, such MAE, PLE, supercritical fluid extraction, UAE, have revealed interesting outcomes and great advantages. Specially, emerging techniques, such as UAE, have confirmed to be highly selective when dealing with the extraction of specific target molecules, e.g., it has shown exceptional recovery (over 90%) toward zingerone, 6-gingerol, 8-gingerol and 10-gingerol, while an almost

complete recovery (ca. 97.36%) of 6-shogaol has been also observed. In the coming future, it is likely that novel and emerging techniques will be evaluated for their ability in recovering such compounds.

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Conflict of Interest

The authors declare no conflict of interest.

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