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Review

Identification and Isolation Techniques for Plant Growth Inhibitors in Rice

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Abstract: Plant growth inhibitors (PGIs) in rice (*Oryza sativa*), or rice allelochemicals, are secondary metabolites that are either exudated by rice plants to cope with natural competitors or produced during the decomposition of rice by-products in the paddy fields. Of these, the major groups of rice PGIs include phenolics, flavonoids, terpenoids, alkaloids, steroids, and fatty acids, which also exhibit potential medicinal and pharmaceutical properties. Recently, the exploitation of rice PGIs has attracted considerable attention from scientists worldwide. The biosynthesis, exudation, and release of PGIs are dependent on environmental conditions, relevant gene expression, and biodiversity among rice varieties. Along with the mechanism clarification, numerous analytical methods have been improved to effectively support the identification and isolation of rice PGIs during the last few decades. This paper provides an overview of rice PGIs and techniques used for determining and extracting those compounds from rice. In particular, the features, advantages, and limitations of conventional and upgraded extraction methods are comprehensively reported and discussed. The conventional extraction methods have been gradually replaced by advanced techniques consisting of pressurized liquid extraction (PLE), microwave-assisted extraction (MAE), and solid-phase extraction (SPE). Meanwhile, thin-layer chromatography (TLC), liquid chromatography (LC), gas chromatography (GC), mass spectrometry (MS), nuclear magnetic resonance (NMR), high-resolution mass spectrometry (HR-MS), infrared spectroscopy (IR), near-infrared spectroscopy (NIRS), and X-ray crystallography are major tools for rice PGI identification and confirmation. With smart agriculture becoming more prevalent, the statistics of rice PGIs and extraction methods will help to provide useful datasets for building an autonomous model for safer weed control. Conceivably, the efficient exploitation of rice PGIs will not only help to increase the yield and economic value of rice but may also pave the way for research directions on the development of smart and sustainable rice farming methods.

Keywords: rice; allelochemicals; extraction; isolation; identification; chromatography; smart agriculture

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1. Introduction

According to the Food and Agriculture Organization (FAO), world rice production in 2022 was 519.5 million tonnes, which supplies starchy cereal grain to more than half of the world's population [1,2]. Basically, rice grain consists of endosperms, husks, brans, and germs at around 70%, 20%, 8%, and 2% of the rough rice weight, respectively, which are a plentiful source of nutrients such as minerals, fiber, carbohydrates, vitamins, and proteins [3,4]. Along with nutritional and pharmaceutical values, rice products and by-products from rice production have attracted more consideration in terms of application for weed and pest control. Among the proposed approaches, the exploitation of natural

molecules in rice for suppressing the growth of weeds and pests is a promising direction thanks to its availability and environmentally friendly advantage.

Laboratory, greenhouse, and field experiments indicate that rice produces secondary metabolites comprising phenolics, flavonoids, terpenoids, steroids, and alkaloids which exhibit inhibitory activities against weeds and ambient species [5–11]. Such phytocompounds are considered plant growth inhibitors (PGIs) or allelochemicals. Rice can either accelerate or retard the growth of neighboring plants and natural enemies by exudating allelochemicals into the surrounding environment (soil, water, and air) [12]. The yield and quality of rice are influenced by their allelochemicals, which can cause positive or negative effects on the plant–plant, plant–microorganism, and microorganism–microorganism relationships. Additionally, the allelopathic mechanisms that impact receiver plants and soil microorganisms have been studied through physiological, biochemical, and molecular pathways [13,14].

In the 1970s, scientists reported the positive side of PGIs released from rice straw and rice hulls, which acted as natural herbicides against weeds via plant models including barnyard grass (*Echinochloa crus-galli*), orchardgrass (*Dactylis glomerata*), lettuce (*Lactuca sativa* L.), and duck salad (*Heteranthera limosa*). Dilday et al. [15] performed experiments on five thousand rice accessions to evaluate their suppression ability on the growth of duck salad and other aquatic weeds, which resulted in around 3.82% of cultivars exhibiting allelopathic activity. In 2008, Chau et al. [16] indicated that the water extracted from 18 Vietnamese rice varieties could inhibit 81.5% of the root growth of both cress (*Lepidium sativum* L.) and barnyard grass (*Echinochloa crus-galli*). Previous reports also revealed that allelopathic rice varieties suppressed 75% of the growth of indicator plants in comparison with non-allelopathic cultivars [17]. Parallelly, popular rice diseases such as bacterial blight (*Xanthomonas oryzae* pv. *oryzicola*), blast (*Magnaporthe oryzae*), and fungi were efficiently treated by phytochemicals derived from rice [18–22]. In recent years, allelochemicals with medicinal properties including anti-cancer, anti-diabetic, anti-inflammatory, antioxidant, anti-HIV, and anti-SARS-CoV-2 potential have been increasingly elaborated upon [23–28].

To date, there have been numerous reports regarding the characterization and identification of PGIs from rice. The major groups of PGIs can be listed as phenolic acids, polyphenols, terpenoids, phenylamides, fatty acids, indoles, and steroids. Among these, phenolic acids are known as a major class of allelochemicals [29]. In addition, sesquiterpenoids detected in aqueous extracts of some rice varieties were indicated as important rice PGIs [30,31]. Noticeably, momilactones belonging to the diterpene lactone group were detected in minor amounts in rice husks but expressed potent allelopathic activity against weeds [32]. In addition, tricin (5,7,4′-trihydroxy-3′,5′-dimethoxyflavone) found in rice bran revealed potent allelopathic activities [19]. In recent studies, polyphenolic and flavonoid glycosides from rice straw and leaves have been reported as having significant inhibitory effects on the seed germination and growth of paddy weeds comprising barnyard grass and pigweed [33].

Although research on allelochemicals has been performed since the 1960s, the identification and isolation of these compounds in rice have faced many challenges due to their complex properties, such as their solubility, volatility, and stability. Over the years, supercritical fluid extraction (SFE), ionic liquid extraction (ILE), solid-phase extraction, and column chromatography have been the most common methods used for the extraction and isolation of rice PGIs. Meanwhile, gas chromatography (GC), liquid chromatography (LC), and their improvements are essential techniques to determine the chemical constituents. The integration of GC or LC with mass spectrometry (MS), nuclear magnetic resonance (NMR), electron ionization mass spectrometry (EI/MS), infrared spectroscopy (IR), and X-ray crystallography made it convenient for the identification and quantification of rice allelochemicals [24,34–37].

