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ZINGIBER ZERUMBET: PHARMACOLOGICAL VALUES OF ZERUMBONE AND THE EXTRACTION TECHNOLOGY EVOLUTION

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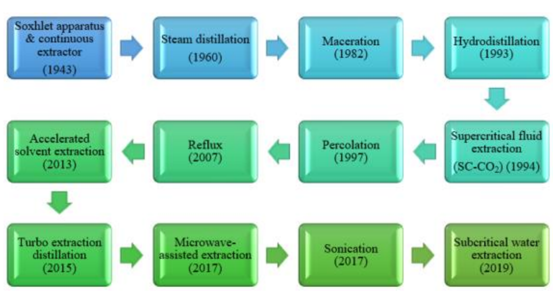
Graphical abstract



Technology evolution of zerumbone extraction from *Zingiber zerumbet*

Abstract

Over the past eight decades, numerous research has been conducted on the extraction of *Zingiber zerumbet* rhizome. The mini-review includes information on the pharmacological properties of zerumbone extracted from *Z. zerumbet* rhizome and the extraction methods conducted over the previous 80 years. Zerumbone is recognised as having a proven pharmacological effect and is a significant medicinal component used to treat various ailments. The pharmacological values are stated based on the research findings. The extraction method and technology are essential to extract zerumbone. Thus, the review helps the reader keep up with the history of each technique or technology used in extracting zerumbone from Z. zerumbet rhizome, starting with conventional technology and moving toward advanced technology.

Keywords: *Zingiber zerumbet*, rhizome, zerumbone, pharmacological value, extraction technology

Abstrak

Sejak lapan dekad yang lalu, banyak penyelidikan telah dijalankan terhadap pengekstrakan rizom *Zingiber zerumbet*. Kajian mini ini memberikan maklumat tentang sifat farmakologi zerumbon yang diekstrak daripada rizom *Z. zerumbet* dan kaedah pengekstrakan yang telah dijalankan sejak 80 tahun lalu. Zerumbone diiktiraf mempunyai nilai farmakologi yang terbukti dan merupakan komponen perubatan penting yang digunakan untuk merawat pelbagai penyakit. Nilai farmakologinya disenaraikan berdasarkan hasil penyelidikan. Kaedah dan teknologi pengekstrakan adalah penting untuk mengekstrak zerumbon. Oleh itu, kajian ini membantu pembaca mengetahui sejarah setiap teknik atau teknologi yang digunakan untuk mengekstrak zerumbone daripada rizom *Z. zerumbet*, bermula dengan teknologi konvensional dan ke arah teknologi canggih.

Kata kunci: *Zingiber zerumbet*, rizom, zerumbon, nilai farmakologi, teknologi pengekstrakan

1.0 INTRODUCTION

Zingiber zerumbet is a fragrant plant called 'Lempoyang' in Malaysia. Commercially, it is a medicinal plant with excessive potential for cultivation with low growing expenses [1]. Due to its vast benefits and cheap cost of cultivation, it is massively planted and utilised in Malaysia and other tropical and subtropical regions, including Sri Lanka, Nepal, Bangladesh, India, Thailand and Southwest China [2]. Its leaves, rhizomes, seeds, and flowers have many traditional uses and biological and pharmacological properties. The most crucial part is its rhizomes, which relate to all medical uses [3]. The predominant component found in the rhizome was zerumbone (2,6,9,9-tetramethyl-[2E,6E,10E]-cycloundeca-2,6,10-trien-1-one), a mono-cyclic sesquiterpene compound that belongs to the terpenes group [4][5]. It has multiple biomedical properties, such as anti-oxidant, anti-cancer, anti-inflammatory and anti-microbial activity [2]. In addition, a recent study supports the potential use of the plant as a complementary therapy for anxiety[6].

An effective extraction procedure is critical to get the advantage of *Z. zerumbet* rhizome. Conventional solid-liquid extraction is a frequently used approach for extracting the bioactive compound from the plant. Several examples of the conventional technique are hydrodistillation [4][7][8], maceration using methanol and ethanol [9][10], n-hexane and ethyl acetate [11], and the Soxhlet method with chloroform and methanol [12][13]. Despite their affordability and simplicity, conventional methods require a lengthy extraction time and frequently use toxic solvents [14]. These techniques may also result in significant organic solvent waste, which may be the forerunner to environmental problems if the hazardous solvent residue is not managed correctly. Nevertheless, extraction techniques prioritise separating bioactive compounds with environmentally-friendly methods without compromising safety and health [15].

