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A Review on Extraction, Antimicrobial Activities and Toxicology of *Cinnamomum cassia* in Future Food Protection

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Abstract: *Cinnamomum cassia* is a tropical medicinal and aromatic plant from the Lauraceae family, which is commonly used as a natural spice in food preparation and traditional medicine to treat respiratory and digestive disorders. The extract of *C. cassia* contains bioactive compounds, such as cinnamaldehyde, cinnamic alcohol, cinnamic acid, and cinnamate. Recent studies have found that these bioactive compounds of *C. cassia* have a broad range of biological activity, such as antioxidant, anti-inflammatory, anti-diabetic, antibacterial, anti-tumor, and other therapeutic effects in both *in vitro* and *in vivo*. The present review examines the effect of different types of conventional and non-conventional extraction technologies on the yield and quality of *C. cassia*, the relationship between extraction methods and extraction solvents on antimicrobial activity, and the toxicological safety of *C. cassia*. The reviewed studies show that cinnamaldehyde is the major extracted bioactive component, accounting for more than 60 %. Novel extraction technologies such as ultrasound-assisted, microwave-assisted, and supercritical fluid extraction are highly effective processes requiring low solvent and energy consumption. This review deeply discusses the various extraction technologies and their effect on extraction efficiency. The antimicrobial activity of *C. cassia* and the influences of different extraction methods and extraction solvents on the antimicrobial activity is also introduced. Moreover, the application of *C. cassia* in food protection is also discussed in terms of antimicrobial activity, food quality, and sensory evaluation. Furthermore, toxicological safety has been identified and discussed.

Keywords: antimicrobial; bioactive compounds; *Cinnamomum cassia*; extraction methods; toxicological safety.

1. Introduction

Fresh foods, such as seafood, meat, and horticulture goods, have a short shelf life and have been implicated in the outbreaks of foodborne diseases caused by pathogenic microbes. To reduce the outbreaks of foodborne diseases, both physical (i.e., thermal and non-thermal sterilization) and chemical methods (i.e., chlorine, peracetic acid, sodium benzoates, propionates, and potassium lactate) are applied in the food industry to remove any pathogenic microbes [1,2]. However, these methods have several disadvantages in the application of food protection. The thermal sterilization processes, such as heat pasteurization and high pressure, can eventually change the color and flavor of the food and reduce the nutritional content [3,4]. Non-thermal sterilization processes, such as irradiation, have a negative impact on the

organoleptic properties of foods, low acceptance by consumers, and some safety issues [5,6]. In most food industries, chemical sanitizers are often used to protect fresh food from microbial contamination. However, chemical sanitizers have corrosive properties which may damage the food processing equipment, are not environmentally friendly, non-selective (kill both pathogenic and normal flora bacteria), and are detrimental to human health [1]. Although different types of food protection methods have been established, outbreaks of foodborne diseases still frequently happen globally [7]. Because of those reasons, the demand for organic and minimally processed food has increased over the years [8,9]. Herbs and spices have been used to prevent a wide range of pathogenic microbes' growth in food due to the presence of phytochemical compounds [10–12]. Herbs and spices are ideal alternatives to chemical sterilizers since they are Generally Recognized as Safe (GRAS) ingredients [13].

Herbs or spices are also known as medicinal and aromatic plants (MAPs). MAPs have been widely used for centuries as a flavoring agent to enhance food's flavor, improve the food's organoleptic properties, and be used as preservatives and medicine [14–16]. Nowadays, MAPs are recognized as functional foods due to their superior physiological benefits, which contribute to reducing the chances of suffering from chronic diseases [17]. The benefits of MAPs have been widespread from the ancient as a wildcrafted raw material, and the MAPs market has successfully expanded worldwide. The production of MAPs is approximately 467,000 tons per year, with a total value of USD 1.2 billion [18]. According to a World Health Organization survey, 70–80% of the global population relies on modern medication, primarily from the source of MAPs, for their treatment option [19]. Moreover, MAPs usually contain a high level of ascorbic acid, carotenoids, and phenolic compounds (i.e., alcohols, flavonoids, phenolic acid, stilbenes, tocopherols, tocotrienols), which have been shown to have superior antioxidant activity [20]. Therefore, the research on MAPs has become significant in fulfilling health-oriented social trends and improving living standards.

Cinnamomum cassia, generally known as Chinese cinnamon, belongs to the Lauraceae family and is found in Asian countries such as China, India, Vietnam, Indonesia, Sri Lanka, and Nepal [21,22]. The bark of *C. cassia* has attracted consumers' attention from different countries because of its unique fragrance and spicy flavor [22]. In ancient times, the *C. cassia* bark was employed as raw material in traditional medical treatments for amenorrhea, arthritis, cardiomyopathy, diarrhea, dizziness, emesis, erectile dysfunction, fever, menstrual cramps, prostate gland inflammation, and stomach aches [23]. Moreover, previous studies have proved that *C. cassia* has a broad range of biological activities, including antioxidant [24], antimicrobial [25], anti-inflammatory and analgesic [26], anti-diabetic [27], anti-arthritic [27], anti-tumor [28], cardiovascular protection [29], immunoregulation [30], cytoprotection [31], and neuroprotection [32].

Currently, *C. cassia* bark has been found in various applications in pharmaceutical, chemical, foods, and cosmetics [21]. US Food and Drug Administration has recognized *C. cassia* essential oil as safe, and the US Environmental Protection Agency exempts it from toxicity reporting requirements [33,34]. *C. cassia* has been reported as a source of various bioactive compounds. It was reported that *C. cassia* bark contains 1 to 3 % volatile oil, and cinnamaldehyde is the primary volatile component present in the oil, which accounts for 55 to 75 % of the total composition [35,36]. Cinnamic acid is another principal constituent of *C. cassia* which exists as a white crystalline phenolic compound with a low-intensity sweet and honey-like aroma [37]. Other compounds such as coumarin, 2-methoxycinnamaldehyde, 2-hydroxycinnamaldehyde, and procyanidin B2 can also be detected in *C. cassia* [23,38,39].

Terpenes such as anhydrocinnzeylanine, anhydrocinnzeylanol, cinnamoid, cinncassiol A, cinncassiol B, cinnzeylanone, cinnzeylanine, cinnzeylanol, perseanol, and trans-caryophyllene can be found in the bark of *C. cassia* [30,40–43]. The chemical structures of the bioactive compounds in *C. cassia* are shown in Figure 1.

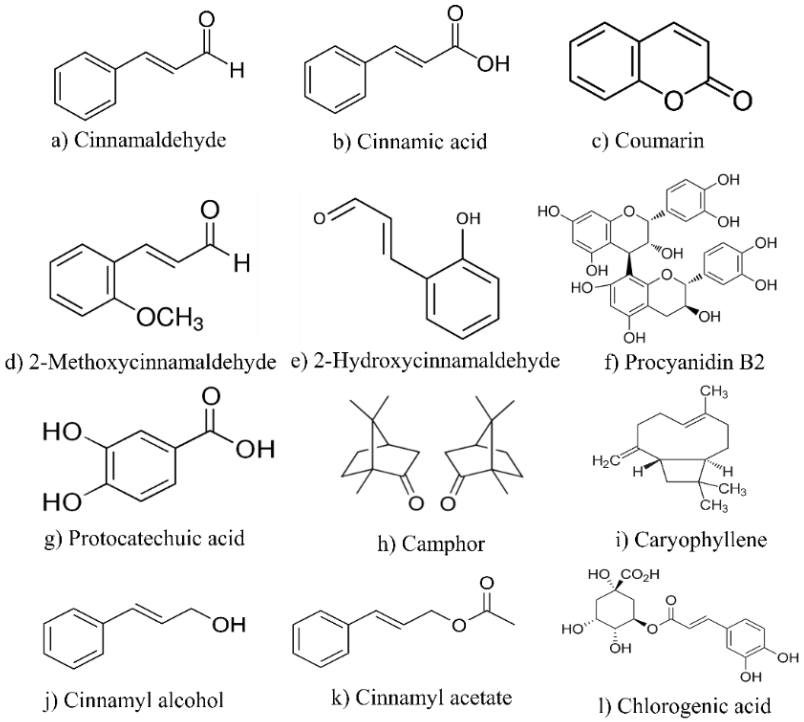

Figure 1. Chemical structure of **(a)** cinnamaldehyde, **(b)** cinnamic acid, **(c)** coumarin, **(d)** 2-Methoxycinnamaldehyde, **(e)** 2-Hydroxycinnamaldehyde, **(f)** procyanidin B2, **(g)** protocatechuic acid, **(h)** camphor, **(i)** caryophyllene, **(j)** cinnamyl alcohol, **(k)** cinnamyl acetate and **(l)** chlorogenic acid in the bark of *C. cassia*.

Sample preparation, extraction, and purification are the standard phases of isolating bioactive compounds from plant sources. Because the sample preparation stage consumes more than 60 % of the entire time, selecting a suitable extraction procedure is critical [44]. Extraction methods such as Soxhlet extraction, hydrodistillation, and steam distillation are still the conventional methods for the extraction of bioactive compounds from *C. cassia*. However, these methods are frequently time-consuming, expensive, and inefficient due to the large quantities of organic solvents required, have a low yield due to thermal degradation, and have poor solvent disposal and recycling practices [45]. In recent years, numerous green extraction technologies such as microwave-assisted extraction, ultrasound-assisted extraction, enzyme-assisted extraction, supercritical fluid extraction, subcritical fluid extraction, and pulsed electric field extraction or combinations of the conventional extraction methods with these green extraction technologies were developed when circumstances dictate. These green methods require shorter extraction time and temperature, have lower solvent consumption, minimize the presence of solvent residue in extract, have higher purity of target compounds, and are environmentally friendly [45,46] compared to the conventional methods. Although these green methods have been applied in the extraction of *C. cassia*, some limitations still exist in these methods. The research on green extraction technologies is critical for the future industrialization of *C. cassia* extraction. Also, the enhancement of the extraction product in terms of quantity and quality is needed to promote their pharmacological activities. Herein, the conventional and novel extraction technologies for *C. cassia* are reviewed. In addition, the antimicrobial activity of *C. cassia* on different microbes and test methods is characterized.

Lastly, this review also investigates the toxicity profile of *C. cassia in vitro* and *in vivo*. Until now, the information regarding the relationship between the extraction strategies, antimicrobial activity, and toxicity of *C. cassia* is not detailed and documented. This review article provides a comprehensive review of the extraction methods of *C. cassia* which can provide important information for the enhancement and development of new green extraction technologies in *C. cassia*.

2. Techniques for Extracting Bioactive Compounds from *Cinnamomum cassia*

Extraction is a separation process that solubilizes the desired bioactive compounds from plant materials using a solvent and an extraction method. The bioactive compounds are extracted when the solvents diffuse through the cell wall, and the bioactive compounds are dissolved into the solvents [47]. Over the past six years (i.e., from 2016 to 2021), the number of paper publications on *C. cassia* as well as antimicrobial activity and toxicity, has continuously increased every year (Figure 2). Numerous studies regarding *C. cassia* have been published in Scopus and Google Scholar with different topics on extraction, separation, analytical process, medicine, pharmacological activities, and food application. According to the database from Scopus (accessed on 5 September 2022), 1271 articles with the keyword "*Cinnamomum cassia*" have been published. Among the documents type, research articles were mainly published (84.06 %), followed by review papers (12.91 %), conference papers (1.51 %), book chapters (0.96 %), and letters (0.56 %). When analyzing the contribution of documents by subject area, the research of *C. cassia* was mainly focused on the subject area of Pharmacology, Toxicology, and Pharmaceutics (25.34 %) and Medicine (23.79 %), followed by Biochemistry, Genetics, and Molecular Biology (15.44 %), Agricultural and Biological Sciences (13.54 %), and other fields (21.89 %). The numerous research areas studying this spice indicate the great research potential of *C. cassia* that should be further explored.

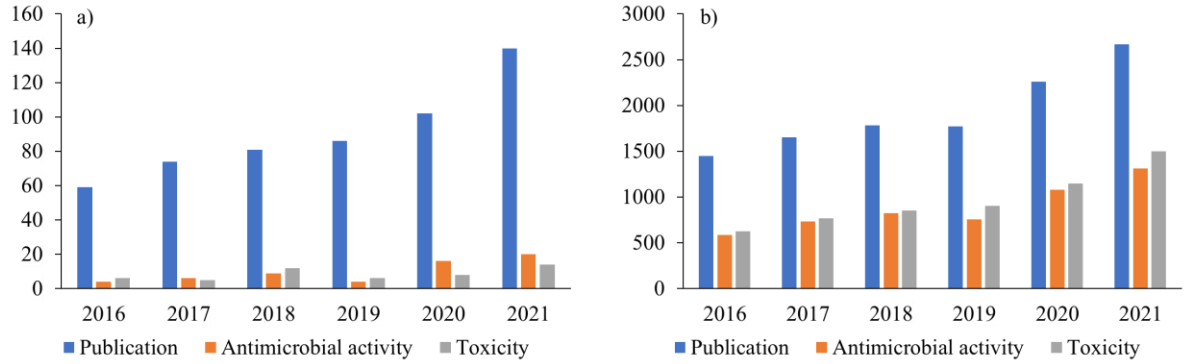

Figure 2. The research trend of *C. cassia* in 2016 to 2021 published in **(a)** Scopus and **(b)** Google Scholar was carried out based on the keyword "*Cinnamomum cassia*", "*Cinnamomum cassia* antimicrobial" and "*Cinnamomum cassia* toxicity".

Aromatic essential oil, extract, or bioactive compounds is often extracted from *C. cassia* using various procedures to obtain high-quality product at a low cost and shorter extraction period. Economic feasibility and suitability in the extraction process are always a concern as the awareness of "go-green" and eco-friendly concepts becomes critical in maintaining the balance between human activity and the environment. Usually, the essential oil, extract, or bioactive compounds from *C. cassia* can be obtained only in small quantities. Therefore, selecting appropriate extraction methods and parameters is critical to maximize the production yield and preserve the target bioactive compounds from *C. cassia*.

2.1. Conventional extraction methods.

It is typical to dry the *C. cassia* before extraction to improve the yield and quality of the final product. Drying after harvesting *C. cassia* bark is to minimize the water content, eliminate any living microorganisms, and terminate chemical reactions in the plant cell. Soxhlet extraction, hydrodistillation, and steam distillation are the most common type of extraction techniques utilized to obtain the essential oil. These extraction methods have various effects on the physicochemical and extraction yield of *C. cassia*.

2.1.1. Soxhlet extraction.

In Soxhlet extraction, the solid materials are enclosed in a porous thimble and then placed in the extraction chamber of the apparatus. The extraction solvent is filled in the round bottom flask and heated at the desired temperature. The solvent vapor is generated during heating and condensed when vapors reach the condenser. The condensate (solvent vapor) drops back to the thimble containing the solid materials, and analyte extraction occurs when the solvent interacts with the solid. When the liquid content (solvent with analyte) exceeds the overflow level, the liquid drains through the siphon device into the round bottom flask. The procedure is repeated for several hours until extraction is completed. However, this extraction method requires an extremely long extraction time and high extraction temperature, which initiate the thermal degradation of volatile compounds [47]. Examples of Soxhlet extraction of target substances from *C. cassia* are shown in Table 1.

Table 1. Some representative studies of Soxhlet extraction to extract bioactive compounds from *C. cassia*.

Plant part	Solvent type	Extraction parameters			Target compounds	Extraction yield	References
		Extraction time (hr)	Extraction temperature (ºC)	Solid to solvent ratio			
Bark	95 % ethanol	72	n.a	1:10	Cinnamaldehyde	Extract yield = 15.5 % (w/w)	[48]
Bark	95 % ethanol	6	65	n.a	Phenolics, flavonoids and tannins	Extract yield = 5.2 %	[49]
Bark	Ethanol	10	n.a	1:5	Trans-cinnamaldehyde	Extract yield = 9.3 % (w/w)	[50]
	Methanol, ethanol and acetone	24	55 to 80	n.a	Alkaloids, flavonoids, terpenoids, saponins, tannins, and glycoside	Methanol extract yield = 22.57 % (w/v) Ethanol extract yield = 17.0 % (w/v) Acetone extract yield = 15.3 % (w/v)	[51]
Bark	Hydroalchol	6	n.a	n.a	n.a	Extract yield = 12.12 % (w/w)	[52]
Bark	Hexane Petroleum ether Dichloromethane	6 6 6	65 60 40	3:25 3:25 3:25	Trans-cinnamaldehyde, 2H-1-benzopyran-2-one, 3-methyl-4-undecene, and 3-phenyl-2-propenal	Hexane extract yield = 5.22 % Mass percentage cinnamaldehyde = 86.67 % Petroleum ether extract yield = 3.84 % Mass percentage cinnamaldehyde = 68.47 %	[53]

Plant part	Solvent type	Extraction parameters			Target compounds	Extraction yield	References
		Extraction time (hr)	Extraction temperature (ºC)	Solid to solvent ratio			
						Dichloromethane extract yield = 3.71 % Mass percentage cinnamaldehyde = 79.43 %	

*Note: n.a = not available

In the Soxhlet extraction of *C. cassia*, organic solvents such as dichloromethane, ethanol, hexane, methanol, petroleum ether, and water were used [49,53,54]. Singh *et al*. (2018) found that the methanolic, ethanolic, and acetone extract of *C. cassia* contained alkaloids, flavonoids, terpenoids, saponins, tannins, and glycosides [51]. Another study by Kaur *et al*. (2018) discovered that 100 g of dried *C. cassia* bark powder subjected to Soxhlet extraction for 6 hours using 95 % (v/v) ethanol resulted in a 5.2 % of extract yield, which contains tannins, flavonoids, phenolic compounds and saponins [49]. In the analysis of a chemical compound of *C. cassia* extract, Nasulhah Kasim *et al*. (2014) discovered the existence of trans-cinnamaldehyde with a yield of 86.67 % using hexane, 79.43 % using dichloromethane and 68.74 % using petroleum ether. They also found other compounds, such as 2H-1-benzopyran-2-one, 3-methyl-4-undecene, and 3-phenyl-2-propenal, in the extract [53]. Shin *et al*. (2017) used 95 % ethanol as an extraction solvent for Soxhlet extraction. In high-performance liquid chromatography fingerprint analysis, they found that cinnamaldehyde was the extract's active constituent, which displayed a major peak under different ultraviolet absorption conditions [48]. Figure 3 summarizes the extraction yield of *C. cassia* using a different organic solvent in Soxhlet extraction.