This review paper aims to summarize major rice PGIs and assemble conventional and modern methodologies for the isolation and identification of PGIs in rice. In addition, the

advantages of these techniques are discussed in order to support optimizing the efficient exploitation of rice PGIs.

2. Literature Sources and Search Methodology

This review is based on published reports about rice PGIs and their biological properties. The search strategy focused on terms including allelochemical, growth inhibitor, allelopathy, herbicide, pesticide, phenolic acid, terpenoid, and polyphenol, which were found together with rice (*Oryza sativa*). The sources include studies and research published between 1971 and 2022, which were indexed in PubMed, ScienceDirect, and the American Chemical Society (ACS).

3. Mechanism of Action of PGIs

Major PGIs and their allelopathic mechanisms and targets are described in Table 1. Accordingly, PGIs can regulate recipient plant growth via various biological pathways including oxidative stress induction and the inhibition of cell division, cell permeability, photosynthesis, respiration, and transpiration. In addition, these substances can impede phytohormone and enzyme activities through the suppression of relevant gene expression. PGIs can also interact with soil microorganisms that affect recipient plant growth.

Table 1. Major PGIs and their allelopathic mechanisms and targets.

Modes of Action	Allelochemicals	Recipient Plant	Rice Organs	References
Growth inhibition				
Inhibition of root and hypocotyl growth	Momilactone A (MA) and B (MB)	*Lepidium sativum* seedlings, *Lactuca sativa* seedlings, *Echinochloa crus-galli*, and *Monochoria vaginalis*	Husks, leaves, brans, roots, and root exudates	[5,38]
Root growth suppression	Gallic acid, protocatechuic acid, *p*-hydroxybenzoic, vanillic acid, syringic acid, *p*-coumaric acid, *m*-coumaric acid, ferulic acid, *o*-coumaric acid	*Brassica rapa* and *O. sativa* seeds.	Leaves and stems	[29]
Inhibition of root and shoot growth	Blumenol A and grasshopper ketone	*L. sativum*, *L. sativa*, *Phleum pratense*, *Digitaria sanguinalis*, *Lolium multiflorum*, and *E. crus-galli.*	Whole plant	[31]
Inhibition of the radicle growth	*p*-Hydroxybenzoic, *p*-coumaric, vanillic, ferulic, and *o*-hydroxyphenylacetic acids, and several unknowns	*L. sativa* seeds, *O. sativa* seeds and seedlings.	Residues in soil	[39]
Inhibition of seed germination, seedling length, and dry weight	*p*-Hydroxybenzoic acid, *p*-coumaric acid, ferulic acid, and *p*-hydroxybenzoic acid	*E. crus-galli*	Straws	[40]
Inhibition of plant height, root length, monocotyledon and fresh weight	Salicylic acid, fumaric acid, *p*-coumaric acid and *p*-hydroxybenzonic acid	*E. crus-galli*	Whole plant	[41]

Table 1. *Cont.*

Modes of Action	Allelochemicals	Recipient Plant	Rice Organs	References
-	Lanast-7,9(11)-dien-3α,15α-diol-3α-*d*-glucofuranoside	*Lemna paucicostata*	Hulls	[42]
Inhibition of germination rate, seedling growth, shoots, and roots	Momilactone E (ME), 7-ketostigmasterol (7KS), MA, and MB	*L. sativa*, *E. crus-galli*, and *Solidago altissima*	Husks	[43]
Algicidal activities	Oleioyl-β-*d*-arabinoside	*Cyanobacteria*	Straws	[44]
Inhibition of spore germination	Sakuranetin	*Pyricularia oryzae*	Leaves	[45]
-	Two flavone *O*-glycosides	Interferes with weeds or microbes in paddy soil.	Seedlings	[46]
		Physiological pathways		
Inhibition of photosynthesis	Caffeic, coumaric, ferulic, cinnamic, and vanillic acids	-	-	[47,48]
Suppress respiration	Benzoic and cinnamic acids	-	-	[49]
		Enzyme functions		
Phosphorylase suppressors	Chlorogenic, caffeic acids, and catechol	-	-	[50,51]
ATPase inhibitors	Cinnamic acid and its derivatives	*E. crus-galli*	Whole plant	[50,51]
		Rhizosphere microorganisms		
Suppression of nitrification process, by inhibiting the activities of vital enzymes such as ammonium mono-oxygenase and hydroxylamine oxidoreductase	Methyl 3-(4-hydroxyphenyl) propionate, linoleic acid, methyl-*p*-coumarate and methyl ferulate	-	Whole plant, root exudates	[6]
Inhibition of the oxidation of NH 4+ to NO2-	Caffeic and ferulic acids, myricetin, tannins and tannin derivatives	-	-	[12]
Synergistic suppressive effect by reducing nitrogen-fixing ability	Different phenolic compounds	Rhizobium strain	Decomposition of rice residue and straw in soil	[6]
Affecting soil community structure and reducing fungi present in paddy soil	Tricin (5,7,4′-trihydroxy-3′,5′-dimethoxyflavone) and aurone isomer (5,7,4′-trihydroxy-3′,5′-dimethoxyaurone) of tricin	*Fusarium oxysporum* and *Rhizoctonia solani*	Hulls, leaves, roots, and root exudates	[19,46]
		Pathogen infection		
Suppressing Xoo growth in rice seedlings	(S)-Limonene, oryzalides A and B, and oryzalic acid A	*Xanthomonas oryzae*	Seedlings and leaves	[20,22]

3.1. Oxidative Stress

The action mechanism of PGIs is described in Figure 1. PGIs can induce oxidative stress in treated plants by inhibiting antioxidant enzymes, thereby enhancing reactive oxygen species (ROS) [49,52,53]. Consequently, oxidative damage increases, negatively affecting treated plant metabolism [49,52,53]. Shearer et al. [54] indicated that allelopathic interactions result in an imbalance between ROS and antioxidant abilities. This imbalance led to rapid protein degradation, which subsequently caused cell apoptosis or necrosis. In the research of Yu et al. [40], allelochemicals inhibited the antioxidant enzymes of cucumber. In addition, membrane peroxidation was enhanced by the effects of root exudates and root extracts [40].