Recent studies have used advanced technology to extract bioactive compounds from *Z. zerumbet* rhizome. The technique includes subcritical water extraction (SWE) [16]–[19], turbo extraction distillation (TED) [20] and microwave-assisted extraction (MEA) with different extraction solvents, including chloroform, methanol, ethanol and n-hexane [21]. Other advanced methods, such as accelerated solvent extraction (ASE) [22] and supercritical fluid extraction (SFE) with high pressure of carbon dioxide, have also been implemented [23], [24]. However, a more advanced technology that outperforms the others in the bioactive extraction process is SWE due to the green concept embodied by this technique. It has garnered significant attention due to its safety, efficacy, and environmental sustainability [25]. Thus, this mini-review offers information about zerumbone extracted from *Z. zerumbet* rhizome, the pharmacological values and extraction technology explored over the past 80 years. The review provides references for future application by systematically reviewing the literature from 1940 to 2020. It brings the reader to keep up on the chronological evolution of zerumbone extraction technology from *Z. zerumbet* rhizome, along with the timeline of each technique. Each extraction produced different findings in addition to helping future researchers to conduct extensive investigations or adopt the appropriate technique based on the available facilities.

2.0 BACKGROUND OF *ZINGIBER ZERUMBET*

Zingiberaceae is a perennial herbaceous plant comprising around 53 genera and over 1200 species across the tropics, notably in Southeast Asia. The members of this family include *Zingiber officinale* (ginger), *Curcuma longa* (turmeric) and *Zingiber zerumbet* (wild ginger), which are used for numerous beneficial purposes [26]. *Z. zerumbet* refers to the spreading and antler-like appearance of the stems. Carl Linnaeus named the species as *Amomum zerumbet* in 1753. However, later in 1806, Smith assigned *Z. zerumbet* to the genus *Zingiber*. Besides shampoo ginger, *Z. zerumbet* is also called wild ginger or pinecone ginger. Historically, all parts of *Z. zerumbet*, such as leaves, flowers (pinecone), and rhizome, have been utilised as a culinary spice, herbal tea, and therapeutic agent. However, numerous scientific studies have reported that most of the extraordinary medicinal benefits of *Z. zerumbet* was from its rhizomes [26][27]. Table 1 simplifies the profile of *Z. zerumbet*. Meanwhile, Figure 1(a) depicts the rhizomes with the roots, while Figure 1(b) shows the rhizomes cross-sectioned.

Table 1 Profile of *Zingiber zerumbet*

Scientific classification	
Domain	: Eukaryota
Kingdom	: Plantae
Phylum	: Spermatophyta
Subphylum	: Angiosperms
Class	: Monocotyledone
Order	: Zingiberales
Family	: Zingiberaceae
Genus	: Zingiber
Species	: *Zingiber zerumbet*
Vernacular names	
Malaysia	: Lempoyang
Indonesia	: Lempuyang gajah
India	: Ghatian, Yaiimu
Bangladesh	: Jangli adha
China	: Hong qiu jiang
Thailand	: Haeo dam
English	: Shampoo ginger, Bitter ginger
Japanese	: Niga shouga
Philippines	: Lungkawas
Vietnamese	: gừng đại, gừng gió
Synonyms	
Zingiber amaricans Blume	
Zingiber aromaticum Valeton	
Cardamomum spurium	
Reference: [3], [29]–[37]	

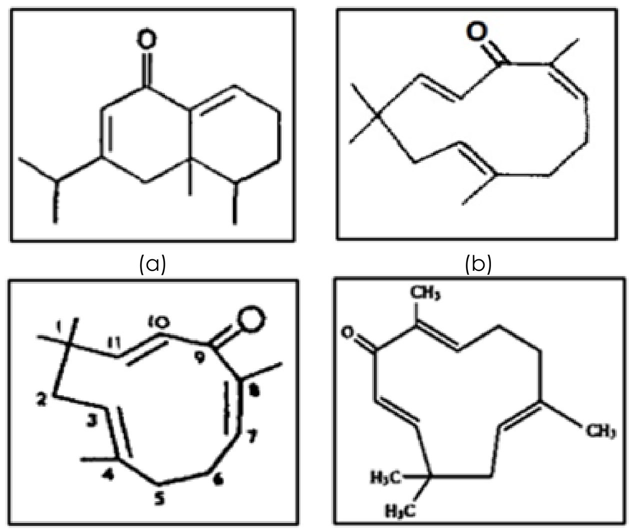
(a) (b)