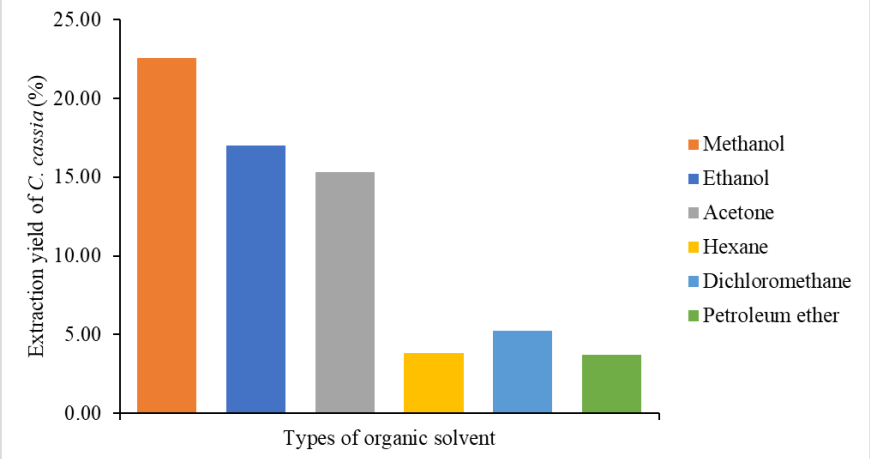

Figure 3. Extraction yield of *C. cassia* using different types of organic solvent in Soxhlet extraction [51,53].

2.1.2. Hydrodistillation and steam distillation.

Essential oils have long been extracted from plant sources using hydrodistillation through water distillation, steam distillation, and direct steam distillation methods [55]. In this extraction method, only water or hot steam is used as a solvent to extract essential oils from the plant tissue [56]. After the extraction, the water and essential oils vapor mixture is condensed and collected in a decanter. The essential oils are separated naturally from the water

[57]. More examples of hydrodistillation and steam distillation of target substances from *C. cassia* are shown in Table 2.

Hydrodistillation using distilled water has been used to extract dried leaves and dried bark powder of *C. cassia*. The essential oil of *C. cassia* bark obtained by hydrodistillation yielded the volatile trans-cinnamaldehyde at the highest composition (85.06 %), followed by o-methoxy-cinnamaldehyde at 8.79 %, and a trace amount of other compounds such as benzaldehyde, alcohol, and terpenoids [58]. Besides, the presence of bioactive compounds such as coumarin, cinnamaldehyde, and cinnamic acid, which commonly exist in the *C. cassia* bark, have also been identified from the hydrodistillation's product [59,60]. Moreover, Jiang *et al*. (2013) discovered that the steam distillation of 30 g *C. cassia* bark powder for 3 hrs using a solid-to-water ratio of 3:10 (w/v) yielded a 1.4 % (w/w) of essential oil composed of ten compounds which are trans-cinnamaldehyde (74.9 %), 2'-methoxycinnamaldehyde (3.6 %), δ-cadinene (2.6 %), ylangene (2.5 %), γ-cadinene (1.9 %), sativene (1.8 %), trans-α-bergamotene (1.5 %), β-caryophyllene (1.2 %), cadalene (0.6 %), and cis-cinnamaldehyde (0.2 %) [61]. Ma *et al*. (2019) investigated the essential oil yield of *C. cassia* obtained from dry bark, fresh bark, and fresh leaf using steam distillation. The results showed that the dry bark has a higher essential oil yield (1.65 %), followed by fresh leaf (0.24 %), and fresh bark (0.07 %). According to the analysis of the chemical composition of *C. cassia* essential oil from dry bark, fresh leaf, and fresh bark, trans-cinnamaldehyde was the highest in the dry bark (75.66 ± 1.73%) compared to the fresh leaf (28.44 ± 1.69 %), and the fresh bark (24.41 ± 0.46 %) [62]. Li *et al*. (2018) optimized the steam distillation process. The result showed that the maximum C. cassia essential oil yield was 1.44 % under optimum mesh size 40, solid-to-liquid ratio 1:10, and extraction time 2 hr [63].

2.2. Non-conventional extraction methods.

According to Castejón *et al*. (2018), green extraction technologies improve the extraction process while also increasing quality, yield, and functional stability [73]. Microwave-assisted extraction, ultrasound-assisted extraction, supercritical fluid extraction, subcritical fluid extraction, enzyme-assisted extraction, and pulsed electric field extraction are some of the recent advancements in *C. cassia* extraction technology. However, the mechanism of plant cell breakdown, the intensity of temperature, time, pressure, and power for the extraction of *C. cassia* vary among these extraction processes. The following subsections thoroughly evaluate and contrast the non-traditional extraction techniques for *C. cassia*.

2.2.1. Microwave-assisted extraction.

Microwave-assisted extraction (MAE) is a method of extracting analytes from a sample matrix into a solvent by utilizing microwave energy [74]. Ionic conduction and dipole rotation are the two mechanisms that convert microwaves to heat energy [75]. Microwaves generate heat by interacting with polar components in the plant matrix, which result in heating near the material's surface, and heat is transferred by conduction. The dipole rotation of molecules caused by microwave electromagnetic disruption weakens hydrogen bonds, allowing dissolved ions to migrate more freely and facilitating solvent penetration into the matrix [47,76].

Table 2. Some representative studies of hydrodistillation and steam distillation to extract bioactive compounds from *C. cassia*.

Plant part	Solvent type	Extraction parameters			Target compounds	Extraction yield	References
		Extraction time (hr)	Extraction temperature (ºC)	Solid-to-solvent ratio			
Bark	Distilled water	6	100	1:10	Benzaldehyde, phenylacetaldehyde, hydrocinnaaldehyde, trans-cinnamaldehyde, o-anisaldehyde, o-methoxycinnamaldehyde, octadecane, phenylethyl alcohol, borneol, spathulenol, 3-phenylpropanol, coumarin, δ-cadinene, 4-carene, guaiacol, cinnamic acid	Mass percentage cinnamaldehyde = 67.16 to 81.70 %	[60]
Bark	Distilled water	2	100	1:10	Coumarin, cinnamaldehyde, and cinnamic acid	Extract yield = 3.001 %	[59]
Bark	Distilled water	3	100	2:7	Essential oil	n.a	[25]
Bark	Distilled water	6	100	1:10	Cinnamaldehyde	Mass percentage cinnamaldehyde = 84 %	[64]
Bark	Distilled water	2	100	1:7	trans-Cinnamaldehyde, 2-methoxycinnamaldehyde, copaene	Essential oil yield = 1.68 % Mass percentage cinnamaldehyde = 78.31 %	[65]
Bark	Distilled water	n.a	100	n.a	Tetrahydro-2-furanol, butyrolactone, 2-furanmethanol, benzaldehyde, (Z)-cinnamaldehyde, (E)-cinnamaldehyde, copaene, Trans-cinnamic acid, Cinnamyl ester, coumarin, γ-muurolene, cadina-1(10),4-diene, 2-methoxycinnamaldehyde, benzene, 2-methyl-1-naphthalenol, 1-phenyl-hexa-1,5-dione	Mass percentage cinnamaldehyde = 89.95 %	[66]
Bark and leaf	Distilled water	4	100	1:5	Bark Eucalyptol, 2-methylbenzofuran, (E)-cinnamaldehyde, α-copaene, (E)-cinnamyl acetate Leaf 2-Methylbenzofuran, (E)-cinnamaldehyde, eugenol, β-caryophyllene, (E)-cinnamyl acetate, (E)-nerolidol	Bark Essential oil yield = 2.2 % (v/w) Mass percentage cinnamaldehyde = 91.5 % Leaf Essential oil yield = 1.2 % (v/w) Mass percentage cinnamaldehyde = 28.2 %	[36]
Essential oil	Distilled water	n.a	100	n.a	Cinnamaldehyde (cis + trans), o-methoxycinnamaldehyde, cinnamyl acetate, coumarin, D-limonene, benzaldehyde, phenylethyl alcohol, styrene, salicylaldehyde, cinnamic acid, cinnamyl alcohol, benzyl benzoate	Mass percentage cinnamaldehyde = 79.98 %	[67]
Bark	Distilled water	6	100	1:10	Trans-cinnamaldehyde, 1,2-naphthalenedione, ethenone, borneol	Essential oil yield = 1.82 % Mass percentage cinnamaldehyde = 84.97 %	[53]
Bark	Water	3	100	1:25	(Z)-Cinnamaldehyde, (E)-cinnamaldehyde, cyclosativene, α-cubebene, (Z)-caryophyllene, (E)-cinnamyl acetate, γ-cadinene,	Essential oil yield = 2.34 %	[68]

Plant part	Solvent type	Extraction parameters			Target compounds	Extraction yield	References
		Extraction time (hr)	Extraction temperature (ºC)	Solid-to-solvent ratio			
					isoledene, α-muurolene, (E)-ortho-methoxycinnamaldehyde, cis-calamenene, delta-cadinene, cubenol, α-muurolol, epi-α-cadinol, α-cadinol, α-bisabolol, cyclohexadecane, N-hexadecanoic acid	Cinnamaldehyde yield = 2096.5 µL/100 mL Percentage recovery of oil = 54.5 %	
Bark	Distilled water	2.5	100	1:8	trans-Cinnamaldehyde, coumarin/cinnamic acid, linalool, copaene, β- caryophyllene tetradecanal, calarene, cedrene, β-cadinene	Mass percentage cinnamaldehyde = 79.6 ± 0.5 %	[69]
Bark	Distilled water	3	100	3:25	α-Cadinol, α-bisabolol, α-copaene, α-muurolene, humulene, α-calacorene, isosativene, (E)-cinnamaldehyde	Essential oil yield = 2.98 % Mass percentage cinnamaldehyde = 76.98 %	[21]
Bark	Steam	2	100	n.a	Cinnamic aldehyde, 2-methoxycinnamaldehyde, cinnamyl acetate, spathulenol, benzaldehyde, nerolidol, globulol, γ-muurolene	Essential oil yield = 3.91 ± 0.09 % Mass percentage cinnamaldehyde = 73.345 ± 0.005 %	[70]
Bark and leaf	Steam	6	100	1:8	trans-Cinnamaldehyde, cinnamaldehyde, benzenepropanal, 2-methoxyphenylacetone, cinnamyl acetate, (E)-2-methoxycinnamaldehyde	Bark Essential oil yield = 1.65 % Mass percentage cinnamaldehyde = 75.66 ± 1.7 % Leaf Essential oil yield = 0.24 % Mass percentage cinnamaldehyde = 28.44 ± 1.69 %	[62]
Bark	Steam	3 to 4	100	1:10	Trans-cinnamylaldehyde, 2-methoxycinnamaldehyde, copaene, β-cadinene, eugenol	Mass percentage cinnamaldehyde = 69.75 %	[71]
Bark	Steam	4	100	n.a	E-Cinnamaldehyde, α-cubebene, eugenol, γ-muurolene, α-calacorene, copaene, coumarin	Essential oil yield = 1.58 ± 0.04 % Mass percentage cinnamaldehyde = 57.72 ± 0.33 %	[72]
Bark	Steam	4.1	101	1:5	Cyclosativene, cinnamaldehyde, cinnamyl acetate, α-copaene, coumarin, cubinene, α-humulene, 3-ethoxy-hexa-1,5-dienyl-benzene, δ-cadinene, muurolene, α-cedrene, cadinol, α-calacorene	Essential oil yield = 0.65 % Mass percentage cinnamaldehyde = 83.19 %	[33]

*Note: n.a = not available

Typically, water is considered the best solvent for MAE due to its high dielectric constant (80.1), which increases the polarity indices of other solvents (ethanol, methanol, acetone) and also increases the mixture's dielectric constant [77]. The studies of microwave-based extraction methods for *C. cassia* are summarized in Table 3.

Kim (2017) found that the extract of *C. cassia* bark powder produced by MAE using distilled water as the solvent contained 2-hydroxycinnamaldehyde, 2-methoxycinnamaldehyde, cinnamaldehyde, cinnamic acid, cinnamyl alcohol, and coumarin [38]. A study by Lee *et al*. (2018) found that using MAE was much more advantageous than UAE and reflux extraction in terms of extraction time, energy consumption, and carbon dioxide emissions. Although the extraction yield and the concentrations of cinnamic acid and cinnamaldehyde obtained through reflux extraction were slightly higher than MAE, and UAE, the optimum extraction time for MAE was only 3.41 min compared to 33.12 min for UAE and 2.25 hrs for reflux extraction. In addition, the energy consumption and carbon dioxide emissions in MAE (0.000023 TOE, 0.000047 tonnes CO_2) were the lowest compared to UAE (0.000089 TOE, 0.000177 tonnes CO_2), and reflux extraction (0.001035 TOE, 0.002063 tonnes CO_2) [35], indicating that the MAE is more environmentally friendly.

Over the years, a combination of MAE with hydrodistillation (known as microwave-assisted hydrodistillation, MAHD) has emerged, and a comparison with traditional hydrodistillation was conducted by Jeyaratnam *et al*. (2016). In this study, *C. cassia* bark powder was pre-soaked in distilled water at a water-to-solid ratio of 8:1 (w/w) and later placed in a modified microwave oven. The essential oil obtained using MAHD consisted of 6.3 % oxygenated monoterpenes, 2.1 % sesquiterpene hydrocarbons, 0.4 % oxygenated sesquiterpenes, and 89.9 % other oxygenated compounds. On the other hand, the extract obtained from hydrodistillation consisted of 4.6 % oxygenated monoterpenes, 10.3 % sesquiterpene hydrocarbons, 0.7 % oxygenated sesquiterpenes, and 82.8 % other oxygenated compounds. This study also showed that the oxygenated compound obtained through MAHD is 8.6 % higher than traditional hydrodistillation [69]. This method has one disadvantage: some of the non-volatile components have low water solubility, which could cause the loss of certain essential non-volatile components in the extract [78]. To further extract the non-volatile component from the water extract (after the MAHD process), ethanol was used to solubilize the non-volatile components from the water extract. However, to ensure the ethanol can fully extract the non-volatile components in the water extract, a high volume of ethanol was required to reduce the water content in the extract (i.e., achieve a high ethanol concentration) and increase the solubility of non-volatile components in ethanol [78]. The increase in the total volume of the extract increased the difficulty in concentrating the compounds and the purification process.

Later a new microwave-assisted extraction method called microwave-assisted steam distillation (MASD) was established to overcome the MAHD's limitation. Using the MASD method, the plant materials are separated from the water, preventing excessive loss of non-volatile components during extraction. During the MASD extraction process, water is heated and converted into steam; the steam passes through the plant materials and extracts the volatile components or essential oil from the plant tissues [79]. The residue remained almost dry since the plant materials were absent from water throughout the extraction process. Thus the non-volatile components can be easily separated at a higher ethanol volume fraction [78]. This method has been applied in the extraction of *C. cassia* where the extract contained cinnamic aldehyde (67.211 %), 2-methoxycinnamaldehyde (15.900 %), benzaldehyde (0.536 %), o-

anisaldehyde (0.531 %), phenylethyl acetate (0.460 %), cinnamyl acetate (9.553 %), benzyl benzoate (0.152 %), 7 alcohols (2.325 %), 17 terpenes (2.724 %), aromatics and ketones (less than 0.3 %) [70]. To summarise, microwave technology has an impact on the extraction efficiency of *C. cassia* essential oil that is not only due to microwave technology but also due to its combination technology. As a result, in order to maximize extraction productivity while minimizing extraction time, all variables that may affect the yield of *C. cassia* essential oil in the MAE process must be fully evaluated.

2.2.2. Ultrasound-assisted extraction.

The ultrasonic-assisted extraction (UAE) uses ultrasonic wave energy to produce cavitation bubbles in the extraction solvent. Ultrasound is based on the propagation of mechanical waves that are generated by a number of cycles that are characterized by compressions (high pressure) and rarefactions (low pressure) [80,81]. The ultrasound used mechanical effects that modified the matrix surface of the plant material, which promotes the solvent to access the plant's internal structure and allows for the dissolution of the desired compound in the solvent [82,83]. However, high-frequency ultrasound reduces the extraction efficiency due to forming free radicals that can cause the degradation of extracted components [84]. This method provided a short extraction time, ease of operation, the requirement of moderate capital, quality retention of the extracts, and low consumption of solvent and energy [84–86]. Thus, it is practical to use UAE to extract thermolabile and unstable compounds [47]. This method also provided the best recovery of total phenolic, phlorotannins, and flavonoid content [87]. The research on the extraction of essential oils or phenolic compounds from *C. cassia* using ultrasound-based extraction in recent years is shown in Table 4.

Michalczyk *et al*. (2015) found that the *C. cassia* extraction using organic solvents such as ethanol (2.200 g), ethyl acetate (1.237 g), hexane (0.405 g), and dichloromethane (0.650 g) showed a higher yield compared to ionic liquid of benzalconium lactate (0.244 g), didecyldimethyl lactate (0.118 g), benzalconium nitrate (0.138 g), didecyldimetthyl nitrate (0.236 g), and tris(2-hydroxyethyl)methylammonium methylsulfate (0.350 g). The bioactive compounds obtained from the *C. cassia* extract in this study were trans-cinnamaldehyde, coumarin, α-copaene, and β-caryophyllene [88].

A recent study has found that applying ultrasound combined with hydrodistillation in the extraction of *C. cassia* showed better yield than the extraction conducted solely with hydrodistillation (without ultrasound pre-treatment). Jadhav *et al*. (2021) stated that the yield of *C. cassia* essential oil increased by 6.37 % when the powder was pre-treated with ultrasound for 15 min at 50 °C compared to hydrodistillation. Moreover, samples pre-treated with ultrasound lead to a shorter extraction time (35 min), lesser sample loading (25 g), and lower solvent consumption (100 mL) and energy usage (0.291 kWh) compare to conventional hydrodistillation (extraction time: 180 min, sample loading: 30 g, solvent consumption: 250 mL, energy usage: 1.14 kWh) [21]. It can be concluded that ultrasound is a safe and clean green technology that can be a promising eco-friendly method in the extraction process.

Table 3. Some representative studies of microwave-assisted extraction, microwave-assisted hydrodistillation, and microwave-assisted steam distillation to extract bioactive compounds from *C. cassia*.