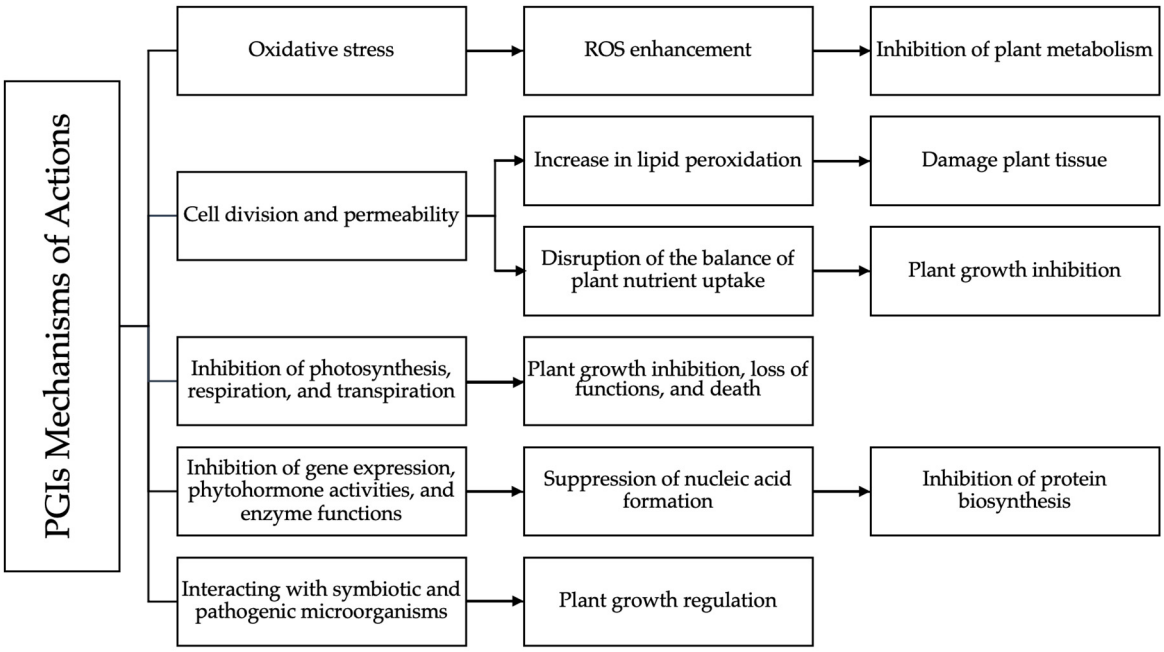


Figure 1. Allelopathic mechanisms of PGIs.

3.2. Cell Division and Permeability

In addition, PGIs can prevent cell division, which subsequently causes the inhibition of plant growth [55]. PGIs can also affect cell permeability, leading to an increase in lipid peroxidation [52,56,57]. As a result, plant tissue will be damaged [37]. Additionally, the inhibition of cell permeability can disrupt the balance of plant nutrient uptake, causing growth suppression [57].

3.3. Photosynthesis, Respiration, and Transpiration

PGIs can also inhibit photosynthesis, which is an indispensable process in plants. Caffeic, coumaric, ferulic, cinnamic, and vanillic acids found in rice can be mentioned as photosynthetic inhibitors [47,48]. These allelochemicals can disrupt the photosynthesis process via the inhibition of or damage to the synthesis apparatus and the stimulation of the degradation of photosynthetic pigments. Accordingly, energy and electron transfer are prevented due to the reduced content of photosynthetic pigments. In addition, PGIs can reduce ATP synthase catalytic activities, ATP synthesis, and transpiratory conductivity, thereby inhibiting photosynthesis [58]. Allelochemicals affect photosynthesis primarily by affecting PS II function [59]. In addition, PGIs can affect respiration at different stages, which is related to the energy metabolism in plants. In particular, PGIs can suppress available oxygen, NADH oxidation, ATP synthase catalysis, and mitochondrial ATP formation. In addition, these compounds can inhibit the plant's oxidative phosphorylation process, and consequently disrupt the respiratory process [58]. Benzoic and cinnamic acids derived from rice were reported to suppress respiration, leading to plant growth inhibition [49]. Transpiration is another important process that can be impeded by PGIs, resulting in the loss of functions or even the death of plant leaves [60].

3.4. Gene Expression, Protein Biosynthesis, Phytohormone Activities, and Enzyme Functions

In the report of Anh et al. [61], the inhibition of gene expression, protein biosynthesis, phytohormone activities, and enzyme functions under PGIs' effects was discussed. PGIs can impede the formation of nucleic acid, which subsequently disrupts cellular metabolism and gene expression. Consequently, protein biosynthesis is suppressed [50,51,62]. In addition, important regulatory phytohormones involved in plant development, such as indole-3-acetic acid (IAA), gibberellin, and ethylene, can be diminished by PGIs [50,51]. These substances also have various inhibitory effects on enzyme activities. For example,

chlorogenic, caffeic acids, and catechol are phosphorylase suppressors. Cinnamic acid and its derivatives are ATPase inhibitors [50,51]. Gomes et al. [63] described the inhibitory mechanism of PGIs against plant growth by inducing cellular abnormalities. Concretely, PGIs suppress plasma membrane H^+-ATPase, regulate protein metabolism, and generate oxidative stress, resulting in cell morphological disruption and the inhibition of the plant's growth rate [63].

3.5. Symbiotic and Pathogenic Microorganisms

In soil, rhizosphere microorganisms contribute to plant adaptations to the environment. In particular, these organisms can also alter the soil conditions, which determine plant development [63–65]. Thus, PGIs can affect plant growth by interacting with symbiotic and pathogenic microorganisms through various pathways, such as establishing symbiotic relationships, establishing defense responses, negative root–root communication, and root-exudate-mediated environmental feedback [39]. For example, bacteria can convert a compound from a non-toxic form to a toxic form after it is released by host plants into the environment [66]. In addition, the effective dose of PGIs may be regulated through the microbial degradation/transformation process in soil [67,68]. Accordingly, microorganisms can regulate the allelopathic components released into an ecosystem, which highlight their important role in chemical plant-plant interactions.