Figure 1 *Zingiber zerumbet* (L.) Roscoe ex Sm.: (a) Rhizomes with roots (b) Rhizome in cross-section

3.0 ZERUMBONE IN *ZINGIBER ZERUMBET*

3.1 Major Bioactive Compound

Interestingly, zerumbone is the primary bioactive ingredient in *Z. zerumbet* rhizome, which cures illness and disease [38]. In 1943, a pure white crystalline solid was isolated from dried rhizomes. The melting point was identified as around 67°C to 68°C, resulting in the chemical formula of $C_{15}H_{22}O$ with a molecular weight of 218 [39]. Parihar and Dutt (1950) extracted ketone from *Z. zerumbet*, and the structure of the chemical was hypothesised, and it was given the name zerumbone, as shown in Figure 2(a) [40]. The investigation of the zerumbone structure continued until Dev (1956) demonstrated a revised zerumbone structure, as depicted in Figure 2(b) [42]. Since then, other instrument analyses have been conducted to validate the zerumbone structure, whereby their findings agreed on the revised chemical structure [43], [44]. However, further investigation was conducted using ultraviolet spectrum analysis, and a new suggestion on zerumbone structure was exhibited in Figure 2(c) [45]. Although the study of zerumbone structure has a long history, in 1965, the chemical structure of zerumbone was characterised using NMR and X-tray. The finding has concluded the zerumbone structure as 2,6,9,9-tetramethyl-2,6,10-cyclo-undecatrien-1-one, as demonstrated in Figure 2(d) [46]. The chemical structure was finalised and used to date.



(a) (b) (c) (d)

Figure 2 (a) Earliest suggestion of zerumbone structure [47] (b) Prediction of zerumbone structure based on degradation studies and analysis of infrared spectra [41], [43], [44], [48] (c) Further suggestion on zerumbone structure after an ultraviolet spectrum analysis [45] (d) Finalised zerumbone structure as 2,6,9,9-tetramethyl-2,6,10-cyclo-undecatrien-1-one [46].

Additionally, the zerumbone characteristic features have been collectively investigated and are summarised in Table 2. Numerous studies have revealed that zerumbone is the most significant component in *Z. zerumbet* rhizome. A team of researchers extracted zerumbone from *Z. zerumbet* rhizome using an ethanolic maceration technique [49]. The extraction took seven days to complete, whereby the zerumbone extract composition was rich, dominating over 95.37%, showing the highest quantity to date. The composition of zerumbone reported from Brazil was 87.93% after six hours of hydrodistillation [50]. Previously, a study on Tahiti Island and Japan indicated that zerumbone content in the rhizome was around 65.30% [51] and 48.13% [52], respectively. The variation in zerumbone compositions was caused by various circumstances, including the age of the plant and the handling or harvesting technique. Additionally, environmental and climatic circumstances and geographic location differences have influenced the zerumbone composition [5][26].

Table 2 Characteristic features of zerumbone

Characters	Description
Natural occurrence	: Zingiber species
Chemical class	: Sesquiterpene
IUPAC name	: (2E,6E,10E)-2,6,9,9-tetramethyl-cycloundeca-2,6,10-trien-1-one
Molecular weight	: 218.33 g/mol
Chemical formula	: $C_{15}H_{22}O$
Flashing point	: 133°C
Boiling point	: 321-322°C at 760 mmHg
Melting point	: 65.3°C
Vapour pressure	: 0.000295 mm/Hg at 25°C
Appearance	: Solid white crystals or powder
Short term storage	: +4°C
Stability	: Stable for at least two years when stored at -20°C
Solubility	: Completely soluble in ethanol and DMSO (≥10 mg/ml), while solubility in water is approximately 1.296 mg/L at 25°C

Reference: [36], [53], [54]

3.1 Pharmacological Values

Traditionally, *Z. zerumbet* rhizome has been extensively used in the everyday lives of the elderly to cure stomach problems, including stomach cramps, bloating, poisoning, colic pain, and diarrhoea. It was also used to treat colds, sore throat, cough, fever, swelling, loss of appetite, leprosy, inflammation, allergies, skin diseases, and microbe infections [1], [55], [56]. The elderly have received health benefits from the rhizome. Thus, it has been the subject of extensive chemical investigations. The researchers discovered that the rhizome exhibited high medicinal value and various pharmacological effects, including anti-oxidant, anti-microbial, and anti-cancer properties. Various in vitro and in vivo studies have confirmed the strong pharmacological properties of *Z. zerumbet*. Table 3 summarises the various pharmacological values of *Z. zerumbet* rhizome.