Plant part	Solvent type	Extraction parameters				Target compounds	Extraction yield	References
		Extraction time (min)	Extraction temperature (°C)	Solid-to-solvent ratio	Microwave power (W)			
Bark	Water	25	n.a	3:25	700	Cinnamaldehyde	Essential oil yield = 4.169 % (w/w) Mass percentage cinnamaldehyde = 89.324 %	[89]
Bark	Distilled water	2 to 12	70 to 95	25:1	n.a	2-Hydroxycinnamaldehyde, coumarin, cinnamyl alcohol, cinnamic acid, cinnamaldehyde, 2-methoxycinnamaldehyde.	Cinnamaldehyde yield = 52.416 mg/g	[38]
n.a	59.13 % ethanol	3.41	n.a	1:20	147.59	Cinnamaldehyde, cinnamic acid	Essential oil yield = 0.90 ± 0.02 % Cinnamaldehyde yield = 226.26 ± 1.56 mg/100 mL	[35]
Bark	Distilled water	90	n.a	1:8	250	trans-Cinnamaldehyde, cinnamyl acetate, coumarin/cinnamic acid, anethole, benzaldehyde	Mass percentage cinnamaldehyde = 84.4 ± 0.7 %	[69]
Bark	Water	5 (microwave treatment) 3 hr (hydrodistillation)	50 (microwave treatment) 100 (hydrodistillation)	1:2.5 (microwave treatment) 1:25 (hydrodistillation)	200	Phenyl propanal, (Z)-cinnamaldehyde, (E)-cinnamaldehyde, coumarin, α-cubebene, (Z)-caryophyllene, (E)-cinnamyl acetate, γ-muurolene, α-muurolene, (E)-ortho-methoxycinnamaldehyde, cis-calamenene, β-cadinene beta, cis-cadina-1,4-diene, cubenol, α-muurolol, epi-α-cadinol, naphthallene,1,6-dimethyl-4-(1-methylethyl), α-bisabolol, N-hexadecanoic acid	Essential oil yield = 3.09 % (w/w) Cinnamaldehyde yield = 2888.6 µL/100 mL Percentage recovery of oil = 72.7 %	[68]
Bark and leaves	Water	30	n.a	1:5	750	Bark (E)-cinnamaldehyde, (E)-cinnamyl acetate	Bark Essential oil yield = 2.3 % (v/w)	[36]

Plant part	Solvent type	Extraction parameters				Target compounds	Extraction yield	References
		Extraction time (min)	Extraction temperature (ºC)	Solid-to-solvent ratio	Microwave power (W)			
						Leaf 2-Methylbenzofuran, (E)-cinnamaldehyde, eugenol, β-caryophyllene, (E)-cinnamyl acetate, (E)-nerolidol	Mass percentage cinnamaldehyde = 99.8 % Leaves Essential oil yield = 1.0 % (v/w) Mass percentage cinnamaldehyde = 41.4 %	
Bark	Water (for microwave pre-treatment) Steam (for extraction)	5 (microwave treatment) 2 hr (hydrodistillation)	n.a	1:16	400	Cinnamic aldehyde, 2-methoxycinnamaldehyde, cinnamyl acetate, spathulenol, benzaldehyde, nerolidol, globulol, γ- murolene	Essential oil yield = 5.53 ± 0.03 % Mass percentage cinnamaldehyde = 67.211 ± 0.010 %	[70]

*Note: n.a = not available

Table 4. Some representative studies of ultrasound-assisted extraction, ultrasound-assisted hydrodistillation, ultrasound-assisted steam distillation, and ultrasound-enhanced subcritical water extraction to extract bioactive compounds from *C. cassia*.

Plant part	Solvent type	Extraction parameters					Target compounds	Extraction yield	References
		Extraction time (min)	Extraction temperature (ºC)	Solid-to-solvent ratio	Ultrasonic power (W)	Frequency (Hz)			
n.a	55.34 % ethanol	33.12	n.a	1:20	n.a	n.a	Cinnamaldehyde, cinnamic acid	Essential oil yield = 0.76 ± 0.01 % Cinnamaldehyde yield = 205.26 ± 0.03 mg/100 mL	[35]
Bark	Dichloromethane	40	40	1:20	150	20	E-Cinnamaldehyde, α-cubebene, eugenol, γ-muurolene, α-calacorene, copaene, coumarin	Essential oil yield = 2.10 ± 0.05 % Mass percentage cinnamaldehyde = 46.26 ± 0.58 %	[72]
Bark	Distilled water	15 (ultrasound treatment)	50	1:4	600	20	α-Cadinol, benzaldehyde, α-muurolene, trans-	Essential oil yield = 3.17 % Mass percentage cinnamaldehyde = 90.71 %	[21]

Plant part	Solvent type	Extraction parameters					Target compounds	Extraction yield	References
		Extraction time (min)	Extraction temperature (ºC)	Solid-to-solvent ratio	Ultrasonic power (W)	Frequency (Hz)			
		35 (hydrodistillation)					calamenene, (E)-cinnamaldehyde		
Bark	Distilled water	35 (ultrasound treatment) 60 (hydrodistillation)	n.a	1:7	300	25	trans-Cinnamaldehyde, 2-methoxycinnamaldehyde, copaene	Essential oil yield = 2.14 % Mass percentage cinnamaldehyde = 81.86 %	[65]
Bark	Steam	25 (ultrasound treatment) 120 (steam distillation)	40	1:16	250	n.a	Cinnamic aldehyde, 2-methoxycinnamaldehyde, cinnamyl acetate, spathulenol, benzaldehyde, nerolidol, globulol, γ-muurolene	Essential oil yield = 8.33 ± 0.02 % Mass percentage cinnamaldehyde = 72.371 ± 0.004 %	[70]
Bark	Water	140	25	1:8	145	18.5	E-Cinnamaldehyde, α-cubebene, eugenol, γ-muurolene, α-calacorene, copaene, coumarin	Essential oil yield = 1.78 ± 0.02 % Mass percentage cinnamaldehyde = 71.33 ± 0.33 %	[72]
Bark	Ethyl acetate, hexane, dichloromethane, ethanol, benzalconium lactate, didecyldimethyl lactate, benzalconium nitrate, didecyldimetthyl nitrate, tris(2-hydroxyethyl)methylamonium methylsulfate	10	20	5:6	n.a	35	Trans-cinnamaldehyde, coumarin, α-copaene, β- caryophyllene	Ethyl acetate Essential oil yield = 1.237 % Mass percentage cinnamaldehyde = 84.04 % Hexane Essential oil yield = 0.405 % Mass percentage cinnamaldehyde = 75.79 % Dichloromethane Essential oil yield = 0.65 % Mass percentage cinnamaldehyde = 87.66 %	[88]

Plant part	Solvent type	Extraction parameters					Target compounds	Extraction yield	References
		Extraction time (min)	Extraction temperature (ºC)	Solid-to-solvent ratio	Ultrasonic power (W)	Frequency (Hz)			
								Ethanol Essential oil yield = 2.2 % Mass percentage cinnamaldehyde = 84.42 % Benzalconium lactate Essential oil yield = 0.2444 % Mass percentage cinnamaldehyde = 12.5 % Didecyldimethyl lactate Essential oil yield = 0.118 % Mass percentage cinnamaldehyde = 29.29 % Benzalconium nitrate Essential oil yield = 0.138 % Mass percentage cinnamaldehyde = 50.33 % Didecyldimetthyl nitrate Essential oil yield = 0.236 % Mass percentage cinnamaldehyde = 10.19 % Tris(2-hydroxyethyl)methylamonium methylsulfate Essential oil yield = 0.35 % Mass percentage cinnamaldehyde = 80.72 %	

*Note: n.a = not available

2.2.3. Supercritical fluid extraction.

Supercritical fluid extraction (SCFE) is a green extraction technology that uses supercritical fluid as an extraction solvent. Carbon dioxide (critical conditions: 30.9 °C and 73.8 bar) is one of the most popular supercritical fluids having both liquid and gas-like characteristics. These characteristics make it excellent for rapidly extracting flavor and bioactive components from plant sources while maintaining high yields at low temperatures. Moreover, carbon dioxide has high selectivity, inertness, low cost, non-toxicity, and capability to extract thermally labile compounds [47].

An antioxidant activity study conducted by Yang and co-workers (2012) on the extracts of *C. cassia* buds, barks, and leaves obtained using the SFE demonstrated that the extract contained a total phenolic content (TPC) of 0.151 to 2.08 g GAE/100 g DW and a total flavonoids content (TFC) of 0.031 to 2.504 g/100 g DW. In that study, 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging ability and Trolox equivalent antioxidant capacity (TEAC) was used to evaluate the antioxidant activity. In the DPPH results, the IC_{50} value of the *C. cassia* extract (collected from "washing" fraction ethanol) from leaves (0.593 mg/mL) is the lowest compared to buds (1.457 mg/mL) and bark (2.446 mg/mL). According to the findings, the leaves had the most antioxidant activity, followed by the buds and the bark. From the result of TEAC, the ABTS cation radical scavenging activity of *C. cassia* extract (collected from "washing" fraction ethanol) from buds, barks, and leaves were 58.34, 55.67, and 45.82 mmol Trolox/g, respectively [90].

Another extraction of *C. cassia* bark powder studied by Wang *et al*. (2018) using the SFE method at 50 °C, 5 to 6 MPa, a flow rate of carbon dioxide at 30 L/hr and extraction time of 1 hr yielded a yellow oily liquid composed of thirty-three volatile compounds. The major compounds in the extract were 32.1 % trans-cinnamaldehyde, 10.6 % 3,3-dimethylhexane, and 7.9 % 2,4-di-tert-butylphenol [91]. In addition, Kang & Lee (2018) showed that the extraction efficiency of *C. cassia* essential oil yield by supercritical fluid extraction was 7.61 % and was far higher than steam distillation and organic solvent extraction with a yield of 0.65 % and 4.06 %, respectively [33].

2.2.4. Subcritical fluid extraction.

Subcritical fluid extraction (SFE), also known as pressurized low-polarity fluid extraction, is one of the green techniques for overcoming the drawbacks of conventional organic solvent extraction and expeller pressing methods [83]. The most widely used extractant is subcritical water, with a critical temperature and pressure of 374 °C and 22.1 MPa. It is nontoxic, inexpensive, and highly diffusive. SFE accelerated the extraction process compared to conventional extraction methods, improved the quantity and quality of the extracted material, and reduced the usage of solvent and energy [93].

Cha *et al*. (2019) showed that the extraction yield of *C. cassia* by subcritical water extraction was 14.76 % under optimum conditions (extraction temperature: 130 °C, pressure: 40 bar, and extraction time: 60 min), and the predicted optimum cinnamaldehyde yield was 55 mg/g under 110 °C extraction temperature, the pressure of 37 bar, and 34.62 min extraction time [94]. A study by Liang *et al*. (2019) showed that the yield of the ethanol extract (12.49 %) of *C. cassia* was significantly higher than n-butane extract (3.45 %) under optimum conditions. This could be related to the higher polarity of ethanol and the extraction temperature [95]. The

higher polarity and extraction temperature accelerated the mass transfer rate of solvent and solubility of target compounds. However, the high extraction temperature of SFE results in the thermal decomposition of several thermolabile substances. The SFE process consumes a larger volume of extraction fluid (subcritical water), which restricts the usage of the SFE process in the industry [78]. In addition, the influences of SFE on the quality of *C. cassia* essential oil has been further studied by Guo *et al*. (2021), where the physical and chemical properties of extracted oil remain the same as steam distillation, and ultrasound-enhanced subcritical water extraction. Moreover, there is no difference in the infrared spectra of cinnamaldehyde obtained from subcritical fluid extraction [72].

2.2.5. Enzyme-assisted extraction.

Enzyme-assisted extraction (EAE) involves the application of enzymes to extract bioactive compounds from natural materials. Enzymes such as cellulase, α-amylase, hemicellulose, and pectinase hydrolyze the polysaccharides and lipid complexes in the cell wall and membrane to extract phytochemicals that are inaccessible with a solvent in a routine extraction process and improve the extraction recovery [56]. Enzyme-assisted extraction has a short extraction time, low solvent consumption, and increased yield and product quality [96,97]. However, the high cost is usually the main problem in using enzymes due to their expensive production and purification process. Other problems in using EAE include the incomplete hydrolysis of the plant cell wall and difficulty in industry scale-up, as the environmental condition may limit the enzyme's behavior [98]. In addition, the characteristic of the enzyme might further increase the cost of building up the particular environment to suit the enzyme activity.

Few studies on the bioactive compounds or other analyses of C. cassia were obtained using the EAE method. One of the studies by Bich *et al*. (2017) was on the extraction of *C. cassia* leaves and branches powder treated with the enzyme laccase from *Ganoderma lucidum*, cellulase, and xylanase from Cellic Htec2. The optimum extraction conditions for this study were medium pH 5.2, extraction temperature 44 ^{o}C, extraction time 5 hrs 30 minutes, laccase concentration 0.42 mL/g, and Cellic Htec2 concentration 1.15 g/100g substrate with essential oil yield of 0.982 % [99].

2.2.6. Pulsed electric field extraction.

Pulsed electric field extraction (PEFE) uses short and high-voltage electric fields to produce pores in the cell walls of plant material, resulting in a better release of cellular contents and thereby improving the extraction process [56,100]. This method is suitable for extracting heat-labile compounds as little or no heat is generated during extraction. However, non-polar compounds are difficult to extract as they are resistant to electricity [101]. Additionally, PEFE is expensive and difficult to apply on an industrial scale since it requires a high-power supply generator and a treatment chamber with a special design [102].

Pashazadeh *et al*. (2020) have studied the antioxidant activity of cinnamon extracted using the PEFE method. In this study, a yield of 5.06 % was obtained when 10 g of cinnamon powder was added to ethanol in solid to solvent ratio of 1:10 (w/v) in a chamber with a pulse frequency of 1 Hz, optimum voltage of 5.12 kV/cm and an optimum pulse number of 40 [103]. It was found that the increase of voltage to 4 kV/cm increased the extraction yield. However, the extraction yield decreased when the voltage was further increased to 6 kV/cm. The increase

in yield was mainly attributable to the exposure of plant material to the electrical field, which significantly increases the cell wall porosity and increases the extraction of intercellular components from the plant. The increased pulse number from 40 to 60 also contributed to the increment of the extraction yield, which is related to the disruption of the plant cell wall and the enhanced solubilization of intracellular components from the destroyed cells [104]. Through these optimum extraction conditions, the total phenolic content, DPPH free radical scavenging assay, and EC_{50} were 505.93 mg GA/g, 91.70 %, and 1.04 mg/mL, respectively. By comparing commercialized antioxidants, α-Tocopherol, and ascorbic acid, the antioxidant activity of the extract was significantly higher than α-Tocopherol (25.48 %, 31.50 mg/mL) but slightly lower than ascorbic acid (92.45 %, 0.04 mg/mL) [103].

Only a few studies have looked into the efficacy of using SCFE, SFE, EAE, and PEFE to extract *C. cassia*. These methods' effectiveness, economic viability, and industrial safety need to be investigated further. The effects of multiple novel extraction technologies on *C. cassia*'s cinnamaldehyde composition require additional investigation to replace the conventional extraction procedures with a green and effective extraction technology.

3. Antimicrobial Studies of *C. cassia*

In the past few years, the over usage of antibiotics in hospitals has caused serious nosocomial infections by drug-resistant bacteria [105]. The advent of antibiotic-resistant bacteria, such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*, has initiated interest in developing new antibiotics. Despite the continual development of synthetic antibiotics, new diseases and drug-resistant strains of known infections continue to arise. As a result, the potential of fully manufactured drugs with simple structures and well-understood mechanisms of action is beginning to dwindle [106]. The plant phenolic compounds have shown antimicrobial effects and serve as plant defense mechanisms against pathogenic microorganisms [107]. Various plant phenolic compounds are investigated on their natural and excellent antimicrobial properties towards microbes and are constantly compared with synthetic or commercialized antibiotics such as ampicillin and tetracycline. Antimicrobial susceptibility testing is crucial in discovering new types of bioactive compounds or drugs, the potential of microbial drug resistance, and ensuring susceptibility to the drug of choice for specific diseases [108–110]. The previous study showed that *C. cassia* has a broad range of antimicrobial effects on different types of microorganisms. However, the effectiveness of inhibition towards the growth of microbes is directly influenced by the types of extraction methods, as different extraction methods show different outcomes in terms of extraction yield and target bioactive compounds. Moreover, the antimicrobial test method also affects the result of the antimicrobial test [111]. In addition, the selection of different microbes, cultivation time, and surrounding temperature may also affect the final outcome [111,112].

A study by El Atki *et al*. (2019) showed that the extract of *C. cassia* bark obtained by the hydrodistillation method was able to inhibit *Escherichia coli*, *S. aureus*, and *P. aeruginosa*. The MIC against the strains tested was 4.88 μg/mL for *E. coli* and *S. aureus*, and 19.53 μg/mL for *P. aeruginosa*. The inhibition zone diameter for the three tested species was 29.0 ± 0.7 mm, 40.0 ± 0.5 mm, and 30.5 ± 1.0 mm, respectively. It was also found that the commercialized antibiotics, ampicillin and chloramphenicol have no inhibitory effect on *P. aeruginosa* [25]. Bereksi and co-workers (2018) found that the refluxed and macerated methanolic *C. cassia* extract inhibited the growth of *E. coli*, *E. faecalis*, *Entrobacter cloacae*, *K. pneumoniae*, *P. aeruginosa*, and *S. aureus*. The inhibition zone diameter ranged from 7.0 mm to 11.0 mm for

refluxed methanolic extract and from 7.0 mm to 12.0 mm for macerated methanolic extract [113]. The study found that the extraction methods may influence the antimicrobial activity where the refluxed methanolic extract more effectively inhibited the growth of *E. coli*, *E. cloacae*, and *P. aeruginosa* but not for *S. aureus*, and *E. faecalis*. In a preliminary study by Singh *et al*. (2020), it was discovered that the methanol, ethanol, and acetone extracts of *C. cassia* from Soxhlet extraction exhibited antimicrobial activity against Gram-positive bacteria *Bacillus cereus*, *Enterococcus faecalis*, *S. aureus* and, *Streptococcus pyogenes*. However, for Gram-negative bacteria, only *P. aeruginosa* and *Salmonella bongori* were inhibited by these three extracts, but not *E. coli* [114]. Through this study, it can be concluded that the *C. cassia* extract using acetone as an extraction solvent effectively restricted the survival of Gram-positive and Gram-negative bacteria compared to methanol and ethanol in a maximum extract concentration of 150 mg/mL.

Generally, most of the investigation on the antimicrobial activity of the *C. cassia* extract was done using extracts obtained by conventional methods such as hydrodistillation, maceration, reflux, and Soxhlet extraction. Still, several studies have used extracts obtained from non-conventional methods, such as UAE, where the extract of *C. cassia* prevented the growth of microbes. Extracts of *C. cassia* from UAE with petroleum ether as the solvent can inhibit the growth of *E. coli* and *B. subtilis* up to 76.31 ± 0.53 % and 66.03 ± 0.55 %, respectively, at 1.00 mg/mL [115]. Similarly, Michalczyk *et al*. (2015) found that the *C. cassia* bark extract from UAE using an ionic liquid, tris(2-hydroxyethyl) methylammonium methylsulfate exhibited stronger antimicrobial activity on yeasts and fungus strains compared to an organic solvent such as ethyl acetate, hexane, methylene chloride, methanol [88]. Liang *et al*. (2019) compared the antimicrobial activity of *C. cassia* extract obtained from a subcritical extraction method using n-butane and ethanol as extraction solvents. The result showed that n-butane and ethanol extract of *C. cassia* inhibited four foodborne pathogens *Listeria monocytogenes*, *S. aureus*, *E. coli*, and *Salmonella anatum*. However, n-butane extract showed a better antimicrobial effect compared to ethanol extract in terms of a larger diameter of inhibition zone and lower minimum bactericidal concentration. This could be due to more bioactive compounds from *C. cassia* being dissolved by n-butane compared to ethanol [95]. The *C. cassia* extracts obtained using non-conventional methods showed promising antimicrobial activity. The distinction of antimicrobial activity between conventional, non-conventional extraction, or a combination of both should be further investigated. Besides, the selection of extraction solvent also influences antimicrobial activity as it affects the content of bioactive compounds dissolved in the solvent. Therefore, the relationship between the types of extraction solvent and the antimicrobial activity also needs to be studied. Table 5 shows the details of the antimicrobial study of *C. cassia* to different types of microbes, the method to obtain the essential oil or extract, antimicrobial test methods, and the outcomes.