4. Major PGIs in Rice

4.1. Phenolic Acids

Phenolic acids are known as derivatives of benzoic and cinnamic acids, which are popularly present in cereals. These natural compounds are detected and quantified with different contents among rice cultivars and among plant parts. Structurally, they are grouped into insoluble-bound, soluble-free, and soluble-conjugated forms [39,69,70]. In 1976, allelopathic compounds, including *p*-hydroxybenzoic, *p*-coumaric, vanillic, ferulic, and *o*-hydroxyphenyl acetic acids, were detected in extracts of rice straw by thin-layer chromatography (TLC) [71]. Subsequently, by using HPLC-EI/MS, phenolic phytotoxic compounds were intermittently discovered in the leaf and stem of four rice cultivars, including Philippine 2 (0.05 mg/g of ferulic acid), Gin Shun and Juma 10 (6.87 mg/g and 6.34 mg/g of *p*-hydroxybenzoic acid, respectively), and Kasawala mundara (0.34 mg/g of *p*-coumaric acid) [40]. The structures of phenolic acids, which are confirmed as PGIs in rice, are shown in Figure 2. In addition, the previous studies also indicated that these compounds significantly inhibit the germination and seedling length of barnyard grass. For instance, the reduction in seed germination and in root and shoot growth caused by 10^{-3} M *p*-hydroxybenzoic acid (PHDB) was 27%, 28%, and 43%, respectively [40]. Xu et al. [72] also indicated that rice straw of wild rice (*Oryza longistaminata*, S37) contains fumaric acid, *p*-coumaric acid, and *p*-hydroxybenzoic acid. At 100 ppm, fumaric acid reduced plant height by approximately 38.12% and significantly inhibited the root length and fresh weight of *Echinochloa crus-galli* as well. In addition, foliar application of the two phenolic acids PHDB and vanillic acid (VB) enhanced the drought tolerance of two rice cultivars, Q2 and Q8 [73]. Furthermore, sinapic acid and ferulic acid were found only in high-yield rice cultivars at the vegetative stage at amounts of 3.7 mg/g and 1.2 mg/g, respectively [74]. In reality, Asian farmers traditionally leave a huge amount of rice straw in the field after harvesting, which causes price yield loss in the next cultivation. Khanh et al. [75] found that the productivity of rice decreased by 25% compared to the first crop in Taiwan due to the autotoxicity produced during the decomposition of rice residues left in the soil. Another hypothesis noted that allelochemicals in rice and emitted from rice roots are different. With self-defense, the living rice can detect the receiver plants and release allelochemicals at higher concentrations. However, the allelochemical content is over the threshold (demand on the agronomic traits of rice cultivars) that inhibits rice growth [75]. This problem is discussed in this section, owing to phenolic acids accounting for the main allelochemicals in rice.

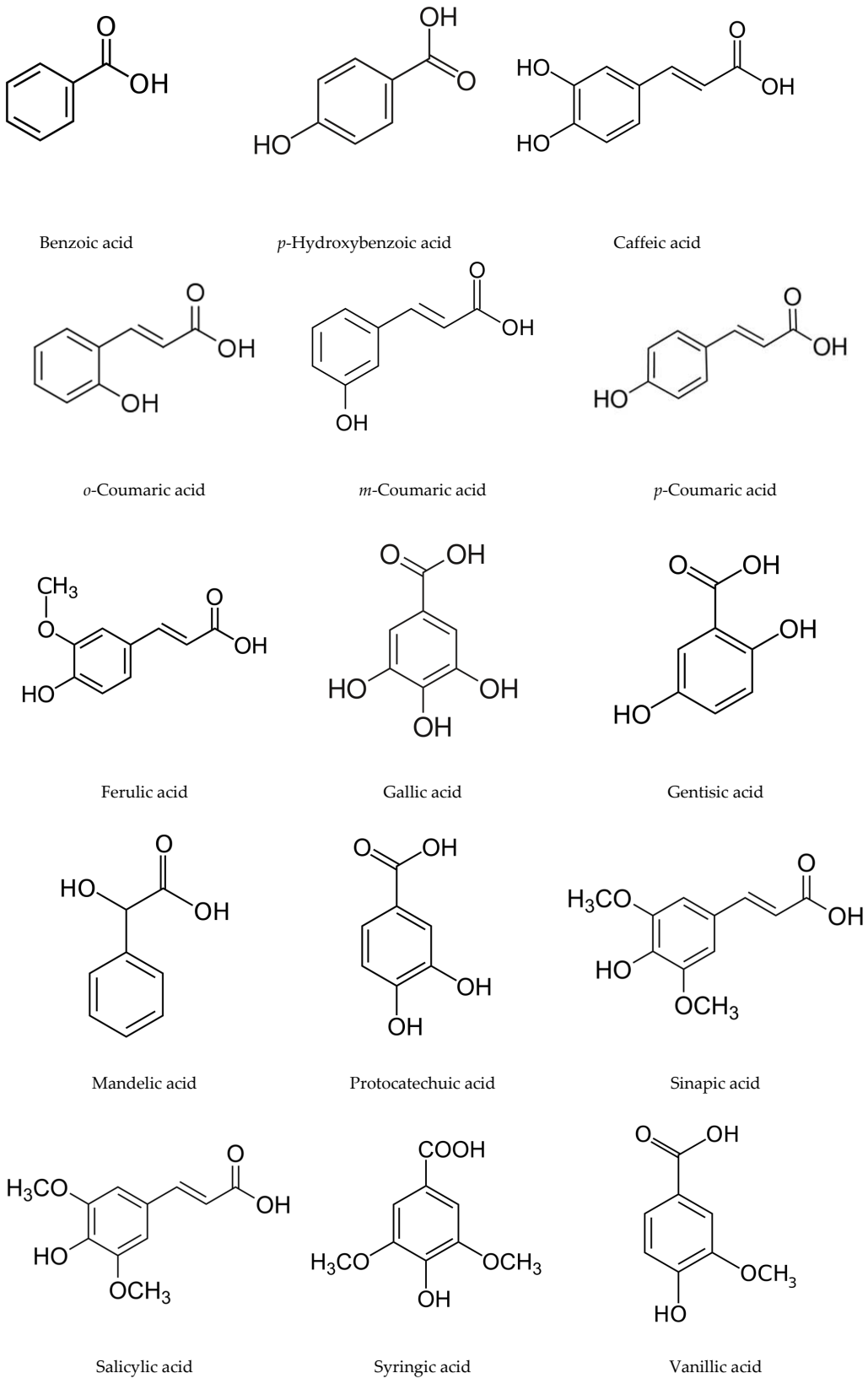
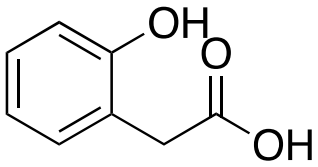


Figure 2. *Cont.*



o-Hydroxyphenyl-acetic acid

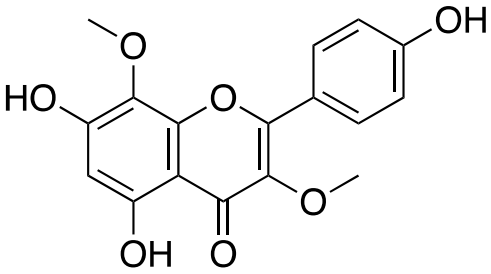
Figure 2. The structure of allelopathy-phenolic acids in rice.