Table 3 reveals that *Z. zerumbet* possesses therapeutic benefits when used in both rhizome conditions, fresh or dried. However, some gaps in the pharmacological activity are still noticeable and should be further investigated and validated. It is supposed that the studies on fresh and dried rhizomes be conducted simultaneously to compare and confirm whether the fresh or dried rhizome conditions demonstrate the equal pharmacological value of zerumbone extracts. For instance, will fresh rhizome exhibit the same genotoxic, immunosuppressive, and HIV-inhibitory effects as dried rhizomes? Or, when compared to the fresh rhizome, will dried rhizome exhibit the same anti-proliferative, anti-nociceptive, anti-leishmanial, anti-obesity, anxiolytic or anti-dementia properties? Therefore, the gap should be viewed as a chance to conduct more in-depth research.

Table 3 Pharmacological value of *Z. zerumbet*

Pharmacological Activity	References	
	Fresh rhizome	Dried rhizome
Anti-oxidant	[5][55][57]	[5][19][17][58][59][60][61][18][60]
Anti-microbial	[5][35][56][62][63][64]	[5][20][35][50][65][58][66][67]
Anti-cancer	[42][68]	[4][9][11][22][58][69][70][71]
Anti-leukemia	[42][70][72][73]	[74]
Anti-malarial	[63]	[65][75][76]
Anti-tumour	[5][77][78][79]	[80][81][82][83][60]
Anti-inflammatory	[8]	[84][85]
Anti-allergic	[86]	[87]
Anti-proliferative	[62][77][88][89]	[60]
Anti-nociceptive	[90][91]	
Anti-leishmanial	[63]	
Anti-dementia	[92][93]	
Ameliorative		[94][95][96]
Anti-pyretic		[97]
Anti-dermatophytic		[98]
Anxiolytic		[6]
Anti-obesity		[99]
Immunomodulatory	[86][100]	[10][101][102]
HIV inhibitory		[82]
Genotoxicity		[103]
Immunosuppressive		[10][86][101][104]
Hepatocurative		[49]

3.2 Extraction Technology Evolution

There are two categories of techniques for extracting *Z. zerumbet* rhizomes. The technique comprises conventional and advanced methods. Figure 3 and Table 4 summarise the technical advancement in *Z. zerumbet* rhizome extraction from 1943 to date, focusing on the extract with zerumbone identified.

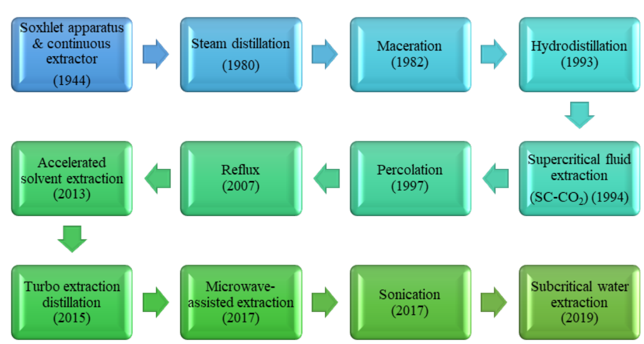


Figure 3 Technology evolution in *Zingiber zerumbet* rhizome extraction

The soxhlet apparatus and continuous extractor have been believed to be the earliest technique used to extract *Z. zerumbet* rhizome. Varier (1943) investigated and extracted the compounds using a variety of organic solvents, including petrol, chloroform, ether, and alcohol. The extracts were recrystallised many times, and a pure, white solid crystallising in long needles was produced. The material was found to melt at a temperature between 67°C to 68.5°C, whereby the solid distilled unchanged at 155°C to 157°C. The analysis found that the carbon and hydrogen composition was 82.9% and 10.13%, respectively, with a molecular weight of 203 g/mol. However, the study did not conclude that the product represented was zerumbone, and it left with a question mark. However, the actual chemical formula of zerumbone requires carbon and hydrogen proportions percentages of 82.96% and 10.1%, respectively. In addition, the molecular weight of the zerumbone is 218.33 g/mol. The study conducted by Varier (1943) reveals close and nearly precise values for the three parameters compared to the actual value. Thus, zerumbone can be regarded as the substance that Varier (1943) came across.