The antimicrobial activity of *C. cassia* extract has been investigated by Doyle and co-workers (2019). Cinnamaldehyde and 2-methoxycinnamaldehyde were the primary active components present in *C. cassia*. The mode of antimicrobial mechanism could be related to the cell membrane destabilization, release of the cellular constituent, inhibition of energy (adenosine triphosphate, ATP) synthesis, inhibition of FtsZ protein for cell division, suppression of quorum sensing and biofilm formation [135].

Table 5. Antimicrobial activity of *C. cassia*.

Extraction or preparation method	Type of extraction solvent	Test method	Type of microbes	Result	References
Commercially procured (branches essential oil)	n.a	Broth microdilution assay	*S. aureus* *E. coli*	MIC = 50 µg/ml (brand: Neumond GmbH, Frey&Lau GmbH and Düllberg Konzentra GmbH) MIC = 50 µg/ml (brand: Frey&Lau GmbH and Düllberg Konzentra GmbH), 200 µg/ml (brand: Neumond GmbH)	[116]
Commercially procured (cinnamon oil) Ultrasonicator (Cinnamon oil nano emulsion)	n.a	Broth micro-dilution	*Salmonella enterica* (strain-S11975, SalI) *Salmonella enetrica* (strain-E2002001708, SalII) *Salmonella choleraesuis subsp. Choleraesuis*, SalIII *L. monocytogenes* (strain- FSL N1-017, LMI) *L. monocytogenes* (strain- FSL J2-064, LMII) *L. monocytogenes* (strain- FSL N3-165, LMIII)	MIC = 0.039 % MIC = 0.039 % MIC = 0.039 % MIC = 0.078 % MIC = 0.078 % MIC = 0.078 %	[117]
Commercially procured (essential oil of cassia)	n.a	Disc-volatilization, agar plug-based vapour phase assay	*Salmonella enterica* ser. Typhi *Yersinia enterocolitica* *E. coli*	IC50 = 0.15 µL/cm^3 IC50 = 0.08 µL/cm^3 IC50 = 0.53 µL/cm^3	[118]
Commercially procured (essential oil)	n.a	Fumigation mode based on transpiration of volatile odor	*A. flavus* *Aspergillus carbonarius* *Penicillium viridicatum*	MIC = 1.67 µL/mL MIC = 1.67 µL/mL MIC = > 5.0 µL/mL	[91]
Commercially procured (essential oil)	n.a	Disc diffusion assay, two-fold microdilution broth method	*Salmonella enteritidis* *Salmonella tennessee*	MIC = 0.05 % (v/v) MBC = 0.1 % (v/v) MIC = 0.05 % (v/v) MBC = 0.1 % (v/v)	[119]
Commercially procured (essential oil)	n.a	Disc diffusion, agar microdilution	*S. maltophilia* *B. subtilis* *P. expansum* *P. crustosum* *P. citrinum*	MIC = 0.05 µL/mL MIC = 0.10 µL/mL MIC = 0.20 µL/mL MIC = 0.39 µL/mL MIC = 0.78 µL/mL	[120]
Commercially procured (essential oil)	n.a	Serial two-fold dilutions	*C. albicans* *C. glabrata*	MIC = 0.002 - 0.125 % (v/v) MFC = 0.002 - 0.125 % (v/v) MIC = 0.002 - 0.125 % (v/v) MFC = 0.002 - 0.125 % (v/v)	[121]
Commercially procured (essential oil)	n.a	Disk diffusion	*E. coli* *S. aureus* *Penicillium spp*	MIC = 0.07 mg/mL MIC = 0.04 mg/mL MIC = 0.04 mg/mL	[122]

Extraction or preparation method	Type of extraction solvent	Test method	Type of microbes	Result	References
Commercially procured (essential oil)	n.a	Serial dilution method	*E. coli* *Salmonella enterica subsp. enterica serovar Choleraesius* *S. aureus* *L. monocytogenes*	MIC = 0.024 % MBC = 0.048 % MIC = 0.012 % MBC = 0.024 % MIC = 0.095 % MBC = 0.19 % MIC = 0.0015 % MBC = 0.0030 %	[123]
Commercially procured (essential oil)	n.a	Agar dilution	*Alternaria grisea* *Alternaria humicola* *Aspergillus chevalieri* *A. flavus* *Aspergillus fumigatus* *Aspergillus luchuensis* *A. niger* *Aspergillus penicilloides* *Aspergillus repens* (Corda) Sacc *Aspergillus sydowii* *Aspergillus versicolor* *Cladosporium herbarum* Mucor species *Penicillium chrysogenum* *Penicillium italicum*	MIC = 0.06 µL/mL MIC = 0.06 µL/mL MIC = 0.06 µL/mL MIC = 0.06 µL/mL MIC = 0.06 µL/mL MIC = 0.06 µL/mL MIC = 0.06 µL/mL MIC = 0.06 µL/mL MIC = 0.06 µL/mL MIC = 0.06 µL/mL MIC = 0.06 µL/mL MIC = 0.06 µL/mL MIC = 0.06 µL/mL MIC = 0.06 µL/mL MIC = 0.06 µL/mL	[124]
Commercially procured (essential oil)	n.a	Broth microdilution	*Botrytis cinerea* *Cercospora beticola* *Colletotrichum lindemuthianum* *Fusarium culmorum* *Fusarium graminearum* *P. expansum* *Pectobacterium atrosepticum* *Pectobacterium carotovorum* *Phytophthora infestans* *Pythium ultimum*	Concentration = 500 ppm Concentration = 500 ppm Concentration = 500 ppm Concentration = 1000 ppm Concentration = 500 ppm Concentration = 1000 ppm Concentration = 500 ppm Concentration = 500 ppm Concentration = 1000 ppm Concentration = 500 and 1000 ppm	[125]
Commercially procured (leaf oil)	n.a	Agar well diffusion, microdilution broth	*S. aureus*	MIC = 1.25 % MBC = 1.25 % MBIC = 1.25 % MBEC = 2.5 %	[126]

Extraction or preparation method	Type of extraction solvent	Test method	Type of microbes	Result	References
Commercially procured (*C. cassia* essential oil extracted from the leaves, bark, and branches by steam distillation)	n.a	Agar disk diffusion, broth microdilution	*K. pneumoniae* *S. marcescens*	Essential oil only MIC = 281.25 µg/mL MIC = 281.25 µg/mL	[127]
Commercially procured (*C. cassia* essential oil extracted from the bark by steam distillation)	n.a	Broth microdilution	*E. coli* *P. aeruginosa* *S. aureus* *S. pyogenes* *Streptococcus epidermidis*	MIC = 0.25 mg/mL MBC = n.a MIC = 0.50 mg/mL MBC = n.a MIC = 0.25 mg/mL MBC = 1.00 mg/mL MIC = 0.50 mg/mL MBC = n.a MIC = 0.25 mg/mL MBC = 1.00 mg/mL	[128]
Continuous flow leaching or percolation	70 % ethanol	Agar diffusion, microdilution broth	*Fusobacterium nucleatum* *Parvimonas micra* *Porphyromonas gingivalis* *Prevotella intermedia*	MIC = > 400 µg/mL MIC = 50 µg/mL MIC = 190 µg/mL MIC = > 400 µg/mL	[129]
Hot water extraction	Double distilled water	Disc diffusion	*E. coli*	Inhibition zone = 8 to 20 mm	[130]
Hydrodistillation followed by solvent extraction	Water Petroleum ether	Poisoned food method	*Fusarium oxysporum* *Rhizoctonia solani*	IC50 = > 200 µg/mL IC50 = > 200 µg/mL	[131]
Hydrodistillation	Water	Rapid INT colorimetric assay	*Salmonella pullorum*	MIC = 0.31 mg/mL	[60]
Hydrodistillation	Water	Agar disc diffusion, broth microdilution	*E. coli* *S. aureus* *P. aeruginosa*	MIC = 4.88 µg/ml MIC = 4.88 µg/ml MIC = 19.53 µg/ml	[25]
Hydrodistillation	Water	Oxford cup method, double dilution method	*Botrytis cinerea* *Colletotrichum gloeosporioides* *Cylindrocarpon destructans* *Fusarium oxysporum* *Fusarium solani* *Pythium aphanidermatum*	MIC = 146.88 µg/mL MIC = 548.44 µg/mL MIC = 138.44 µg/mL MIC = 138.44 µg/mL MIC = 147.50 µg/mL MIC = 494.06 µg/mL	[62]

Extraction or preparation method	Type of extraction solvent	Test method	Type of microbes	Result	References
Hydrodistillation	Water	broth microdilution, microtiter plate, swimming motility assay	*S. typhimurium*	MBC = 312.5 µg/mL Biofilm inhibition = 72.4 % (200 µg/mL) Swimming diameters = 5.87 cm (50 µg/mL)	[67]
Microwave-assisted hydrodistillation	Water	Broth dilution	*A. niger* *Bacillus subtillis* *C. albicans* *E. coli* *Fusarium oxysporum* *P. aeruginosa* *S. aureus* *Saccharomyces cerevisiae*	Leaf MIC for all tested microorganisms was more than 200 µg/mL Bark MIC for all tested microorganisms was more than 200 µg/mL, except MIC for *Saccharomyces cerevisiae* at 200 µg/mL	[36]
Maceration	80 % methanol	Disc diffusion, broth micro-dilution	*E. cloacae* *E. coli* *E. faecalis* *K. pneumoniae* *P. aeruginosa* *S. aureus*	MIC = 6.4 mg/mL MIC = 3.2 mg/mL MIC = 0.8 mg/mL MIC = 12.8 mg/mL MIC = 12.8 mg/mL MIC = 0.1 mg/mL	[113]
Maceration	Methanol Distilled water Chloroform n-Hexane	Agar well disc diffusion	*E-coli* *Salmonella* *Shigella* *MRSA*	Inhibition zone = 9.06 to 12.03 mm Inhibition zone = 9.20 to 12.13 mm Inhibition zone = 9.06 to 12.03 mm Inhibition zone = 8.03 to 14.06 mm	[132]
Reflux extraction	80 % ethanol	Broth dilution method	*E. coli* *Mycobacterium tuberculosis* *S. aureus*	MIC = 640 µg/mL MIC = 10 µg/mL MIC = 320 µg/mL	[133]
Reflux extraction	80 % methanol	Disc diffusion, broth micro-dilution	*E. coli* *E. faecalis* *Entrobacter cloacae* *K. pneumoniae* *P. aeruginosa* *S. aureus*	MIC = 1.6 mg/mL MIC = 6.4 mg/mL MIC = 1.6 mg/mL MIC = 12.8 mg/mL MIC = 3.2 mg/mL MIC = 0.8 mg/mL	[113]
Soxhlet extraction	Methanol, ethanol and acetone	Agar well-diffusion, broth dilution	*B. cereus* *E. coli* *E. faecalis* *P. aeruginosa* *S. aureus* *S. bongori* *S. pyogenes*	Inhibitory action to all microbes except *E. coli*	[114]

Extraction or preparation method	Type of extraction solvent	Test method	Type of microbes	Result	References
Soxhlet extraction	Ethanol	Agar well diffusion	*S. typhimurium* strain TA97a TA98 TA100 TA102 TA104 *E. coli* *K. pneumoniae* *P. aeruginosa* *Proteus vulgaris* *S. aureus* *S. typhimurium*	Dose = 1.0 mg/plate (- S9) Dose = 1.0 mg/plate (- S9) Dose = 1.0 mg/plate (- S9) Dose = 1.0 mg/plate (- S9) Dose = 1.0mg/plate (- S9) Concentration = 200 mg/mL Inhibition zone = 16.83 mm Inhibition zone = 17.11 mm Inhibition zone = 14.07 mm Inhibition zone = 18.02 mm Inhibition zone = 20.86 mm Inhibition zone = 17.32 mm	[50]
Subcritical extraction	n-butane Ethanol	Agar well diffusion, twofold microdilution broth	*E. coli* *L. monocytogenes* *S. anatum* *S. aureus* *E. coli* *L. monocytogenes* *S. anatum* *S. aureus*	MBC = 0.625 mg/mL MBC = 0.31 mg/mL MBC = 1.25 mg/mL MBC = 1.25 mg/mL MBC = 20.00 mg/mL MBC = 20.00 mg/mL MBC = 40.00 mg/mL MBC = 20.00 mg/mL	[95]
Supercritical fluid extraction	Carbon dioxide	Poisoned food method	*Botrytis cinerea*	MIC = 600 µL/L MFC = 600 µL/L	[134]
Supercritical fluid extraction Solvent extraction	Carbon dioxide Ethanol	Disk diffusion	*A. Baumannii* *P. aeruginosa* *S. aureus* *A. Baumannii* *P. aeruginosa* *S. aureus*	MIC = 0.4 - 0.6 mg/mL MIC = 1.1 - 1.2 mg/mL MIC = 0.5 – 0.7 mg/mL MIC = 1.4 mg/mL MIC = 1.8 mg/mL MIC = 2.0 mg/mL	[106]
Ultrasound-assisted extraction	Petroleum ether Ethyl ether 95 % ethanol Cyclohexane Dichloromethane	Disk diffusion	 *E. coli* *B. subtilis*	Concentration = 1 mg/mL (extracted by petroleum ether) Inhibition zone = 25.33 mm Inhibition zone = 17.67 mm	[115]

Extraction or preparation method	Type of extraction solvent	Test method	Type of microbes	Result	References
Ultrasound-assisted extraction	Organic solvent Ethyl acetate, hexane, methylene chloride, methanol Ionic liquid Benzalkonium lactate, didecyldimethyl lactate, benzalkonium nitrate, didecyldimetthyl nitrate, tris(2-hydroxyethyl)methylamonium Methylsulfate (Solvent E)	Disk diffusion, poisoned food method	 Yeast strains *C. albicans* *Rhodotorula rubra* *Malassezia furfur* Fungi strains *Fusarium culmorum* *Phytophthora cactorum* *Fusarium graminearum* *Rhizoctonia solani* *Alternaria alternata* *Geumannomyces graminis* *Trichophyton mentagrophytes* *Microsporum gypseum* *Microsporum coockei* *Scopulariopsis brevicualis* *A. niger* *Chaetomium globusom* *Paecilomyces varioth* *Ascosphaera apis*	Solvent E showed strongest antimicrobial activity Inhibition zone = 50 mm Inhibition zone = 50 mm Inhibition zone = 45.5 mm Growth inhibition = 100 % Growth inhibition = 68 % Growth inhibition = 100 % Growth inhibition = 90 % Growth inhibition = 88 % Growth inhibition = 100 % Growth inhibition = 100 % Growth inhibition = 100 % Growth inhibition = 100 % Growth inhibition = 93 % Growth inhibition = 40 % Growth inhibition = 100 % Growth inhibition = 68 % Growth inhibition = 100 %	[88]
Ultrasound-assisted extraction	Water with 2 % sodium chloride	Paper diffusion method, broth dilution	*E. coli*	MIC = 0.118 µg/mL MBC = 0.710 µg/mL	[24]
			S. aureus	MIC = 0.355 µg/mL MBC = 0.710 µg/mL	
			B. subtilis	MIC = 0.355 µg/mL MBC = 0.710 µg/mL	
			S. typhimurium	MIC = 0.118 µg/mL MBC = 0.355 µg/mL	
			P. aeruginosa	MIC = 0.118 µg/mL MBC = 0.710 µg/mL	
			S. epidermidis	MIC = 0.355 µg/mL MBC = 0.710 µg/mL	

Abbreviations: n.a = not available, MIC = minimum inhibitory concentration, MBC = minimum bactericidal concentration, MFC = minimum fungicidal concentration, MBIC = minimum biofilm inhibitory concentration, MBEC = minimum biofilm eradication concentration, metabolic activation = S9, - = present, MRSA = methicillin-resistant *S. aureus*

Figure 4 presents the graphical explanation of the antimicrobial mechanism mode of cinnamaldehyde from *C. cassia*. Moreover, cinnamic acid is also a chemical constituent in C. cassia, which is a white crystalline phenolic compound with a low-intensity sweet and honey-like aroma [37]. Cinnamic acid has shown potent efficacy against several microbes, such as *Acanthamoeba castellanii*, methicillin-resistant *S. aureus*, *E. coli* K1, *Salmonella typhimurium*, and *P. aeruginosa* [136,137].

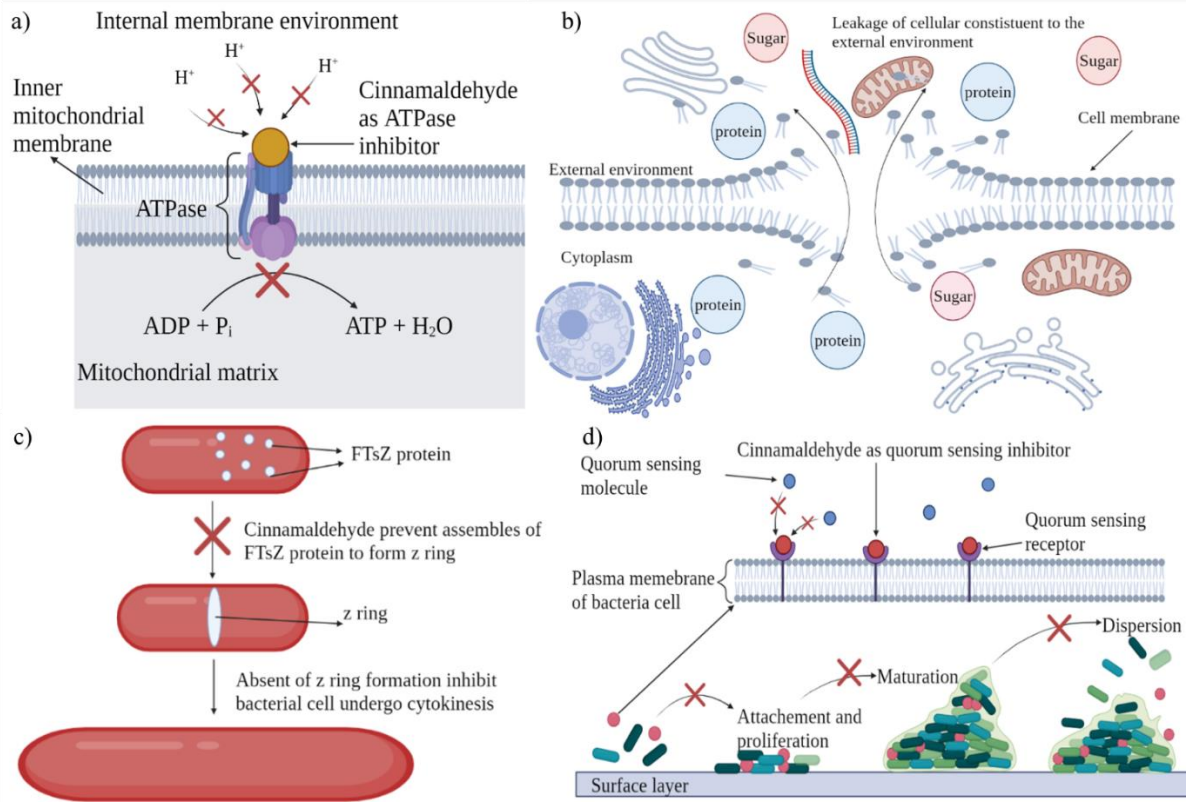

Figure 4. Antimicrobial mode of the mechanism of cinnamaldehyde from *C. cassia*. **(a)** Inhibition of ATPase for the synthesis of ATP, **(b)** Cell membrane destabilization and release of a cellular constituent from cell cytoplasm to external environment, **(c)** Inhibition of z ring formation and prevent cytokinesis, **(d)** Inhibition of quorum sensing and biofilm formation.