Recently, epidemiological studies demonstrated that the existence of antioxidant compounds such as phenolic acids in rice may contribute to reducing the risks of certain chronic diseases in some rice-consuming regions of the world. Chemically, the antioxidant properties of such compounds depend on the number and the position of hydroxyl groups on the phenolic ring [76]. In addition, previous reports indicated that soluble free, soluble, conjugated, and insoluble bound forms of phenolic acids are highly associated with hydroxylation and methylation in the human body [42]. Among the nineteen prevalently identified phenolic acids in rice, ferulic acid is the most abundant substance, constituting 56% of the total phenolic acids in rice bran and 77% in polished rice, while caffeic and cinnamic acids occupy under 1% [69,70,77]. These phenolic acids have also been researched for their role in some human diseases [78]. In detail, research in 2000 showed that 50 μM of caffeic acid extracted from brown rice bran reduced the number of MDA-MB-468 breast cells and colon-derived SW-480 and human colonic epithelial cells [78]. This research also indicated that the clonogenicity of MDA MB 468 cells was inhibited by caffeic acid, ferulic acid, and tricin [78]. In the published reports, phenolic acids provided therapeutic potential with some antioxidant, anti-inflammatory, and anti-cancer activities. In addition, the soluble phenolic acids in millet grains and hulls would be absorbed into the stomach, small intestine, and spread throughout the whole body, inhibiting the oxidation of low-density lipoproteins (LDLs), cholesterol, and liposomes [42].

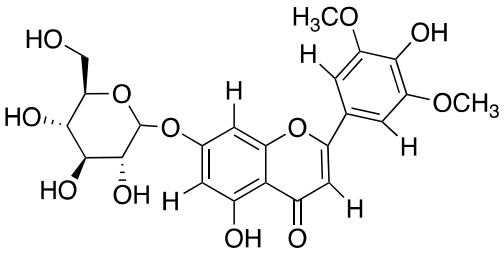
4.2. Polyphenols

Polyphenols are the main constituents of rice, and their distribution is varied among rice varieties and rice plant parts. Based on their structure, polyphenol compounds can be classified into flavones, flavonols, flavanols (flavan-3-ols), flavanonols, isoflavones, flavanones, anthocyanins, and chaconnes with *O*- or *C*-glycosides forms, of which some of the flavonoids are allelochemicals [79]. Published papers showed that the polyphenols were simultaneously determined in rice and evaluated their inhibitory effects on weeds and rice diseases [33,45,80–82]. The structures of phenolic compounds are shown in Figure 3. For example, sakuranetin, a flavanone, was investigated from ultraviolet-irradiated rice leaves in 1992 by Osamu et al. [45]. This compound not only prevented the spore germination of *Pyricularia oryzae* at 15 ppm but was also observed in blast-infected rice leaves. Sakuranetin provides typical evidence of the negative aspect of allelochemicals [45]. In 2013, five new compounds, including the derivatives of flavonols and flavanones, were elucidated in rice straw by using one- and two-dimensional NMR, combined with IR, electrospray ionization-mass spectrometry (ESI-MS), and high resolution-electrospray ionization-Fourier transformation-mass spectrometry (HR-ESI-FT-MS). The algicidal activities of the new compounds were evaluated with blue-green algae (*M. aeruginosa*) by bioassays. In the results, oleioyl-*β*-d-arabinoside had the highest growth inhibition (92.6%) against *M. aeruginosa* UTEX 2388 at a concentration of 100 mg/L [44]. From rice seedlings, two kinds of flavone *O*-glycosides (5,4′-dihydroxy-3′,5′-dimethoxy-7-*O*-*β* glucopyranosyl flavone, and 7,4′-dihydroxy-3′,5′-dimethoxy-5-*O*-*β*-glucopyranosyl flavone) have been identified, which act as agents to interfere with the growth of weeds and microbes in rice

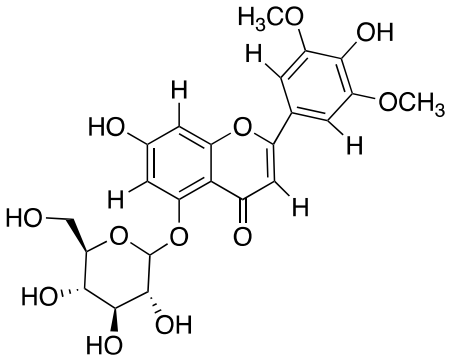
fields [46]. One of the significant phenolic allelochemicals is tricin, which was isolated from allelopathic rice cultivars and other plant species. Tricin exists in different parts of rice in either free or conjugated forms such as tricin-free, tricin-glycosides, tricin lignans, and tricin-lignan-glycosides [83]. Tricin and its isomer can suppress the fungi *Fusarium oxysporum* Schlecht and *Rhizoctonia solani* Kühn, which are the main causes of rice seedling rot disease [19].



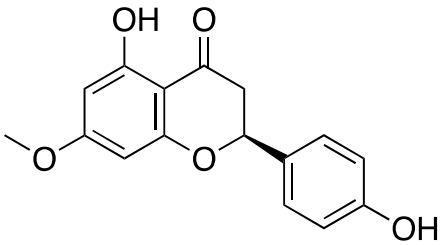
5,7,4′-Trihydroxy-3,8-dimethoxyflavone



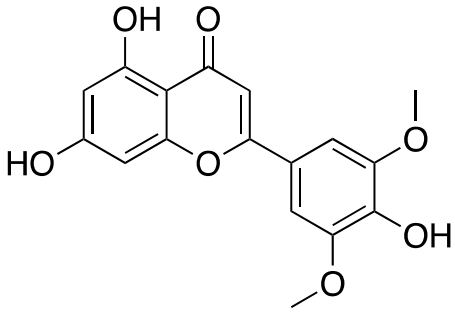
5,4′-Dihydroxy-3′,5′-dimethoxy-7-*O*-*β*-glucopyranosylflavone



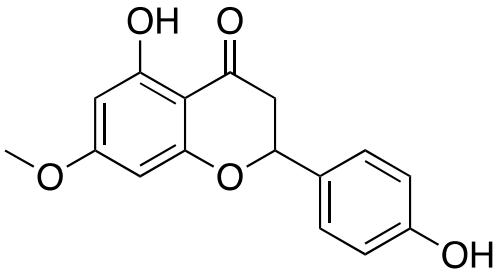
7,4′-Dihydroxy-3′,5′-dimethoxy-5-*O*-*β*-glucopyranosylflavone



4′,5-Dihydroxy-7-methoxyflavanone



5,7-Dihydroxy-2-(4-hydroxy-3,5-dimethoxyphenyl) chromen-4-one



(2S)-5-Hydroxy-2-(4-hydroxyphenyl)-7-methoxy-2,3-dihydrochromen-4-one

Figure 3. The structure of allelopathy-polyphenols in rice.