Table 4 Emerging extraction technologies of *Z. zerumbet* rhizome containing zerumbone

Year	Category	Method	Form	Yield	Ref.
1943	Conventional	Soxhlet apparatus and continuous extractor	Dried	0.5%[a]	[39]
1960	Conventional	Steam distillation	Dried	0.3-0.55%[a]	[40]
1982	Conventional	Maceration	Fresh	N/A	[64]
1993	Conventional	Hydrodistillation	Fresh	0.37%[b]	[51]
1994	Advanced	Supercritical fluid extraction	Dried	1.92%[a]	[23]
1997	Conventional	Percolation	Dried	6.3%[a]	[82]
2007	Conventional	Reflux	Dried	EtOH: 8.7% (w/w)[a] Water: 24.6% (w/w)[a]	[87]
2013	Advanced	Accelerated solvent extraction	Dried	N/A	[22]
2015	Advanced	Turbo extraction distillation	Fresh	0.35±0.09%[b]	[57]
2017	Advanced	Microwave-assisted extraction	Dried	4.82 mg/g[a]	[21]
2019	Advanced	Subcritical water extraction	Dried	16.1%[a]	[16]

[a]crude extract, [b]essential oil

In 1960, Dev (1960) introduced steam distillation, which produced 40 g of colourless, flat needles of zerumbone after a few steps of refinement and crystallisation procedure. The research advised that zerumbone degraded at room temperature after 10 to 30 days, becoming a sticky substance from which any remaining zerumbone could be recovered using distillation. The study outlined the best storage for zerumbone, which was best stored as a saturated ethanolic solution in a refrigerator to extend its shelf life for years. However, it can only stand for months in solid form at 0°C.

In 1982, the maceration technique was applied by Ungsurungsie and Suthienkul (1982), whereby water was used as the solvent. Maceration is a simple and commonly used procedure in research on herbal extract, whereby the extracted material becomes softened by soaking in a liquid [105]. The study used two conditions for the dried rhizome extraction processes. The first condition was heated in a boiling water bath for an hour, while the other was macerated for five days at room temperature. The water-macerated residues inhibited *Bacillus subtilis*, demonstrating that the herb contained anti-microbial action capable of halting the growth of microorganisms.

In late 1994, advanced technology was first introduced. The study was conducted by Ahmad *et al.* (1994) through supercritical fluid extraction by carbon dioxide (SFE-CO_2) at 60°C and 200 bars to extract zerumbone from the dried rhizome. The extract was fractionated by placing an on-line silica column before the pressure relief valve. The extracts were analysed using capillary GC and GCMS, and about 58.8% zerumbone extract composition was discovered. Meanwhile, a control sample was prepared by a conventional method, maceration, which used dichloromethane (CH_2Cl_2) and contained 55.4% zerumbone. The result showed that SFE-CO_2 produced a comparable zerumbone extract with the maceration method. Despite that, the study also concluded that GC and GCMS were effective methods of sample analysis and a relatively fast way of determining the constituents of plant materials.

In 1997, Dai *et al.* (1997) used another conventional method called percolation to extract about 192 g from the entire plant. Percolation is a continuous process in which the fresh solvent slowly passes through an extracted material to extract a particular substance into the solvent [105]. The extraction solvent in this procedure was dichloromethane in methanol (MeOH-CH_2Cl_2) at a 1:1 ratio. The extraction resulted in 12.10 g (6.3%) of crude organic extract and exhibited HIV-inhibitory and cytotoxic activities. The percolation approach may provide more extract than when the maceration technique is used. It is more efficient than maceration since the saturated solvent is continuously replaced by a fresh solvent. [106].

Around ten years later, Tewtrakul and Subhadhirasakul (2007) employed a different traditional approach named the reflux technique. It has been found that reflux extraction is more efficient than percolation or maceration and requires less extraction time and solvent [106]. The solvents used in the study were ethanol and water separately, which took approximately three hours to complete. The ethanolic and water extracts yields were 8.7% (w/w) and 24.6% (w/w), respectively. Both extracts showed an anti-allergic effect. However, water extract was inhibited more than ethanolic extract at varying concentrations.

In 2013, another advanced method emerged whereby Norfazlina *et al.* (2013) employed accelerated solvent extraction (ASE), also known as pressurised liquid extraction (PLE), to extract dried *Z. zerumbet* rhizome using hexane and ethanol as the extraction solvent. The extraction process took around ten minutes to complete, deemed a quick extraction approach compared to earlier traditional methods. The study indicated that the hexane extract has a cytotoxic effect on Human Myeloid Leukemia (HL60) cells and triggers apoptotic cell death, effective as an anti-cancer therapeutic agent for alleviating human myeloid leukaemia.