Gucwa *et al*. (2018) studied the activity of *C. cassia*, *Citrus limonum*, *Eugenia caryophyllus*, *Ocimum basilicum*, *Pelargonium graveolens*, and *Thymus vulgaris* essential oils against the human pathogenic fungus *Candida albicans* and *Candida glabrata* using serial two-fold dilutions method. Among the six types of essential oil, *C. cassia* essential oil showed the highest antifungal activity against both species, with MIC and MFC values in the range of less than 0.002 to 0.125% (v/v) [121]. Moreover, their study found that combining *C. cassia* essential oil with the antifungal drug, amphotericin B, showed a synergistic effect against Candida species using a disc-diffusion assay, as shown in Figure 5. A similar study by Vasconcelos *et al*. (2020) discovered the combination of *C. cassia* essential oil with polymyxin B against carbapenemase-producing *Klebsiella pneumoniae* and *Serratia marcescens* with a fractional inhibitory concentration value index of 0.006 for both multidrug-resistant strains which indicated this combination showed synergistic effects [127]. In addition, the synergistic effects of *C. cassia* and *T. vulgaris* essential oil mixture have also been studied by Pekmezovic *et al*. (2015) to maximize their antifungal activity towards the spores of *Aspergillus flavus* in a shorter time. The results showed that essential oil composition (*T. vulgaris*:*C. cassia*) at the ratio of 14:1, the time taken to achieve 100 % inhibition was 90 minutes, which was the lowest

compared to the ratio of 7:1 and 1:1, with the time taken of 110 and 120 minutes, respectively. In this study, all the essential oil mixtures showed a partial synergistic effect with a fractional inhibitory concentration value index of 0.75 [138].

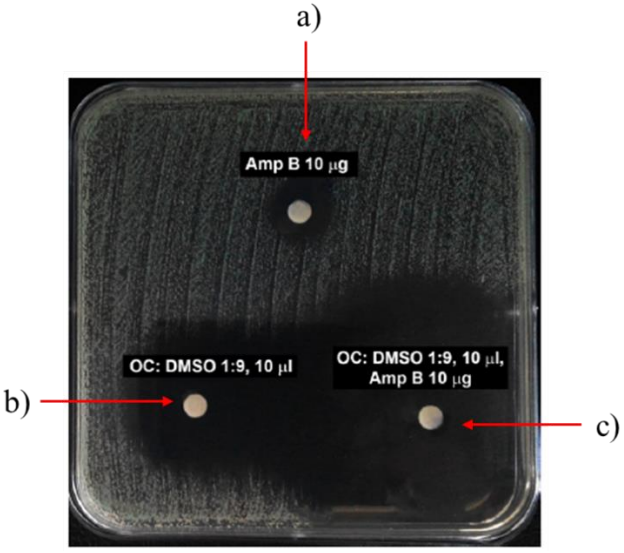

Figure 5. Synergism action study between *C. cassia* essential oil and amphotericin B (Amp B) using disc diffusion assay. **(a)** Disc with 10 µg amphotericin only, **(b)** Disc with 10 µL *C. cassia* essential oil (diluted 10 times with dimethyl sulfoxide, DMSO) only, **(c)** Disc with the combination of 10 µL *C. cassia* essential oil (diluted 10 times with DMSO) and 10 µg Amp B. DMSO does not cause any inhibition to the tested species. Figure and caption reused from Gucwa *et al*. (2018) [110]. Used under the Creative Commons License (http://creativecommons.org/licenses/by/4.0/ (accessed on 1 September 2022)).

In another research conducted by Kacaniova *et al*. (2021) using the disc diffusion method, it was found that *C. cassia* essential oil was effective against *Stenotrophomonas maltophilia* (27.33 ± 0.58 mm), *Bacillus subtilis* (20.33 ± 1.53 mm) but less effective against *Penicillium citrinum* (13.53 ± 1.15 mm), *Penicillium crustosum* (10.64 ± 0.58 mm), and *Penicillium expansum* (10.33 ± 1.53 mm). Besides, through the analysis of *in situ* antifungal activity, *C. cassia* essential oil reduced the growth of *Penicillium* species, *Aspergillus niger*, *B. subtilis* on bread, carrot, potato, and apple [120]. Šernaitė and co-workers (2020) discovered using the poisoned food method that the *C. cassia* carbon dioxide extract (MFC = 600 µL/L) exhibited higher antifungal activity toward *B. cinerea* compared to *Syzygium aromaticum* carbon dioxide extract (MFC =1400 µL/L) [134]. Furthermore, it was found in a study by Ribeiro-Santos *et al*. (2017) that among the *O. basilicum*, *C. cassia*, *Cinnamomum zeylanicum*, and *Rosmarinus officinalis*, *C. cassia* has shown the highest microbial growth inhibition on *E. coli*, *S. aureus*, and *Penicillium* spp, due to the primary active component of cinnamaldehyde, which has the potential application in biodegradable food packaging [122]. The *C. cassia* essential oil incorporated in cassava starch film as a bread product packaging successfully inhibited the growth of *Penicillium commune* and *Eurotium amstelodami* in the formulation of 1.5 g/100 g of glycerol, 0.020 g/100g of emulsifier, and 0.80 g/100g of *C. cassia* essential oil [139].

In a strawberry packaging experiment, *C. cassia* essential oil was used as an active ingredient in poly (butylene adipate-co-terephthalate) active film preparation, which showed no fungal growth on the surface of the strawberry and improved freshness preservation after 15 days of storage at 4 °C [140]. A study also reported chitosan added with *C. cassia* essential oil for edible coating had reduced the growth of mold and yeast within 15 days of storage at 5 °C. The research also discovered that the application of chitosan with *C. cassia* essential oil on

minimally processed pineapple could reduce weight loss, reduce the titratable acidity, which can slow down the respiratory activity of pineapple, maintain low pH to prevent microbial growth, reduce solid soluble content, decrease the rate of fruit surface brightness and firmness loss [141]. Moreover, the vapor phase of cinnamon essential oil inside packaging with the concentration of 556 μL/$L_{headspace}$ reduced the colony count of *Listeria grayi* on frozen green peppers at 22 ºC from 3.44 log CFU/g on day 0 to 1.00 log CFU/g in day two and remain constant until day 5. Furthermore, after eight days of storage, no growth of *L. grayi* was observed on the frozen green peppers. This indicated that the cinnamon essential oil vapors showed bactericidal effects that completely killed the *L. grayi* at the early storage stage [142].

In preserving dairy products, cross-contamination in cheese production was an issue that shortened curd cheese's shelf life. A curd cheese coating experiment was conducted by Mileriene *et al*. (2021), whereby liquid whey protein concentrate-based edible coating impregnated with 0.3 % (wt/wt) of *C. cassia* carbon dioxide extract (LWPC-CE) was coated on the curd cheese and vacuum-packed. The data shows that the yeast and mold count decreased significantly in 31 days of storage at 8.5 °C under 85 % relative humidity. However, the LWPC-CE coating does not harm the growth of dairy microflora, predominantly lactic acid bacteria. The presence of LWPC-CE coating on curd cheese decreased the loss of lactic acid bacteria compared to without LWPC-CE coating during 31 days of storage. From this study, the LWPC-CE coating does not cause considerable changes in moisture, color, texture, lactic acid, protein, and fat contents. For sensory analysis, the appearance, odor, taste, and overall acceptance are almost the same in curd cheese coated with LWPC-CE and vacuum packaged compared to the control (no LWPC-CE coating, no vacuum packaged) [143].

In recent years, Barbosa *et al*. (2021) have investigated the antimicrobial activity of *C. cassia* essential oil capsules using poly(butyleneadipate-co-terephthalate) as encapsulation material. The results have shown that the capsules inhibited *E. coli* (44.1 ± 0.9 mm), *L. monocytogenes* (56.6 ± 0.6 mm), *S. enterica* (51.9 ± 0.5 mm), and *S. aureus* (55.3 ± 0.8 mm) [121]. A similar study was also reported by Campini and co-workers (2021), where the *C. cassia* essential oil-poly (lactic acid) microcapsules gradually increased the growth inhibition of foodborne pathogen up to 28 days with adequate sustained-release of active components from *C. cassia* essential oil through the polymeric walls [123].

A comparison study of four essential oils found that 0.25 % of *C. cassia* essential oil incorporated in vacuum-packaged fresh chicken sausages and stored under -18 °C for 45 days was able to reduce the oxidation rate in sausages, lower the decrease of total phenolic content, increased the antioxidant activity, and has the lowest increase of microbial count compared to clove oil, holy basil oil, and thyme oil [145]. Zhang and co-workers (2017) studied the effect of *C. cassia* essential oil coating on the microbiota diversity and quality evaluation of the vacuum-packaged *Cyprinus carpio* fillets stored at 4 °C for 14 days of storage. The results showed that the application of *C. cassia* essential oil coating suppressed the growth of *Aeromonas* and *Lactococcus*, which is responsible for the main fish spoilage. For the sensory evaluation, the sensory score of coated fish fillets was significantly higher than fish fillets without coating, indicating the application of the *C. cassia* essential oil coating on fish fillets is acceptable for consumers. Furthermore, the presence of *C. cassia* essential oil coating showed a lower value of total volatile basic nitrogen, which indicates the coated fish fillets were fresher than those without coating. No significant difference was observed in color change between coated and without coated fish fillets after 14 days of storage [146]. A similar study was investigated by Meenatchisundaram *et al*. (2016), where the white shrimps wrapped with

C. cassia incorporated edible starch films significantly extended the shelf life of white shrimps up to 21 days in storage temperature of 10 °C, and 29 days in storage temperature of 4 °C. The increased shelf life in wrapped white shrimps was mainly due to the major bioactive component of cinnamaldehyde that reduced the bacterial count, lipid oxidation, and total volatile basic nitrogen in white shrimps. In terms of sensory quality, the odor, taste, and color on the wrapped white shrimps after 20 days of storage at 4 and 10 °C were still acceptable for consumption [147].

In general, *C. cassia* has demonstrated a wide range of antimicrobial activity, indicating that *C. cassia* is an excellent antimicrobial agent that can be utilized in food, medical, and nutraceutical industries. The essential oil or extract is rich in cinnamaldehyde, cinnamate, cinnamic acid, and other phenolic compounds such as borneol, coumarin, gallic acid, p-coumaric acid, protocatechuic acid, and δ-cadinene [60,148,149].

4. Toxicological Safety of *C. cassia*

Although many bioactive compounds showed benefits in maintaining and enhancing human health, not all bioactive compounds are always safe to apply and may cause some undesirable effects, such as allergic dermatitis. This situation is usually related to the relationship between food, pharmaceuticals, and toxicity to the organ [150]. Understanding the safety concerns regarding cinnamon and its components is vital for building effective methods to optimize the advantages of cinnamon while reducing exposure to its negative effects. The Food and Drug Administration (FDA) stated that *C. cassia* is GRAS in quantity, typically found in food as a spice, food additive, and flavoring ingredient. This suggests that *C. cassia* is likely to be safe [151,152]. This statement is further supported by the Flavor and Extract Manufacturers Association (FEMA), where the *C. cassia* bark extract or essential oil is safe to be used as a flavor ingredient [153]. However, excess consumption of *C. cassia* might suffer respiratory distress, increased heart rate, hyperhidrosis, dysthymia, and somnolence [154]. Coumarin, cinnamaldehyde, and styrene in *C. cassia* show toxicity symptoms in a dose-dependent response [155].

A 14-day acute toxicity study of *C. cassia* methanolic extract on healthy adult female Sprague-Dawley rats does not show any significant toxic effects, although the extract concentration was up to 2000 mg/kg. The *C. cassia* extract exhibited antidiabetic activity on streptozotocin-induced Sprague-Dawley rats at a dose level between 125 to 500 mg/kg [27]. The sub-acute oral administration of *C. cassia* bark ethanolic extract on healthy male albino Wistar rats at doses lower than 400 mg/kg does not cause any toxic effect on the hematological parameters (white blood cell total, platelets count, packed cell volume, neutrophils, and lymphocytes) and reduction of serum cholesterol levels. However, this study also found that treatment with 400 mg/kg of *C. cassia* extracts significantly increased ($P < 0.05$) the level of alkaline phosphatase and creatinine, which might cause damage to the liver, the presence of bone disease and kidney malfunction [156]. The ethanolic extract of *C. cassia* did not cause any adverse effects in Albino Wistar male rats at a high dose of 5000 mg/kg body weight. The extract showed an anti-diabetic effect in rats treated with streptozotocin, improving the activity of mitochondrial enzymes, hepatic marker enzymes, renal markers, and histopathology [157].

Yun *et al*. (2018) discovered that the 13-week repeat-dose oral toxicity study of *C. cassia* freeze-dried extract consumption at high-dose (2000 mg/kg) exhibited potential nephrotoxicity and hepatotoxicity to both males and females' specific pathogen-free F344 rats. When compared to the negative control, there are noticeable increases in heart, kidney, and

liver weight. In addition, the total cholesterol level also increased for both males and females after consuming 2000 mg/kg of *C. cassia* compared to the negative control group of males and females. This study proved that the freeze-dried cinnamon extract does not show mutagenic and clastogenic effects in the Ames test, *in vitro* mammalian cell micronucleus assay, and *in vivo* bone marrow micronucleus assay [158].

A brine shrimp cytotoxicity bioassay test was used to assess the cytotoxicity of *C. cassia* essential oil, with brine shrimp *Artemia salina* representing mammalian cell functions [137]. The cytotoxicity of plant extract is expressed in terms of lethal concentration 50 (LC50) compared to Clarkson's toxicity index [160]. The LC_{50} value of water extract of *C. cassia* bark obtained using microwave-assisted hydrodistillation and conventional hydrodistillation methods was 51.2 mg/L and 68.9 mg/L, respectively. This indicated that the lower value of LC_{50} of extract using microwave-assisted hydrodistillation exhibits higher toxicity [69]. The study's findings showed that the type of extraction method used affected the quality and quantity of the extract, which directly influenced the LD_{50} results for toxicity screening.

Moreover, the types of solvent used in the extraction process also altered the values of LD_{50}. The solvent used in brine shrimp cytotoxicity bioassay may give false-positive signals due to the toxicity of the solvent itself. It is well-known that some organic solvents have high cytotoxicity *in vivo* [161]. Organic solvents commonly used in extraction, such as acetone, methanol, and ethanol, increased the percentage of brine shrimp mortality [162].

4. Conclusions

C. cassia has a broad range of bioactive components, the most abundant of which are diterpenoids, sesquiterpenoids, and flavonoids. These bioactive components make *C. cassia* have a significant medical value in disease treatment. Recent pharmacological research has confirmed that *C. cassia* has biological activities such as anti-inflammatory and analgesic effects, anti-diabetic, anti-tumor, antimicrobial, cardiovascular protection, immunoregulation, cytoprotection, neuroprotection, acaricidal and insecticidal activity, which caused this medical plant to have an indispensable application value in the pharmaceutical, food and agricultural industries. In order to take full advantage of *C. cassia*, it is important to develop an extraction methodology that requires low energy consumption, low usage of organic solvent, and high extract yield without compromising its quality.

The development and commercialization of plant-based bioactive compound products are expanding fast, especially in the food, pharmaceutical, and nutraceutical industries. However, the current trend of bioactive compounds extraction, especially in *C. cassia* is based on conventional extraction techniques such as hydrodistillation or organic solvent extraction, which have high labor costs, long extraction time, high carbon footprint, environmentally unfriendly, low extraction efficiency (low quality and quantity are caused by thermal degradation), low selectivity, exposure of process safety issue (uses of a large quantity of highly flammable or volatile organic solvent) and food safety issue (risk of organic solvent contamination in the end product). In promoting the "go-green" and eco-friendly concept in the 21st century, more efforts are required to design an extraction process from the aspect of social, economic, and environmental must be considered. Non-conventional green approaches and environmentally friendly extraction techniques such as UAE, MAE, enzyme-assisted extraction, subcritical extraction, supercritical extraction, pulsed electric field assisted extraction, and a combination of non-conventional methods or a combination of the non-conventional and conventional methods are considered. These techniques mostly have short

extraction times, low energy usage, low carbon footprint, uses of low to moderate quantity of organic solvent, are environmentally friendly, high selectivity, and have high quality and quantity of extract. Furthermore, a green solvent such as natural deep eutectic solvent (NADES) can be used to reduce and substitute the usage of hazardous organic solvent in the extraction process. The NADES comprises abundant cellular constituents that are naturally present in all types of cells and organisms, such as sugars, amino acids, carboxylic acids, alcohols, and choline derivatives [163,164]. This green solvent can combine with non-conventional extraction techniques such as UAE or MAE to reduce negative environmental impact and further enhance the *C. cassia* extraction efficiency in terms of shorter extraction time, lower cost, higher quality, and quantity of extract without harming effect to human safety and the environment.

Before commercializing or applying plant-based products or extract to human beings, an antimicrobial test is always an important step to test the product or extract bioactivity and understand the inhibitory mechanism's mode. However, most of the *C. cassia* extract used in the antimicrobial study is obtained through conventional extraction methods such as Soxhlet extraction and hydrodistillation, which may reduce the quality and quantity of extract. This directly influences the extract's efficacy and the antimicrobial result. In order to improve the effectiveness of the extraction process, the combination of extraction techniques such as UAE and MAE with green solvent, NADES, is highly attractive for obtaining antimicrobial compounds in a shorter extraction time, at lower energy consumption, and better performance compared to conventional methods. The extracts obtained using these techniques with green solvent have a promising antimicrobial effect in long-term usage with more valuable compounds present in the product or extract. The *in vivo* antimicrobial study of *C. cassia* has a potent inhibitory effect against different types of bacteria and fungi. Moreover, the application of *C. cassia* in food protection studies has shown the extracted compound as a promising alternative to chemical sanitizers due to its natural origin, increased shelf-life of food, prevention of different types of foodborne disease, and maintained or enhanced sensory characteristics of the food. In the future, the antimicrobial activity comparison of multiple combinations of *C. cassia* with others MAPs and individual MAPs on different microbes and food products should be studied.