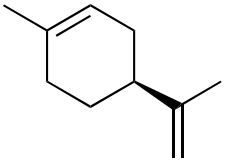
Polyphenols, as one of the most abundant secondary metabolites in rice, have been acknowledged as having benefits for human health. The published studies indicate that they help to reduce the risk of many chronic disorders, such as cardiovascular diseases, inflammation, type 2 diabetes, obesity, COVID-19, and some types of cancers [23,78,84–86]. This section focuses on summarizing some prominent polyphenols, which have preventive effects on the above-mentioned diseases. Tricin is one of the seven major flavonoids that are usually reported in rice, accounting for 77% of all seven flavonoids (131.5 mg/100 g DW) [79]. Tricin and its derivatives were also reported as being potentially applicable in pharmaceuticals due to their preventive efficacy, low toxicity, and reasonable bioavailability [87]. Tricin and flavonolignan ether have been isolated from medicinal rice Njavara (*Oryza sativa* L.) and were tested for their anti-inflammatory properties in rats. The result showed that carrageenan-induced paw edema effects of more than 65% after 5 h at a dose of 2 mg/kg [88]. In another experiment, 50 μM of extracted tricin in brown rice was the most potent anticholinergic effect of the phenols with IC_{50} of 16 μM in the SW 480 colon cells and 0.6 μM in the MDA-MB-468 breast cells [78]. In addition, anthocyanins and proanthocyanidins are polyphenols, which were found in the pigment rice grain. Many studies have investigated their cytotoxicity against the invasion ability of some cancers and chronic diseases in humans [89–93]. Concretely, proanthocyanidin extracted from red rice can inhibit MDA-MB-231 breast cancer cell invasion via the control of invasive proteins [94]. The black rice anthocyanin extract exerts anti-inflammatory effects via the suppression of the NF-κB/MAPKs signaling pathways in lipopolysaccharide-induced RAW 264.7 cells [43]. Myricetin is another significant polyphenol, occupying less than 1% of rice cultivars. It acts as a strong inhibitor of SARS-CoV helicase, and its effect is mediated through the inhibition of ATPase activity. Its IC_{50} value in vitro was 2.71 μM [95]. According to some reports, myricetin also has the capability to modify the immune response or functioning of the immune system [96].

4.3. Terpenoids

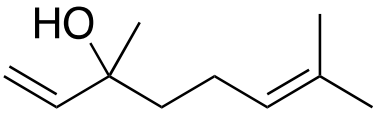
Together with phenolic acids and polyphenols, terpenoids are also a major component in rice and are grouped into monoterpenoids, sesquiterpenoids, diterpenoids, and triterpenoids. Their distribution and content depend on the part of rice or rice varieties. This section discusses some typical terpenoid-allelochemicals, phytohormones, and phytoalexins. The structures of these terpenoids are shown in Figure 4. Rice bacterial blight (*Xanthomonas oryzae* pv. *oryzae*, Xoo) is a severe rice disease, which seriously decreases the crop yield by 50% and even leads to the death of seedlings after a few weeks if the infection occurs at the seedling stage [18]. In 2016, Lee et al. [20] indicated that monoterpene (S)-limonene severely inhibited Xoo growth at 1 mM concentration, as confirmed by disc diffusion and liquid culture assays. Similarly, Morifumi et al. [21] detected diterpene phytoalexin, which can resist blasts in rice plants. In reality, phytocassanes A–E, oryzalexins A–F, oryzalexin S, and momilactones A (MA) and B (MB) in response to biotic stresses were found, and these discoveries provide a strong premise for the control of bacterial blights in rice based on plant-derived natural pesticides [22,97].

More specifically, MA and MB were detected in rice seedlings, rice hulls, rice straws, rice leaves, and exudate roots [5,8,25,26,98]. MA and MB act as growth inhibitors. Barnyard grass (*Echinochloa crus-galli*) and deccan grass (*Echinochloa colona*), the most popular and detrimental weeds for rice growth, are inhibited by MA and MB at 10 and 1 μM, respectively [98]. In more detail, Quan et al. [99] conducted inhibitory experiments of MA, MB, momilactone E (ME), and the mixture MAB on *L. sativa*, *Echinochloa crus-galli*, and *Solidago altissima*. The results showed that MB and MAB were prominent in the inhibition of the germination of *L. sativa* (IC_{50} = 178.46 and 327.20 μg/mL, respectively), while the value of the germination rate of *Echinochloa crus-galli* and *Solidago altissima* was least affected by MA, with an IC_{50} reaching 229.67 and 119.80 μg/mL, respectively. The suppression activity of MA on the growth of *L. sativa*, *Echinochloa crus-galli*, and *Solidago altissima* is weaker compared to MB and MAB. The above evidence proves that the inhibitory effects

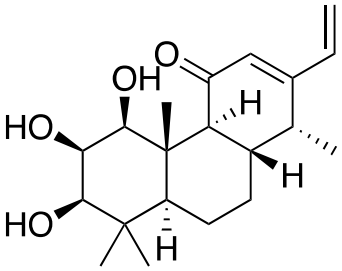
of momilactones on weeds are strong. The role of MA and MB in countering pests and diseases has been suggested. Indeed, the concentration of MA reached 100 to 500 μg/g, which is enough to restrict the growth of the rice blast fungus *Pyricularia oryzae* [100].