Later, Hasham *et al.* (2015) and Azelan *et al.* (2015) used turbo extraction distillation (TED) to extract fresh *Z. zerumbet* rhizomes. TED is a kind of accelerated hydrodistillation in which the input amount increases while the distillation duration decreases. It is a simple, cost-effective method for extracting volatile compounds [107]. Consequently, a highly fresh product was obtained, perfect for producing natural extracts for flavourings and nutraceuticals. A 200 L of TED was used in the study, whereby water was the solvent. The raw material to the solvent ratio used was 1:5, and the time was from 1 hour to 6 hours. The highest essential oil yield was 0.35 ± 0.09%, and 12.65% of zerumbone concentration has been determined.

Soon in 2017, another advanced method, including microwave-assisted extraction (MAE) and sonication, was employed by Ghasemzadeh *et al.* (2017). The study also used the reflux method to compare advanced and conventional methods in zerumbone extraction. The solvents used in these techniques were ethanol, methanol, n-hexane, and chloroform. MAE-ethanol was the superior method among the three, which yielded the highest concentration of zerumbone (4.82 mg/g DM). The extraction of zerumbone from the rhizome using MAE was advised under the following circumstances: ethanol concentration, 44%; irradiation time, 38.5 s; microwave power, 518 W; and liquid-to-solid ratio, 38 mL/g. The optimised microwave protocol developed for extracting zerumbone from *Z. zerumbet* was faster and consumed less solvent than previous methods while improving and enhancing the anti-proliferative activity [21].

It took about two years until the new advanced technology was introduced. Wahab *et al.* (2019, 2022) and Amir *et al.* (2020, 2021) were the first groups to extract dried *Z. zerumbet* rhizome using 1 L and 5 L subcritical water extraction (SWE) and produced 20.82 ± 0.42 mg/g and 8.11 mg/g of zerumbone concentration, respectively. Both investigations concluded that temperature and extraction time significantly influenced zerumbone concentration and yield using the technology. The optimal extraction conditions for both SWE were at 170°C and solid to solvent ratio of 20 ml/g. However, the extraction using 1 L SWE took about 40 minutes, while 20 minutes used 5 L SWE. The latest SWE study by Wahab *et al.* (2022) found that *Z. zerumbet* extract determined a more considerable value of Total Phenolic Content (TPC) with significantly better anti-oxidant capabilities but lower zerumbone concentration values when compared to organic solvent extraction. The study also showed a great deal about SWE, which performed a 12 times faster extraction than the Soxhlet extraction process [18]. Overall, SWE is more environmentally friendly than conventional methods and uses water as a solvent.

4.0 CONCLUSIONS AND FUTURE PERSPECTIVE

Research on *Zingiber zerumbet* offers a wide range of potential, particularly for the pharmaceutical, nutraceutical, and cosmeceutical industries. The proven pharmacological value of *Z. zerumbet* is attributed to zerumbone, which has gained substantial importance as a medicinal ingredient in treating various diseases. Due to the bioactivities outlined in the review section, its potential became increasingly apparent. The extraction technology is crucial in getting zerumbone from *Z. zerumbet* rhizome. Both conventional and advanced methods are still used to date because both have advantages depending on the purpose of extraction. However, advanced technology extraction should be highlighted in extraction industries due to its remarkable features, including environmentally friendly and sustainable aspects.

Moreover, advanced technology extraction promotes Sustainable Development Goal (SDG) 12, referred to as "*responsible consumption and production*", which aims to ensure sustainable consumption and production patterns, or more simply, getting more done with fewer resources. It also aims to encourage sustainable lifestyles, improve resource efficiency, and untangle economic growth from environmental deterioration. Thus, the SWE approach is a potential option for the extraction of bioactive compounds that enables sustainable patterns of use and production. It can address safety and environmental issues using various strategies to avoid adverse environmental and human health effects.

Besides, it is anticipated that zerumbone extraction technology would advance with the Fourth Industrial Revolution (4IR). There is currently not much specific research on which aspects of the 4IR affected herbal extraction technology. However, it is vital to promptly disclose studies that used extraction technology with the 4IR element. The discussion could emphasize the current implementation of autonomous equipment and machinery that mainly relies on wireless sensor networks (WSN) and the Internet of Things (IoT) in laboratory or industrial settings.

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