In the toxicological study of *C. cassia*, although most studies proved that *C. cassia* exhibits a certain degree of toxicity to animal models or humans, the side effects were only exhibited when the dosage was more than the recommended level. Lastly, it is relevant to continue evaluating the toxicity of *C. cassia* via animal models and have an appropriate method for clinical studies assessing health-promoting effects to ensure the consistency, safety, and efficacy of *C. cassia*. Additionally, few types of research are available on the synergistic effect of *C. cassia* or its individual component with some commercialized antibiotic drugs. Therefore, further investigation is required to maximize the medical properties of *C. cassia* in the future. This research would provide a better understanding of *C. cassia* regarding their functional and pharmacological activities and their mode of mechanism.

To this end, it can be seen that *C. cassia* has a crucial economic value and a wide range of biological activities, which has high research potential in the modern food, pharmaceutical, and nutraceutical industries. To maximize the yield and activities of *C. cassia*, the selection of green extraction methodologies is a critical issue. It required consideration in terms of energy usage, solvent consumption, instrumental cost, carbon footprint, process safeness, and environmental friendliness to archive the concept of "go-green" and eco-friendly.

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Conflicts of Interest

The authors declare no conflict of interest.

References

1. Moye, Z.D.; Woolston, J.; Sulakvelidze, A. Bacteriophage Applications for Food Production and Processing. *Viruses*. **2018**, *10*, 205, https://doi.org/10.3390/V10040205.
2. Gutiérrez-del-Río, I.; Fernández, J.; Lombó, F. Plant nutraceuticals as antimicrobial agents in food preservation: terpenoids, polyphenols and thiols. *Int. J. Antimicrob. Agents*. **2018**, *52*, 309–315, https://doi.org/10.1016/j.ijantimicag.2018.04.024.
3. Bajovic, B.; Bolumar, T.; Heinz, V. Quality considerations with high pressure processing of fresh and value added meat products. *Meat Sci.* **2012**, *92*, 280–289, https://doi.org/10.1016/j.meatsci.2012.04.024.
4. Ge, H.; Fu, S.; Guo, H.; Hu, M.; Xu, Z.; Zhou, X.; Chen, X.; Jiao, X. Application and challenge of bacteriophage in the food protection. *Int. J. Food Microbiol.* **2022**, *380*, 109872, https://doi.org/10.1016/j.ijfoodmicro.2022.109872.
5. Suklim, K.; Flick, G.J.; Vichitphan, K. Effects of gamma irradiation on the physical and sensory quality and inactivation of Listeria monocytogenes in blue swimming crab meat (Portunas pelagicus). *Radiat. Phys. Chem.* **2014**, *103*, 22–26, https://doi.org/10.1016/j.radphyschem.2014.05.009.
6. Harrell, C.; Djonov, V.; Fellabaum, C.; Volarevic, V. Risks of Using Sterilization by Gamma Radiation: The Other Side of the Coin. *Int. J. Med. Sci.* **2018**, *15*, 274–279, https://doi.org/10.7150/ijms.22644.
7. Newell, D.G.; Koopmans, M.; Verhoef, L.; Duizer, E.; Aidara-Kane, A.; Sprong, H.; Opsteegh, M.; Langelaar, M.; Threfall, J.; Scheutz, F.; der Giessen, J. van.; Kruse, H. Food-borne diseases — The challenges of 20 years ago still persist while new ones continue to emerge. *Int. J. Food Microbiol.* **2010**, *139*, S3–S15, https://doi.org/10.1016/j.ijfoodmicro.2010.01.021.
8. Dávila-Aviña, J.; Solis, L.; Rojas-Verde, G.; Salazar, N.A. Chapter 12: Sustainability and Challenges of Minimally Processed Foods. Food Engineering Series, p. 279–295, http://dx.doi.org/10.1007/978-3-319-10677-9_12.
9. Hassan, S.; Yee, L.; Ray, K. Purchasing Intention towards Organic Food among Generation Y in Malaysia. *J. Agribus. Mark.* **2015**, *7*, 16–32, https://www.fama.gov.my/documents/20143/555948/Purchasing+intention+towards+organic+food+among+generation+y+in+malaysia.pdf/9c662a8b-ae93-9f88-74e4-0fb9dd391233.
10. Gottardi, D.; Bukvicki, D.; Prasad, S.; Tyagi, A.K. Beneficial effects of spices in food preservation and safety. *Front. Microbiol.* **2016**, *7*, 1394, https://doi.org/10.3389/FMICB.2016.01394/BIBTEX.
11. Liu, Q.; Meng, X.; Li, Y.; Zhao, C.N.; Tang, G.Y.; Li, H. Bin. Antibacterial and Antifungal Activities of Spices. *Int. J. Mol. Sci.* **2017**, *18*, 1283, https://doi.org/10.3390/IJMS18061283.
12. Martínez-Graciá, C.; González-Bermúdez, C.A.; Cabellero-Valcárcel, A.M.; Santaella-Pascual, M.; Frontela-Saseta, C. Use of herbs and spices for food preservation: advantages and limitations. *Curr. Opin. Food Sci.* **2015**, *6*, 38–43, https://doi.org/10.1016/j.cofs.2015.11.011.
13. Nieto, G. Biological Activities of Three Essential Oils of the Lamiaceae Family. *Medicines*. **2017**, *4*, 63, https://doi.org/10.3390/medicines4030063.
14. Przygodzka, M.; Zielińska, D.; Ciesarová, Z.; Kukurová, K.; Zieliński, H. Comparison of methods for evaluation of the antioxidant capacity and phenolic compounds in common spices. *LWT - Food Sci. Technol.* **2014**, *58*, 321–326, https://doi.org/10.1016/j.lwt.2013.09.019.

15. Vallverdú-Queralt, A.; Regueiro, J.; Martínez-Huélamo, M.; Rinaldi Alvarenga, J.F.; Leal, L.N.; Lamuela-Raventos, R.M. A comprehensive study on the phenolic profile of widely used culinary herbs and spices: Rosemary, thyme, oregano, cinnamon, cumin and bay. *Food Chem.* **2014**, *154*, 299–307, https://doi.org/10.1016/j.foodchem.2013.12.106.
16. Yashin, A.; Yashin, Y.; Xia, X.; Nemzer, B. Antioxidant Activity of Spices and Their Impact on Human Health: A Review. *Antioxidants*. **2017**, *6*, 70, https://doi.org/10.3390/antiox6030070.
17. Fares, R.; Bazzi, S.; Baydoun, S.E.; Abdel-Massih, R.M. The Antioxidant and Anti-proliferative Activity of the Lebanese Olea europaea Extract. *Plant Foods Hum. Nutr.* . **2011**, *66*, 58–63, https://doi.org/10.1007/S11130-011-0213-9.
18. Baričevič, D.; Máthé, Á.; Bartol, T. Conservation of Wild Crafted Medicinal and Aromatic Plants and Their Habitats. Medicinal and Aromatic Plants of the World Scientific, Production, Commercial and Utilization Aspects, p. 131–144.
19. Chan, K. Some aspects of toxic contaminants in herbal medicines. *Chemosphere*. **2003**, *52*, 1361–1371, https://doi.org/10.1016/S0045-6535(03)00471-5.
20. Maizura, M.; Aminah, A.; Aida, W.M.W. Total phenolic content and antioxidant activity of kesum (Polygonum minus), ginger (Zingiber officinale) and turmeric (Curcuma longa) extract. *Int. Food Res. J.* **2011**, *18*, 529–534.
21. Jadhav, H.; Jadhav, A.; Morabiya, Y.; Takkalkar, P.; Qureshi, S.S.; Baloch, A.G.; Nizamuddin, S.; Mazari, S.A.; Abro, R.; Mubarak, N.M. Combined Impact of Ultrasound Pre-treatment and Hydrodistillation on Bioactive Compounds and GC–MS Analysis of Cinnamomum cassia Bark Extract. *Waste and Biomass Valorization*. **2021**, *12*, 807–821, https://doi.org/10.1007/s12649-020-01031-3.
22. Zhang, C.; Fan, L.; Fan, S.; Wang, J.; Luo, T.; Tang, Y.; Chen, Z.; Yu, L. Cinnamomum cassia Presl: A Review of Its Traditional Uses, Phytochemistry, Pharmacology and Toxicology. *Molecules*. **2019**, *24*, 3473, https://doi.org/10.3390/molecules24193473.
23. Liu, C.; Long, H.; Wu, X.; Hou, J.; Gao, L.; Yao, S.; Lei, M.; Zhang, Z.; Guo, D. an.; Wu, W. Quantitative and fingerprint analysis of proanthocyanidins and phenylpropanoids in Cinnamomum verum bark, Cinnamomum cassia bark, and Cassia twig by UPLC combined with chemometrics. *Eur. Food Res. Technol.* **2021**, *247*, 2687–2698, https://doi.org/10.1007/s00217-021-03795-x.
24. Liang, D.; Feng, B.; Li, N.; Su, L.; Wang, Z.; Kong, F.; Bi, Y. Preparation, characterization, and biological activity of Cinnamomum cassia essential oil nano-emulsion. *Ultrason. Sonochem.* **2022**, *86*, 106009, https://doi.org/https://doi.org/10.1016/j.ultsonch.2022.106009.
25. El Atki, Y.; Aouam, I.; El Kamari, F.; Taroq, A.; Nayme, K.; Timinouni, M.; Lyoussi, B.; Abdellaoui, A. Antibacterial activity of cinnamon essential oils and their synergistic potential with antibiotics. *J. Adv. Pharm. Technol. Res.* **2019**, *10*, 63–67, https://doi.org/10.4103/japtr.JAPTR_366_18.
26. Liao, J.C.; Deng, J.S.; Chiu, C.S.; Hou, W.C.; Huang, S.S.; Shie, P.H.; Huang, G.J. Anti-Inflammatory Activities of Cinnamomum cassia Constituents *In vitro* and *In vivo*. *Evid. Based. Complement. Alternat. Med.* **2012**, *2012*, 429320, https://doi.org/10.1155/2012/429320.
27. Sharma, H.; Chauhan, P.; Singh, S. Evaluation of the anti-arthritic activity of Cinnamomum cassia bark extract in experimental models. *Integr. Med. Res.* **2018**, *7*, 366–373, https://doi.org/10.1016/j.imr.2018.08.002.
28. Patil, M.; Choudhari, A.S.; Pandita, S.; Islam, M.A.; Raina, P.; Kaul-Ghanekar, R. Cinnamaldehyde, Cinnamic Acid, and Cinnamyl Alcohol, the Bioactives of Cinnamomum cassia Exhibit HDAC8 Inhibitory Activity: An *In vitro* and *In silico* Study. *Pharmacogn. Mag.* **2017**, *13*, S645–S651, https://doi.org/10.4103/PM.PM_389_16.
29. Kwon, H.; Lee, J.J.; Lee, J.H.; Cho, W.K.; Gu, M.J.; Lee, K.J.; Ma, J.Y. Cinnamon and its Components Suppress Vascular Smooth Muscle Cell Proliferation by Up-Regulating Cyclin-Dependent Kinase Inhibitors. *Am. J. Chin. Med.* **2015**, *43*, 621–636, https://doi.org/10.1142/S0192415X1550038X.
30. Zeng, J.; Xue, Y.; Shu, P.; Qian, H.; Sa, R.; Xiang, M.; Li, X.-N.; Luo, Z.; Yao, G.; Zhang, Y. Diterpenoids with Immunosuppressive Activities from Cinnamomum cassia. *J. Nat. Prod.* **2014**, *77*, 1948–1954, https://doi.org/10.1021/NP500465G.
31. Tankam, J.M.; Sawada, Y.; Ito, M. Regular ingestion of cinnamomi cortex pulveratus offers gastroprotective activity in mice. *J. Nat. Med.* **2013**, *67*, 289–295, https://doi.org/10.1007/S11418-012-0680-9.
32. Heo, H.; Han, J.; Jeong, M.; Kim, H.; Jang, I. A Review of the Neuroprotective Effects of Cinnamon in Experimental Studies on Parkinson's Disease. *J. Intern. Korean Med.* **2020**, *41*, 1089–1099, https://doi.org/10.22246/jikm.2020.41.6.1089.

33. Kang, M.S.; Lee, H.S. Acaricidal and insecticidal responses of Cinnamomum cassia oils and main constituents. *Appl. Biol. Chem.* **2018**, *61*, 653–659, https://doi.org/10.1007/s13765-018-0402-4.
34. Jeon, Y.J.; Lee, S.G.; Yang, Y.C.; Lee, H.S. Insecticidal activities of their components derived from the essential oils of Cinnamomum sp. barks and against Ricania sp. (Homoptera: Ricaniidae), a newly recorded pest. *Pest Manag. Sci.* **2017**, *73*, 2000–2004, https://doi.org/10.1002/ps.4627.
35. Lee, H.G.; Jo, Y.; Ameer, K.; Kwon, J.H. Optimization of green extraction methods for cinnamic acid and cinnamaldehyde from Cinnamon (Cinnamomum cassia) by response surface methodology. *Food Sci. Biotechnol.* **2018**, *27*, 1607–1617, https://doi.org/10.1007/s10068-018-0441-y.
36. Le, V.D.; Tran, V.T.; Dang, V.S.; Nguyen, D.T.; Dang, C.H.; Nguyen, T.D. Physicochemical characterizations, antimicrobial activity and non-isothermal decomposition kinetics of Cinnamomum cassia essential oils. *J. Essent. Oil Res.* **2020**, *32*, 158–168, https://doi.org/10.1080/10412905.2019.1700834.
37. Eilerman, R.G. Cinnamic Acid, Cinnamaldehyde, and Cinnamyl Alcohol. *Kirk-Othmer Encycl. Chem. Technol.* **2014**, , 1–11, https://doi.org/10.1002/0471238961.0309141405091205.A01.PUB2.
38. Kim, J.-H. Extraction time and temperature affect the extraction efficiencies of coumarin and phenylpropanoids from Cinnamomum cassia bark using a microwave-assisted extraction method. *J. Chromatogr. B.* **2017**, *1063*, 196–203, https://doi.org/10.1016/j.jchromb.2017.08.008.
39. Li, X.; Lu, H.Y.; Jiang, X.W.; Yang, Y.; Xing, B.; Yao, D.; Wu, Q.; Xu, Z.H.; Zhao, Q.C. Cinnamomum cassia extract promotes thermogenesis during exposure to cold via activation of brown adipose tissue. *J. Ethnopharmacol.* **2021**, *266*, 113413, https://doi.org/10.1016/j.jep.2020.113413.
40. Chang, C.-T.; Chang, W.-L.; Hsu, J.-C.; Shih, Y.; Chou, S.-T. Chemical composition and tyrosinase inhibitory activity of Cinnamomum cassia essential oil. *Bot. Stud.* **2013**, *54*, 10, https://doi.org/10.1186/1999-3110-54-10.
41. Choi, S.M.; Pham, V.C.; Lee, S.; Kim, J.A. Metabolism of diterpenoids derived from the bark of cinnamomum cassia in human liver microsomes. *Pharmaceutics*. **2021**, *13*, 1316, https://doi.org/10.3390/pharmaceutics13081316.
42. Pham, V.C.; Nguyen, T.T.A.; Vu, T.O.; Cao, T.Q.; Min, B.S.; Kim, J.A. Five new diterpenoids from the barks of Cinnamomum cassia (L.) J. Presl. *Phytochem. Lett.* **2019**, *32*, 23–28, https://doi.org/10.1016/j.phytol.2019.04.025.
43. Yan, Y.M.; Fang, P.; Yang, M.T.; Li, N.; Lu, Q.; Cheng, Y.X. Anti-diabetic nephropathy compounds from Cinnamomum cassia. *J. Ethnopharmacol.* **2015**, *165*, 141–147, https://doi.org/10.1016/j.jep.2015.01.049.
44. Yahya, N.A.; Attan, N.; Wahab, R.A. An overview of cosmeceutically relevant plant extracts and strategies for extraction of plant-based bioactive compounds. *Food Bioprod. Process.* **2018**, *112*, 69–85, https://doi.org/10.1016/j.fbp.2018.09.002.
45. Zainal-Abidin, M.H.; Hayyan, M.; Hayyan, A.; Jayakumar, N.S. New horizons in the extraction of bioactive compounds using deep eutectic solvents: A review. *Anal. Chim. Acta*. **2017**, *979*, 1–23, https://doi.org/10.1016/j.aca.2017.05.012.
46. Mwaurah, P.W.; Kumar, S.; Kumar, N.; Attkan, A.K.; Panghal, A.; Singh, V.K.; Garg, M.K. Novel oil extraction technologies: Process conditions, quality parameters, and optimization. *Compr. Rev. Food Sci. Food Saf.* **2020**, *19*, 3–20, https://doi.org/10.1111/1541-4337.12507.
47. Zhang, Q.W.; Lin, L.G.; Ye, W.C. Techniques for extraction and isolation of natural products: a comprehensive review. *Chin. Med.* **2018**, *13*, 1–26, https://doi.org/10.1186/S13020-018-0177-X.
48. Shin, W.Y.; Shim, D.W.; Kim, M.K.; Sun, X.; Koppula, S.; Yu, S.H.; Kim, H.B.; Kim, T.J.; Kang, T.B.; Lee, K.H. Protective effects of Cinnamomum cassia (Lamaceae) against gout and septic responses via attenuation of inflammasome activation in experimental models. *J. Ethnopharmacol.* **2017**, *205*, 173–177, https://doi.org/10.1016/j.jep.2017.03.043.
49. Kaur, G.; Invally, M.; Khan, M.K.; Jadhav, P. A nutraceutical combination of Cinnamomum cassia & Nigella sativa for Type 1 diabetes mellitus. *J. Ayurveda Integr. Med.* **2018**, *9*, 27–37, https://doi.org/10.1016/j.jaim.2017.02.005.
50. Vijayan, V.; Mazumder, A. *In vitro* inhibition of food borne mutagens induced mutagenicity by cinnamon (Cinnamomum cassia) bark extract. *Drug Chem. Toxicol.* **2018**, *41*, 385–393, https://doi.org/10.1080/01480545.2018.1439056.
51. Singh, J.; Parasuraman, S.; Kathiresan, S. Antioxidant and antidiabetic activities of methanolic extract of Cinnamomum cassia. *Pharmacognosy Res.* **2018**, *10*, 237–242, https://doi.org/10.4103/pr.pr-162-17.