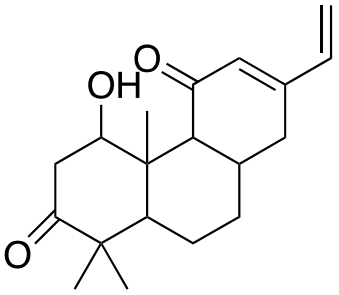
(S)-Limonene



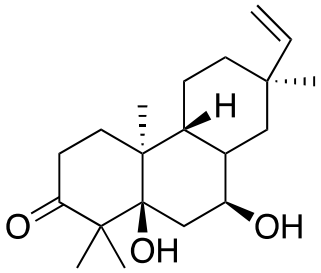
Linalool



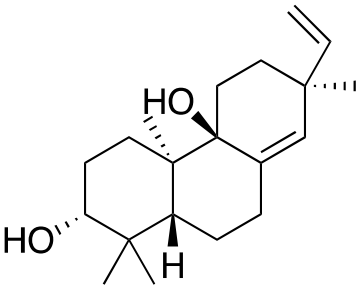
Phytocassane B



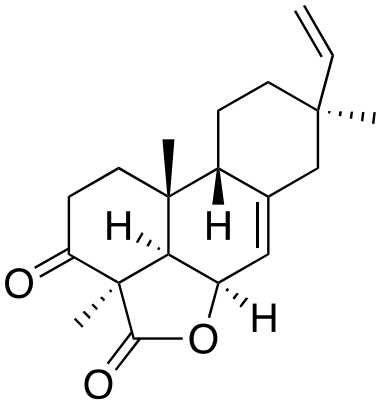
Phytocassane E



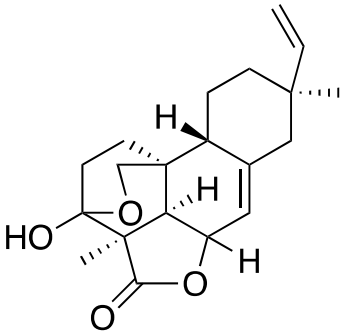
Oryzalexin B



Oryzalexin E



Momilactone A



Momilactone B

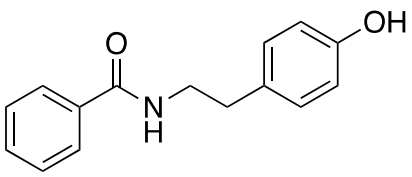
Figure 4. The structure of allelopathy-terpenoids in rice.

Momilactones are significant allelochemicals that can be released from rice seedlings into the environment [98] or extracted from parts of rice [26,101]. The content of MB in the rice is lower than other momilactones, but its biological activities are stronger compared to others [102–104]. Dong et al. [103] reported that the expression of an enzyme that causes ketogenesis, 3-hydroxy-3-methylglutaryl-CoA synthase-2 (HMGCS2), can be suppressed by MB. The anti-cancer role of MB has also been examined. MB accelerates the hypoxia-induced apoptosis of human breast cancer cells through the STAT5b pathway [105] and induces the apoptosis and G1 arrest of the cell cycle in human monocytic leukemia U937 cells [106]. Additionally, MA and MB, extracted from rice hulls, were found to have cytotoxic effects against P388 murine leukemia cells [107]. Regarding antioxidant activities, MA is slightly stronger than MB (EC_{50} was 783.9 and 790.7 μg, respectively) [38]. In 2019, Quan et al. [24] suggested that both MA and MB may be prominent candidates for anti-diabetic therapy by inhibiting α-amylase and α-glucosidase. Based on the above evidence, terpenoids, especially momilactones, are a great resource for developing natural compound-based medicines.

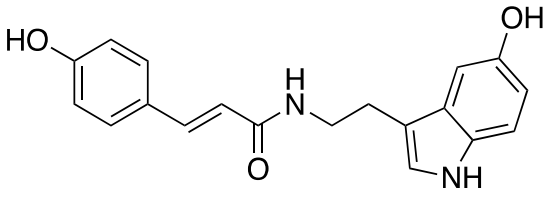
4.4. Other PGIs

Phenylamides are important nitrogen-contain compounds (Figure 5), which not only respond to the growth of weeds but also defend against pathogens. Some phenylamides were isolated from rice leaves infected with *Cochliobolus miyabeanus* and *Xanthomonas oryzae*, named N-benzoyltyramine (BenTry), N-*trans*-cinnamoylserotonin (CinSer), N-*p*-coumaroylserotonin (CouSer), N-feruloylserotonin (FerSer), N-benzoylserotonin (BenSer), N-*trans*-cinnamoyltyramine (CinTyr), N-*trans*-cinnamoyltyramine (BenTyr), N-Feruloylagmatine (FerAgm), and N-feruloylputrescine (FerPut) [108]. N-*trans*-cinnamoyltyramine (NTCT) was purified in OM5930, a Vietnamese rice cultivar, and can retard the root and hypocotyl growth of *Lepidium sativum* L. and *Leptochloa chinensis* L. Nees [109]. Meanwhile, lanast-7,9(11)-dien3α,15α-diol-3α-*D*-glucofuranoside is released from rice hulls and restricts the growth of *Lemna paucicostata*, meaning that it could be able to act as a potential natural herbicide [81]. (E,E)-2,4-Heptadienal, a volatile compound, is harmful to rice plants, but it has both anti-bacterial and anti-fungal activity against Xoo and the rice fungal pathogen *M. oryzae* [110].

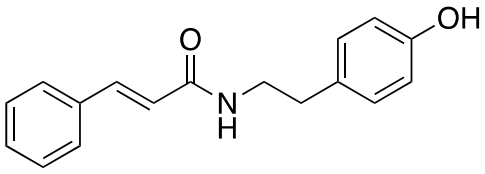
Fatty acids [111], indoles [10,112], steroids [81,113], and other constituents have been explored in rice. However, their effects on human health still need to be examined. The role of stearic acid in some diseases is summarized in this section. In 2020, Yongxiang et al. [114] performed experiments on mice regarding the influence of stearic acid and oleic acid on obesity. The results showed that a diet containing stearic acid increased food reward-related behaviors, decreased leptin levels in the serum, and decreased leptin signaling in the ventral tegmental area (VTA) compared with the oleic acid diet. In addition, a diet containing stearic acid also affects the mesolimbic dopamine system [114]. In other applications, vancomycin hydrochloride (V)-loaded stearic acid (S)/lauric acid (L) in the situ-forming matrix was used for knee joint infection treatment [115]. The solution exhibited effective antimicrobial activities, especially against methicillin-resistant *Staphylococcus aureus*, with the V-loaded 40% 1:1 L:S showing the best performance. It therefore exhibited potential as an intra-articular drug [115].