52. Bugudare, U.S.; Kalyani, D.; Krishnaveni Bai, R.; Ashfaq, M. Influence of hydroalcoholic extract of Cinnamomum cassia on anti-diabetic effect of Glibenclamide, Metformin alone and their combination. *Pharmacologyonline*. **2011**, *2*, 798–807.
53. Nasulhah Kasim, N.; Nursyimi Azlina Syed Ismail, S.; Masdar, N.; Ab Hamid, F.; Nawawi, W. Extraction and Potential of Cinnamon Essential Oil towards Repellency and Insecticidal Activity. *Int. J. Sci. Res. Publ.* **2014**, *4*.
54. Radha Krishnan, K.; Sivarajan, M.; Babuskin, S.; Archana, G.; Azhagu Saravana Babu, P.; Sukumar, M. Kinetic modeling of spice extraction from S. aromaticum and C. cassia. *J. Food Eng.* **2013**, *117*, 326–332, https://doi.org/10.1016/j.jfoodeng.2013.03.011.
55. Vankar, P.S. Essential oils and fragrances from natural sources. *Resonance*. **2004**, *9*, 30–41, https://doi.org/10.1007/bf02834854.
56. Azmir, J.; Zaidul, I.S.M.; Rahman, M.M.; Sharif, K.M.; Mohamed, A.; Sahena, F.; Jahurul, M.H.A.; Ghafoor, K.; Norulaini, N.A.N.; Omar, A.K.M. Techniques for extraction of bioactive compounds from plant materials: A review. *J. Food Eng.* **2013**, *117*, 426–436, https://doi.org/10.1016/j.jfoodeng.2013.01.014.
57. Silva, L. V.; Nelson, D.L.; Drummond, M.F.B.; Dufossé, L.; Glória, M.B.A. Comparison of hydrodistillation methods for the deodorization of turmeric. *Food Res. Int.* **2005**, *38*, 1087–1096, https://doi.org/10.1016/j.foodres.2005.02.025.
58. Ooi, L.S.M.; Li, Y.; Kam, S.L.; Wang, H.; Wong, E.Y.L.; Ooi, V.E.C. Antimicrobial activities of Cinnamon oil and cinnamaldehyde from the Chinese medicinal herb Cinnamomum cassia Blume. *Am. J. Chin. Med.* **2006**, *34*, 511–522, https://doi.org/10.1142/S0192415X06004041.
59. Lee, E.J.; Chung, T.W.; Lee, J.H.; Kim, B.S.; Kim, E.Y.; Lee, S.O.; Ha, K.T. Water-extracted branch of Cinnamomum cassia promotes lung cancer cell apoptosis by inhibiting pyruvate dehydrogenase kinase activity. *J. Pharmacol. Sci.* **2018**, *138*, 146–154, https://doi.org/10.1016/j.jphs.2018.10.005.
60. Huang, Z.; Pang, D.; Liao, S.; Zou, Y.; Zhou, P.; Li, E.; Wang, W. Synergistic effects of cinnamaldehyde and cinnamic acid in cinnamon essential oil against S. pullorum. *Ind. Crops Prod.* **2021**, *162*, 113296, https://doi.org/10.1016/j.indcrop.2021.113296.
61. Jiang, Z.; Jiang, H.; Xie, P. Antifungal activities against Sclerotinia sclerotiorum by Cinnamomum cassia oil and its main components. *J. Essent. Oil Res.* **2013**, *25*, 444–451, https://doi.org/10.1080/10412905.2013.782475.
62. Ma, Y.N.; Chen, C.J.; Li, Q.; Wang, W.; Xu, F.R.; Cheng, Y.X.; Dong, X. Fungicidal Activity of Essential Oils from Cinnamomum cassia against the Pathogenic Fungi of Panax notoginseng Diseases. *Chem. Biodivers.* **2019**, *16*, 1900416, https://doi.org/10.1002/cbdv.201900416.
63. Li, J.; Sun, F.; Wang, W.; Gao, F. Optimization of steam distillation for extracting cinnamomum cassia oil from cinnamomum cassia bark. Proceedings of the 2018 3rd International Conference on Advances in Materials, Mechatronics and Civil Engineering (ICAMMCE 2018), https://www.atlantis-press.com/proceedings/icammce-18/25897663.
64. Saini, A.; Yadav, C.; Sethi, S.K.; Xue, B.-L.; Xia, Y.; Li, K.; Manik, G.; Li, X. Microdesigned Nanocellulose-Based Flexible Antibacterial Aerogel Architectures Impregnated with Bioactive Cinnamomum cassia. *ACS Appl. Mater. Interfaces*. **2021**, *13*, 4874–4885, https://doi.org/10.1021/acsami.0C20258.
65. Chen, G.; Sun, F.; Wang, S.; Wang, W.; Dong, J.; Gao, F. Enhanced extraction of essential oil from Cinnamomum cassia bark by ultrasound assisted hydrodistillation. *Chinese J. Chem. Eng.* **2021**, *36*, 38–46, https://doi.org/10.1016/j.cjche.2020.08.007.
66. Nwanade, C.F.; Wang, M.; Wang, T.; Zhang, X.; Wang, C.; Yu, Z.; Liu, J. Acaricidal activity of Cinnamomum cassia (Chinese cinnamon) against the tick Haemaphysalis longicornis is linked to its content of (E)-cinnamaldehyde. *Parasites Vectors*. **2021**, *14*, 330, https://doi.org/10.1186/s13071-021-04830-2.
67. Lang, M.; Montjarret, A.; Duteil, E.; Bedoux, G. Cinnamomum cassia and syzygium aromaticum essential oils reduce the colonization of salmonella typhimurium in an *in vivo* infection model using caenorhabditis elegans. *Molecules*. **2021**, *26*, 5598, https://doi.org/10.3390/molecules26185598.
68. Kumar, D.H.L.; Anush, S.M.; Rao, L.J.; Sowbhagya, H.B. Microwave Impact on the Flavour Compounds of Cinnamon Bark (Cinnamomum Cassia) Volatile Oil and Polyphenol Extraction. *Curr. Microw. Chem.* **2017**, *4*, 115–121, https://doi.org/10.2174/2213335602666151012193155.
69. Jeyaratnam, N.; Nour, A.H.; Kanthasamy, R.; Nour, A.H.; Yuvaraj, A.R.; Akindoyo, J.O. Essential oil from Cinnamomum cassia bark through hydrodistillation and advanced microwave assisted hydrodistillation. *Ind. Crops Prod.* **2016**, *92*, 57–66, https://doi.org/10.1016/j.indcrop.2016.07.049.

70. Yu, T.; Yao, H.; Qi, S.; Wang, J. GC-MS analysis of volatiles in cinnamon essential oil extracted by different methods. *Grasas y Aceites*. **2020**, *71*, 372, https://doi.org/10.3989/gya.0462191.
71. Li, C.; Luo, Y.; Zhang, W.; Cai, Q.; Wu, X.; Tan, Z.; Chen, R.; Chen, Z.; Wang, S.; Zhang, L. A comparative study on chemical compositions and biological activities of four essential oils: Cymbopogon citratus (DC.) Stapf, Cinnamomum cassia (L.) Presl, Salvia japonica Thunb. and Rosa rugosa Thunb. *J. Ethnopharmacol.* **2021**, *280*, 114472, https://doi.org/10.1016/j.jep.2021.114472.
72. Guo, J.; Yang, R.; Gong, Y.; Hu, K.; Hu, Y.; Song, F. Optimization and evaluation of the ultrasound-enhanced subcritical water extraction of cinnamon bark oil. *LWT - Food Sci. Technol*. **2021**, *147*, 111673, https://doi.org/https://doi.org/10.1016/j.lwt.2021.111673.
73. Castejón, N.; Luna, P.; Señoráns, F.J. Alternative oil extraction methods from Echium plantagineum L. seeds using advanced techniques and green solvents. *Food Chem.* **2018**, *244*, 75–82, https://doi.org/https://doi.org/10.1016/j.foodchem.2017.10.014.
74. Trusheva, B.; Trunkova, D.; Bankova, V. Different extraction methods of biologically active components from propolis; a preliminary study. *Chem. Cent. J.* **2007**, *13*, https://doi.org/10.1186/1752-153X-1-13.
75. Jain, T.; Jain, V.; Pandey, R.; Vyas, A.; Shukla, S. Microwave assisted extraction for phytoconstituents – An overview. *Asian J. Res. Chem.* **2009**, *2*, 19–25, https://www.indianjournals.com/ijor.aspx?target=ijor:ajrc&volume=2&issue=1&article=004.
76. Kaufmann, B.; Christen, P. Recent extraction techniques for natural products: Microwave-assisted extraction and pressurised solvent extraction. *Phytochem. Anal.* **2002**, *13*, 105–113, https://doi.org/10.1002/pca.631.
77. Oreopoulou, A.; Tsimogiannis, D.; Oreopoulou, V. Extraction of Polyphenols From Aromatic and Medicinal Plants: An Overview of the Methods and the Effect of Extraction Parameters. Polyphenols in Plants (Second Edition), p. 243–259, https://doi.org/10.1016/B978-0-12-813768-0.00025-6.
78. Zhang, Q.; Huo, R.; Ma, Y.; Yan, S.; Yang, L.; Chen, F. A novel microwave-assisted steam distillation approach for separation of essential oil from tree peony (Paeonia suffruticosa Andrews) petals: Optimization, kinetic, chemical composition and antioxidant activity. *Ind. Crops Prod.* **2020**, *154*, 112669, https://doi.org/10.1016/j.indcrop.2020.112669.
79. Valderrama, F.; Ruiz, F. An optimal control approach to steam distillation of essential oils from aromatic plants. *Comput. Chem. Eng.* **2018**, *117*, 25–31, https://doi.org/10.1016/j.compchemeng.2018.05.009.
80. Awad, T.S.; Moharram, H.A.; Shaltout, O.E.; Asker, D.; Youssef, M.M. Applications of ultrasound in analysis, processing and quality control of food: A review. *Food Res. Int.* **2012**, *48*, 410–427, https://doi.org/10.1016/j.foodres.2012.05.004.
81. Musielak, G.; Mierzwa, D.; Kroehnke, J. Food drying enhancement by ultrasound – A review. *Trends Food Sci. Technol.* **2016**, *56*, 126–141, https://doi.org/10.1016/j.tifs.2016.08.003.
82. Both, S.; Chemat, F.; Strube, J. Extraction of polyphenols from black tea - Conventional and ultrasound assisted extraction. *Ultrason. Sonochem.* **2014**, *21*, 1030–1034, https://doi.org/10.1016/j.ultsonch.2013.11.005.
83. Xie, P.J.; Huang, L.X.; Zhang, C.H.; You, F.; Zhang, Y.L. Reduced pressure extraction of oleuropein from olive leaves (Olea europaea L.) with ultrasound assistance. *Food Bioprod. Process.* **2015**, *93*, 29–38, https://doi.org/10.1016/j.fbp.2013.10.004.
84. Tao, Y.; Sun, D.W. Enhancement of Food Processes by Ultrasound: A Review. *Crit. Rev. Food Sci. Nutr.* **2015**, *55*, 570–594, https://doi.org/10.1080/10408398.2012.667849.
85. Shahid, M.; Yusuf, M.; Mohammad, F. Plant phenolics: A Review on Modern extraction techniques. *Recent Prog. Med. Plants Anal. Process. Tech.* **2015**, *41*, 265–287.
86. Arya, P.; Kumar, P. Comparison of ultrasound and microwave assisted extraction of diosgenin from Trigonella foenum graceum seed. *Ultrason. Sonochem.* **2021**, *74*, 105572, https://doi.org/10.1016/J.ULTSONCH.2021.105572.
87. Ummat, V.; Jaiswal, A.; Condon, K.; García-Vaquero, M.; O'Doherty, J.; O'Donnell, C.; Rajauria, G. Optimisation of Ultrasound Frequency, Extraction Time and Solvent for the Recovery of Polyphenols, Phlorotannins and Associated Antioxidant Activity from Brown Seaweeds. *Mar. Drugs*. **2020**, *18*, 250, https://doi.org/10.3390/md18050250.
88. Michalczyk, A.; Cieniecka-Rosłonkiewicz, A.; Cholewinska, M. Application of ionic liquids in the ultrasound-Assisted extraction of antimicrobial compounds from the bark of cinnamomum cassia. *J. Chil. Chem. Soc.* **2015**, *60*, 2698–2703, https://doi.org/10.4067/S0717-97072015000400013.
89. Kumar, S. Optimization of Yield for Extraction of an Essential Oil from Cinnamon Using Microwave-Assisted Extraction. *J. Chromatogr. Sep. Tech.* **2017**, *S1*, 1–4, https://doi.org/10.4172/2157-7064.S8-001.

90. Yang, C.H.; Li, R.X.; Chuang, L.Y. Antioxidant activity of various parts of Cinnamomum cassia extracted with different extraction methods. *Molecules* **2012**, *17*, 7294–7304, https://doi.org/10.3390/molecules17067294.
91. Wang, Y.; Dai, P.P.; Guo, S.S.; Cao, J.Q.; Pang, X.; Geng, Z.F.; Sang, Y.L.; Du, S.S. Supercritical carbon dioxide extract of Cinnamomum cassia bark: toxicity and repellency against two stored-product beetle species. *Environ. Sci. Pollut. Res.* **2018**, *25*, 22236–22243, https://doi.org/10.1007/s11356-018-2342-2.
92. Liu, Z.; Mei, L.; Wang, Q.; Shao, Y.; Tao, Y. Optimization of subcritical fluid extraction of seed oil from Nitraria tangutorum using response surface methodology. *LWT - Food Sci. Technol.* **2014**, *56*, 168–174, https://doi.org/10.1016/j.lwt.2013.10.048.
93. Zhang, F.; Zhu, F.; Chen, B.; Su, E.; Chen, Y.; Cao, F. Composition, bioactive substances, extraction technologies and the influences on characteristics of Camellia oleifera oil: A review. *Food Res. Int.* **2022**, *156*, 111159, https://doi.org/10.1016/j.foodres.2022.111159.
94. Cha, J.; Kim, C.T.; Kim, T.E.; Cho, Y.J. Optimization of subcritical extraction process for cinnamon (Cinnamomum Cassia Blume) using response surface methodology. *Food Sci. Biotechnol.* **2019**, *28*, 1703–1711, https://doi.org/10.1007/s10068-019-00616-6.
95. Liang, Y.; Li, Y.; Sun, A.; Liu, X. Chemical compound identification and antibacterial activity evaluation of cinnamon extracts obtained by subcritical n-butane and ethanol extraction. *Food Sci. Nutr.* **2019**, *7*, 2186–2193, https://doi.org/10.1002/FSN3.1065.
96. Meyer, A.S. Enzyme technology for precision functional food ingredient processes. *Ann. N. Y. Acad. Sci.* **2010**, *1190*, 126–132, https://doi.org/10.1111/j.1749-6632.2009.05255.x.
97. Sowbhagya, H.B.; Chitra, V.N. Enzyme-assisted extraction of flavorings and colorants from plant materials. *Crit. Rev. Food Sci. Nutr.* **2010**, *50*, 146–161, https://doi.org/10.1080/10408390802248775.
98. Puri, M.; Sharma, D.; Barrow, C.J. Enzyme-assisted extraction of bioactives from plants. *Trends Biotechnol.* **2012**, *30*, 37–44, https://doi.org/10.1016/j.tibtech.2011.06.014.
99. Bich, H.T.; Huong, L.M.; Chien, N.Q.; Thuy, D.T.T.; Thanh, L.T.; Sy, D.T.; Hang, L.T.T.; Hai, P.H. OPTIMIZATION OF THE ENZYME ASSISTED EXTRACTION OF ESSENTIAL OIL FROM THE LEAVES AND BRANCHES OF CINNAMOMUM CASSIA USING BOX-WILSON METHOD. *Vietnam J. Sci. Technol.* **2017**, *55*, 690–697, https://doi.org/10.15625/2525-2518/55/6/9525.
100. Donsì, F.; Ferrari, G.; Pataro, G. Applications of pulsed electric field treatments for the enhancement of mass transfer from vegetable tissue. *Food Eng. Rev.* **2010**, *2*, 109–130, https://doi.org/10.1007/s12393-010-9015-3.
101. Ngamwonglumlert, L.; Devahastin, S.; Chiewchan, N. Natural colorants: Pigment stability and extraction yield enhancement via utilization of appropriate pretreatment and extraction methods. *Crit. Rev. Food Sci. Nutr.* **2017**, *57*, 3243–3259, https://doi.org/10.1080/10408398.2015.1109498.
102. Aramrueang, N.; Asavasanti, S.; Khanunthong, A. Chapter 10 - Leafy Vegetables. In: Pan, Z., Zhang, R., Zicari, S.B.T.-I.P.T. for F. and A.B.-P., editors. In Integrated Processing Technologies for Food and Agricultural By-Products, Academic Press p. 245–272, https://www.elsevier.com/books/integrated-processing-technologies-for-food-and-agricultural-by-products/pan/978-0-12-814138-0.
103. Pashazadeh, B.; Elhamirad, A.H.; Hajnajari, H.; Sharayei, P.; Armin, M. Optimization of the pulsed electric field-assisted extraction of functional compounds from cinnamon. *Biocatal. Agric. Biotechnol.* **2020**, *23*, 101461, https://doi.org/10.1016/j.bcab.2019.101461.
104. Parniakov, O.; Roselló-Soto, E.; Barba, F.J.; Grimi, N.; Lebovka, N.; Vorobiev, E. New approaches for the effective valorization of papaya seeds: Extraction of proteins, phenolic compounds, carbohydrates, and isothiocyanates assisted by pulsed electric energy. *Food Res. Int.* **2015**, *77*, 711–717, https://doi.org/10.1016/j.foodres.2015.03.031.
105. Gould, I.M. The epidemiology of antibiotic resistance. *Int. J. Antimicrob. Agents*. **2008**, *32*, S2–S9, https://doi.org/10.1016/j.ijantimicag.2008.06.016.
106. Yang, C.H.; Yang, C.S.; Hwang, M.L.; Chang, C.C.; Li, R.X.; Chuang, L.Y. Antimicrobial activity of various parts of cinnamomum cassia extracted with different extraction methods. *J. Food Biochem.* **2012**, *36*, 690–698, https://doi.org/10.1111/j.1745-4514.2011.00584.x.
107. Joshi, J.R.; Burdman, S.; Lipsky, A.; Yedidia, I. Effects of plant antimicrobial phenolic compounds on virulence of the genus Pectobacterium. *Res. Microbiol.* **2015**, *166*, 535–545, https://doi.org/10.1016/j.resmic.2015.04.004.
108. Balouiri, M.; Sadiki, M.; Ibnsouda, S.K. Methods for *in vitro* evaluating antimicrobial activity: A review. *J. Pharm. Anal.* **2016**, *6*, 71–79, https://doi.org/10.1016/j.jpha.2015.11.005.

109. Benkova, M.; Soukup, O.; Marek, J. Antimicrobial susceptibility testing: currently used methods and devices and the near future in clinical practice. *J. Appl. Microbiol.* **2020**, *129*, 806–822, https://doi.org/10.1111/jam.14704.
110. Jorgensen, J.H.; Ferraro, M.J. Antimicrobial susceptibility testing: A review of general principles and contemporary practices. *Clin. Infect. Dis.* **2009**, *49*, 1749–1755, https://doi.org/10.1086/647952.
111. Mith, H.; Duré, R.; Delcenserie, V.; Zhiri, A.; Daube, G.; Clinquart, A. Antimicrobial activities of commercial essential oils and their components against food-borne pathogens and food spoilage bacteria. *Food Sci. Nutr.* **2014**, *2*, 403–416, https://doi.org/10.1002/fsn3.116.
112. Gago, G.; Diacovich, L.; Arabolaza, A.; Tsai, S.-C.; Gramajo, H. Fatty acid biosynthesis in actinomycetes. *FEMS Microbiol. Rev.* **2011**, *35*, 475–497, https://doi.org/10.1111/j.1574-6976.2010.00259.x.
113. Bereksi, M.S.; Hassaïne, H.; Bekhechi, C.; Abdelouahid, D.E. Evaluation of antibacterial activity of some medicinal plants extracts commonly used in algerian traditional medicine against some pathogenic bacteria. *Pharmacogn. J.* **2018**, *10*, 507–512, https://doi.org/10.5530/pj.2018.3.83.
114. Singh, J.; Singh, R.; Parasuraman, S.; Sathasivam, K. Antimicrobial Activity of Extracts of Bark of Cinnamomum cassia and Cinnamomum zeylanicum. *Int. J. Pharm. Investig.* **2020**, *10*, 141–145, https://doi.org/10.5530/ijpi.2020.2.26.
115. Li, P.; Tian, L.; Li, T. Study on ultrasonic-assisted extraction of essential oil from cinnamon bark and preliminary investigation of its antibacterial activity. Advances in Applied Biotechnology. *Lecture Notes in Electrical Engineering 332*. p. 349–360, https://link.springer.com/chapter/10.1007/978-3-662-45657-6_38.
116. Thielmann, J.; Muranyi, P.; Kazman, P. Screening essential oils for their antimicrobial activities against the foodborne pathogenic bacteria Escherichia coli and Staphylococcus aureus. *Heliyon*. **2019**, *5*, e01860, https://doi.org/10.1016/j.heliyon.2019.e01860.
117. Paudel, S.K.; Bhargava, K.; Kotturi, H. Antimicrobial activity of cinnamon oil nanoemulsion against Listeria monocytogenes and Salmonella spp. on melons. *LWT - Food Sci. Technol*. **2019**, *111*, 682–687, https://doi.org/10.1016/j.lwt.2019.05.087.
118. Basak, S.; Singh, J.K.; Morri, S.; Shetty, P.H. Assessment and modelling the antibacterial efficacy of vapours of cassia and clove essential oils against pathogens causing foodborne illness. *LWT - Food Sci. Technol.* **2021**, *150*, 112076, https://doi.org/10.1016/j.lwt.2021.112076.
119. Tsai, H.C.; Sheng, L.; Zhu, M.J. Antimicrobial efficacy of cinnamon oil against Salmonella in almond based matrices. *Food Control*. **2017**, *80*, 170–175, https://doi.org/10.1016/j.foodcont.2017.04.045.
120. Kacaniova, M.; Galovicova, L.; Valkova, V.; Tvrda, E.; Terentjeva, M.; Ziarovska, J.; Kunova, S.; Savitskaya, T.; Grinshpan, D.; Stefanikova, J.; Felsöciova, S.; Vukovic, N.; Kowalczewski, P.L. Antimicrobial and antioxidant activities of Cinnamomum cassia essential oil and its application in food preservation. *Open Chem.* **2021**, *19*, 214–227, https://doi.org/10.1515/chem-2021-0191.
121. Gucwa, K.; Milewski, S.; Dymerski, T.; Szweda, P. Investigation of the Antifungal Activity and Mode of Action of Thymus vulgaris, Citrus limonum, Pelargonium graveolens, Cinnamomum cassia, Ocimum basilicum, and Eugenia caryophyllus Essential Oils. *Molecules*. **2018**, *23*, 1116, https://doi.org/10.3390/molecules23051116.
122. Ribeiro-Santos, R.; Andrade, M.; de Melo, N.R.; dos Santos, F.R.; Neves, I. de A.; de Carvalho, M.G.; Sanches-Silva, A. Biological activities and major components determination in essential oils intended for a biodegradable food packaging. *Ind. Crops Prod.* **2017**, *97*, 201–210, https://doi.org/10.1016/j.indcrop.2016.12.006.
123. Campini, P.A.L.; Oliveira, É.R. de.; Camani, P.H.; Silva, C.G. da.; Yudice, E.D.C.; Oliveira, S.A. de.; Rosa, D. dos S. Assessing the efficiency of essential oil and active compounds/poly (lactic acid) microcapsules against common foodborne pathogens. *Int. J. Biol. Macromol.* **2021**, *186*, 702–713, https://doi.org/10.1016/j.ijbiomac.2021.07.071.
124. Singh, A.; Deepika.; Chaudhari, A.K.; Das, S.; Prasad, J.; Dwivedy, A.K.; Dubey, N.K. Efficacy of Cinnamomum cassia essential oil against food-borne molds and aflatoxin B1 contamination. *Plant Biosyst.* **2021**, *155*, 899–907, https://doi.org/10.1080/11263504.2020.1810804.
125. De Clerck, C.; Maso, S.D.; Parisi, O.; Dresen, F.; Zhiri, A.; Haissam Jijakli, M. Screening of antifungal and antibacterial activity of 90 commercial essential oils against 10 pathogens of agronomical importance. *Foods*. **2020**, *9*, 1418, https://doi.org/10.3390/foods9101418.
126. Raffaella, C.; Casettari, L.; Fagioli, L.; Cespi, M.; Bonacucina, G.; Baffone, W. Activity of essential oil-based microemulsions against Staphylococcus aureus biofilms developed on stainless steel surface in different

culture media and growth conditions. *Int. J. Food Microbiol.* **2017**, *241*, 132–140, https://doi.org/10.1016/j.ijfoodmicro.2016.10.021.
127. Vasconcelos, N.G.; De Sá Queiroz, J.H.F.; Da Silva, K.E.; De Paula Vasconcelos, P.C.; Croda, J.; Simionatto, S. Synergistic effects of Cinnamomum cassia L. essential oil in combination with polymyxin B against carbapenemase-producing Klebsiella pneumoniae and Serratia marcescens. *PLoS One*. **2020**, *15*, e0236505, https://doi.org/10.1371/journal.pone.0236505.
128. Firmino, D.F.; Cavalcante, T.T.A.; Gomes, G.A.; Firmino, N.C.S.; Rosa, L.D.; De Carvalho, M.G.; Catunda, F.E.A. Antibacterial and Antibiofilm Activities of Cinnamomum Sp. Essential Oil and Cinnamaldehyde: Antimicrobial Activities. *Sci. World J.* **2018**, 7405736, https://doi.org/10.1155/2018/7405736.
129. Veloso, D.J.; Abrão, F.; Martins, C.H.G.; Bronzato, J.D.; Gomes, B.P.F.A.; Higino, J.S.; Sampaio, F.C. Potential antibacterial and anti-halitosis activity of medicinal plants against oral bacteria. *Arch. Oral Biol.* **2020**, *110*, 104585, https://doi.org/10.1016/j.archoralbio.2019.104585.
130. Abdalla, K.H.; Al-Hannan, F.; Alghamdi, A.; Henari, F.Z. Green Synthesis of Silver Nanoparticles using Cinnamon (Cinnamomum cassia), Characterization and Antibacterial Activity. *Int. J. Sci. Res.* **2015**, *6*, 965–971, https://doi.org/10.21275/ART20174199.
131. Xie, Y.; Huang, Q.; Wang, Z.; Cao, H.; Zhang, D. Structure-activity relationships of cinnamaldehyde and eugenol derivatives against plant pathogenic fungi. *Ind. Crops Prod.* **2017**, *97*, 388–394, https://doi.org/10.1016/j.indcrop.2016.12.043.
132. Mahmood, N.; Nazir, R.; Khan, M.; Khaliq, A.; Adnan, M.; Ullah, M.; Yang, H. Antibacterial Activities, Phytochemical Screening and Metal Analysis of Medicinal Plants: Traditional Recipes Used against Diarrhea. **2019**, , 194, https://doi.org/10.3390/antibiotics8040194.
133. Wan, C.-J.; Zhang, Y.; Liu, C.-X.; Yang, Z.-C. Cinnamic aldehyde, isolated from Cinnamomum cassia, alone and in combination with pyrazinamide against Mycobacterium tuberculosis *in vitro* and *in vivo*. *South African J. Bot.* **2022**, *144*, 200–205, https://doi.org/10.1016/j.sajb.2021.08.009.
134. Šernaitė, L.; Rasiukevičiūtė, N.; Valiuškaitė, A. The extracts of cinnamon and clove as potential biofungicides against strawberry grey mould. *Plants*. **2020**, *9*, 613, https://doi.org/10.3390/plants9050613.
135. Doyle, A.A.; Krämer, T.; Kavanagh, K.; Stephens, J.C. Cinnamaldehydes: Synthesis, antibacterial evaluation, and the effect of molecular structure on antibacterial activity. *Results Chem.* **2019**, *1*, 100013, https://doi.org/10.1016/j.rechem.2019.100013.
136. Anwar, A.; Siddiqui, R.; Raza, M.; Khan, N. Gold Nanoparticle-Conjugated Cinnamic Acid Exhibits Antiacanthamoebic and Antibacterial Properties. *Antimicrob. Agents Chemother.* **2018**, *62*, e00630-18, https://doi.org/10.1128/AAC.00630-18.
137. Letsididi, K.S.; Lou, Z.; Letsididi, R.; Mohammed, K.; Maguy, B.L. Antimicrobial and antibiofilm effects of trans-cinnamic acid nanoemulsion and its potential application on lettuce. *LWT - Food Sci. Technol.* **2018**, *94*, 25–32, https://doi.org/10.1016/j.lwt.2018.04.018.
138. Pekmezovic, M.; Rajkovic, K.; Barac, A.; Senerović, L.; Arsic Arsenijevic, V. Development of kinetic model for testing antifungal effect of Thymus vulgaris L. and Cinnamomum cassia L. essential oils on Aspergillus flavus spores and application for optimization of synergistic effect. *Biochem. Eng. J.* **2015**, *99*, 131–137, https://doi.org/10.1016/j.bej.2015.03.024.
139. Souza, A.C.; Goto, G.E.O.; Mainardi, J.A.; Coelho, A.C.V.; Tadini, C.C. Cassava starch composite films incorporated with cinnamon essential oil: Antimicrobial activity, microstructure, mechanical and barrier properties. *LWT - Food Sci. Technol.* **2013**, *54*, 346–352, https://doi.org/10.1016/j.lwt.2013.06.017.
140. Montero, Y.; Souza, A.G.; Oliveira, É.R.; Rosa, D. dos S. Nanocellulose functionalized with cinnamon essential oil: A potential application in active biodegradable packaging for strawberry. *Sustain. Mater. Technol.* **2021**, *29*, e00289, https://doi.org/10.1016/j.susmat.2021.e00289.
141. Basaglia, R.R.; Pizato, S.; Santiago, N.G.; Maciel de Almeida, M.M.; Pinedo, R.A.; Cortez-Vega, W.R. Effect of edible chitosan and cinnamon essential oil coatings on the shelf life of minimally processed pineapple (Smooth cayenne). *Food Biosci.* **2021**, *41*, 100966, https://doi.org/10.1016/j.fbio.2021.100966.
142. Tao, R.; Sedman, J.; Ismail, A. Antimicrobial activity of various essential oils and their application in active packaging of frozen vegetable products. *Food Chem.* **2021**, *360*, 129956, https://doi.org/10.1016/j.foodchem.2021.129956.
143. Mileriene, J.; Serniene, L.; Henriques, M.; Gomes, D.; Pereira, C.; Kondrotiene, K.; Kasetiene, N.; Lauciene, L.; Sekmokiene, D.; Malakauskas, M. Effect of liquid whey protein concentrate–based edible coating enriched with cinnamon carbon dioxide extract on the quality and shelf life of Eastern European curd cheese. *J. Dairy Sci.* **2021**, *104*, 1504–1517, https://doi.org/10.3168/jds.2020-18732.

144. Barbosa, R.F. da S.; Yudice, E.D.C.; Mitra, S.K.; Rosa, D. dos S. Characterization of Rosewood and Cinnamon Cassia essential oil polymeric capsules: Stability, loading efficiency, release rate and antimicrobial properties. *Food Control*. **2021**, *121*, 107605, https://doi.org/10.1016/j.foodcont.2020.107605.
145. Sharma, H.; Mendiratta, S.K.; Agrawal, R.K.; Gurunathan, K.; Kumar, S.; Singh, T.P. Use of various essential oils as bio preservatives and their effect on the quality of vacuum packaged fresh chicken sausages under frozen conditions. *LWT - Food Sci. Technol.* **2017**, *81*, 118–127, https://doi.org/10.1016/j.lwt.2017.03.048.
146. Zhang, Y.; Li, D.; Lv, J.; Li, Q.; Kong, C.; Luo, Y. Effect of cinnamon essential oil on bacterial diversity and shelf-life in vacuum-packaged common carp (Cyprinus carpio) during refrigerated storage. *Int. J. Food Microbiol.* **2017**, *249*, 1–8, https://doi.org/10.1016/j.ijfoodmicro.2016.10.008.
147. Meenatchisundaram, S.; Chandrasekar, C.M.; Udayasoorian, L.P.; Kavindapadi Rajasekaran, R.; Kesavan, R.K.; Srinivasan, B.; Muthusamy, S. Effect of spice-incorporated starch edible film wrapping on shelf life of white shrimps stored at different temperatures. *J. Sci. Food Agric.* **2016**, *96*, 4268–4275, https://doi.org/10.1002/jsfa.7638.
148. Vangalapati, M.; Sree Satya, N.; Surya Prakash, D. V.; Avanigadda, S. A review on pharmacological activities and clinical effects of Cinnamon species. *Res. J. Pharm. Biol. Chem. Sci.* **2012**, *3*, 653–663.
149. Klejdus, B.; Kováčik, J. Quantification of phenols in cinnamon: A special focus on "total phenols" and phenolic acids including DESI-Orbitrap MS detection. *Ind. Crops Prod.* **2016**, *83*, 774–780, https://doi.org/10.1016/j.indcrop.2015.11.060.
150. Calixto, J.B. Efficacy, safety, quality control, marketing and regulatory guidelines for herbal medicines (phytotherapeutic agents). *Brazilian J. Med. Biol. Res.* **2000**, , 179–189, https://doi.org/10.1590/S0100-879X2000000200004.
151. Dugoua, J.J.; Seely, D.; Perri, D.; Cooley, K.; Forelli, T.; Mills, E.; Koren, G. From type 2 diabetes to antioxidant activity: A systematic review of the safety and efficacy of common and cassia cinnamon bark. *Can. J. Physiol. Pharmacol.* **2007**, *85*, 837–847, https://doi.org/10.1139/Y07-080.
152. J T Gowder, S. Safety Assessment of Food Flavor - Cinnamaldehyde. *Biosafety*. **2014**, *3*, https://doi.org/10.4172/2167-0331.1000e147.
153. Rietjens, I.M.C.M.; Cohen, S.M.; Eisenbrand, G.; Fukushima, S.; Gooderham, N.J.; Guengerich, F.P.; Hecht, S.S.; Rosol, T.J.; Davidsen, J.M.; Harman, C.L.; Murray, I.J.; Taylor, S. V. FEMA GRAS assessment of natural flavor complexes: Cinnamomum and Myroxylon-derived flavoring ingredients. *Food Chem. Toxicol.* **2020**, *135*, 110949, https://doi.org/10.1016/j.fct.2019.110949.
154. Sharifi-Rad, J.; Dey, A.; Koirala, N.; Shaheen, S.; El Omari, N.; Salehi, B.; Goloshvili, T.; Cirone Silva, N.C.; Bouyahya, A.; Vitalini, S.; Varoni, E.M.; Martorell, M.; Abdolshahi, A.; Docea, A.O.; Iriti, M.; Calina, D.; Les, F.; López, V.; Caruntu, C. Cinnamomum Species: Bridging Phytochemistry Knowledge, Pharmacological Properties and Toxicological Safety for Health Benefits. *Front. Pharmacol.* **2021**, *12*, 600139, https://doi.org/10.3389/fphar.2021.600139.
155. Feng, T.; Liu, X.; Lin, B.; Zhou, Y. Cinnamomum cassia Presl. 肉桂 (Rougui, Cassia Bark Tree). *Dietary Chinese Herbs*, p. 587–595, http://dx.doi.org/10.1007/978-3-211-99448-1_67.
156. Okwuosa, C.N.; Azubuike, N.C.; Okorie, C.P. Evaluation of Changes in Biochemical and Haematological Parameters of Albino Rats Following Subacute Oral Administration of Cinnamomum cassia (Cinnamon) Extract. *Annu. Res. Rev. Biol.* **2021**, *36*, 91–99, https://doi.org/10.9734/arrb/2021/v36i630393.
157. Vijayakumar, K.; R.L., R.; Suganthi, N.; Prasanna, B.; Shanmugam, V.; Shenbagam, M.; Anand, V. Acute toxicity studies and protective effects of Cinnamon cassia bark extract in streptozotocin-induced diabetic rats. *Drug Chem. Toxicol.* **2022**, *45*, 2086–2096, https://doi.org/10.1080/01480545.2021.1907908.
158. Yun, J.W.; You, J.R.; Kim, Y.S.; Kim, S.H.; Cho, E.Y.; Yoon, J.H.; Kwon, E.; Jang, J.J.; Park, J.S.; Kim, H.C.; Che, J.H.; Kang, B.C. *In vitro* and *in vivo* safety studies of cinnamon extract (Cinnamomum cassia) on general and genetic toxicology. *Regul. Toxicol. Pharmacol.* **2018**, *95*, 115–123, https://doi.org/10.1016/j.yrtph.2018.02.017.
159. Elhardallo, S. Cytotoxicity and Biological Activity of Selected Sudanese Medicinal Plants. *Res. J. Med. Plant.* **2011**, *5*, 201–229, https://doi.org/10.3923/rjmp.2011.201.229.
160. Hamidi, M.R.; Jovanova, B.; Panovska, K. Toxicological evaluation of the plant products using Brine Shrimp (Artemia salina L.) model. *Maced. Pharm. Bull.* **2014**, *60*, 9–18.
161. Wu, C. An important player in brine shrimp lethality bioassay: The solvent. *J. Adv. Pharm. Technol. Res.* **2014**, *5*, 57–58.

162. Ohikhena, F.U.; Wintola, O.A.; Afolayan, A.J. Toxicity assessment of different solvent extracts of the medicinal plant, phragmanthera capitata (sprengel) balle on brine shrimp (artemia salina). *Int. J. Pharmacol.* **2016**, *12*, 701–710, https://doi.org/10.3923/ijp.2016.701.710.
163. Espino, M.; de los Ángeles Fernández, M.; Gomez, F.J.V.; Silva, M.F. Natural designer solvents for greening analytical chemistry. *TrAC Trends Anal. Chem.* **2016**, *76*, 126–136, https://doi.org/10.1016/j.trac.2015.11.006.
164. Dai, Y.; van Spronsen, J.; Witkamp, G.J.; Verpoorte, R.; Choi, Y.H. Natural deep eutectic solvents as new potential media for green technology. *Anal. Chim. Acta*. **2013**, *766*, 61–68, https://doi.org/10.1016/j.aca.2012.12.019.