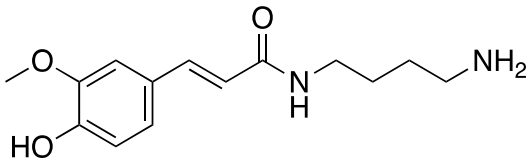
N-Benzoyltyramine



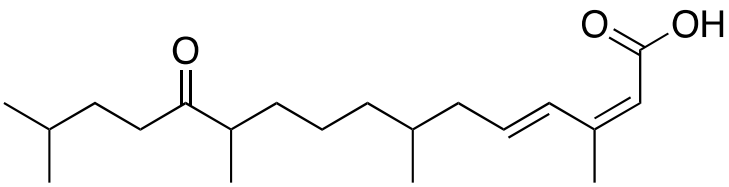
N-*p*-Coumaroylserotonin



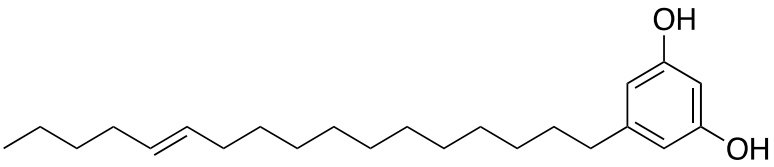
N-*trans*-Cinnamoyltyramine



N-Feruloylputrescine



cis-12-Oxo-Phytodienoic acid



5-(12-Heptadecenyl)-resorcinol

Figure 5. The structure of allelopathy-secondary metabolites in rice.

5. Isolation and Identification Techniques for PGIs in Rice

5.1. Preparation of Rice Samples

The phytochemical composition of rice is different throughout its life cycle. It is possibly influenced by both endogenous (varieties and growing stages) and exogenous (nutrition, climate conditions, and natural enemies) factors [116]. On the other hand, processing and preserving conditions are determinants that likely affect the phytochemicals during the process of analyzing rice samples [79,117]. Therefore, sample preparation and preservation are essential steps prior to the isolation and purification of the bioactive compounds of rice. The selection of the pre-extraction method not only ensures the purity of rice samples from other contaminants, but also probably establishes the target groups which can be obtained.

Rice samples including roots, leaves, husks, brans, and grains can be used in either a combinatory form or a separatory form. After collection, the rice samples should be cleaned and sterilized to eliminate all dirt and other biotic factors such as bacteria and fungi. In the next step, rice samples are dried to reduce the moisture, which is the main cause of the spoilage and hydrolysis of samples by microorganisms. There are various drying methods, among which the use of sunlight and ovens is the most common approach in isolating PGIs from rice. The optimal condition for the drying process is normally recorded at 40 °C within 7–10 days, which can preserve the integrity of most plant growth inhibitor (PGI) compounds [42,69,78,118,119]. Afterward, samples can be ground into powder or cut into small sizes in order to obtain homogeneous materials, which can be easily extracted using an organic solvent in a shorter time. This physical processing helps to partly break down the cutin layer as well as the cell wall, which facilitates a quick release of phytochemicals into the extraction solvent. Subsequently, dried samples can be extracted immediately or kept in a fridge until a later experiment. The storage conditions should consist of a low temperature (−4 °C) and darkness, which help to avoid the natural decomposition of some photosensitive compounds such as phenolics [70,120,121].

5.2. Extraction, Separation, Isolation, and Purification Techniques

5.2.1. Extraction and Separation Techniques

Extraction is the primary and most important stage to isolate, identify, and quantify phytochemicals from the rice. The raw materials have diverse and complex ingredients that are obtained with different solvents of increasing polarity in order to exhaustively extract as many active compounds in rice as possible [122,123]. To improve the conventional extraction techniques, modern extractions such as pressurized liquid extraction (PLE), microwave-assisted extraction (MAE), solid-phase microextraction (SPME), and superheated liquid extraction were applied to extract and isolate organic compounds in plants. This section focuses on reviewing PLE, MAE, and SPME techniques.

Pressurized liquid extraction (PLE) is also known as accelerated solvent extraction (ASE). This methodology is applied for solid extraction, using common solvents at elevated temperatures (temperature range from 50 to 200 °C) and pressures (under the range from 10 to 15 MPa). Extract processing is performed under pressure in order to maintain the solvent in a liquid phase. The PLE overcomes other methods due to pressure flexibility. The analyte is pushed out from the cell with the solvent by the pressure, and the cell pores are filled out quickly by the pressure flow, giving higher efficiency in extraction. The high temperature increases solubility, enhances diffusion, and increases the mass transfer of the analyte, shortening the extraction process by some minutes. Compared with traditional extraction methods, PLE has some advantages, such as lower solvent consumption and higher extraction efficiency. Until now, no evidence has revealed the degradation of temperature-sensitive compounds due to the high temperature [124,125]. On the other hand, PLE and supercritical fluid extraction (SFE) have also been applied to extract the same samples, and the results were similar [126]. However, the obtained extracts need to be cleaned up because the PLE has to use solvents for the extraction. The PLE was used to extract allelochemicals in rice, which are shown clearly in Table 2.

Microwave-assisted extraction (MAE) with microwave energy (ranging from 300 to 300,000 MHz) has been applied for extraction through accelerating the heating speed by direct heat for the extraction of solvents. Two microwave energy extraction technologies have been developed, either using closed systems under controlled temperature and pressure (PMAE: pressurized microwave-assisted extraction) or open systems under controlled atmospheric pressure (FMAE: focused microwave-assisted extraction). The aim of the application of these technologies is to extract compounds selectively and rapidly. Thereby, this technique also remarkably decreases organic solvent consumption. However, the FMAE is suitable in the case of volatile compounds, although the reaction time is longer compared to the PMAE due to the reducing temperature of the systems. The principle of PMAE and

PLE is the same, namely using a difference in energy to heat the solvents [127,128]. MAE was used to extract allelochemicals in rice, which are shown clearly in Table 2.

Solid-phase extraction (SPE) is the process of purifying natural product extracts using adsorption compounds in the solid phase. Natural product purification has high efficiency if the SPE is integrated into automated sample preparation and isolation systems. Silica gel, ion-exchanged resins, mixed-mode materials, or reversed-phase materials are used to pack SPE cartridges. The unwanted compounds are retained in the solid phase and the wanted compounds are eluted. The required compounds retained in the solid phase will be eluted by other compatible solvents [128]. Indeed, the purification of samples by using SPE before liquid or gas chromatography analysis makes the determination of the structure and configuration of compounds more efficient [129,130]. Solid-phase microextraction (SPME) is an optimized type of SPE due to its speed, simplicity, and sensitivity, with a trillion detection limits. The stationary phase of this technique depends on the mixing extraction, such as polar or non-polar analytes, which plays a significant role by increasing the efficiency by 10 to 20 times [131]. The applications of SPME in the separation of allelochemicals in rice are shown in Table 2.

Table 2. Extraction techniques used in the separation of PGIs in rice.

Rice Samples	Compounds	Techniques	Conditions	Tested Plants	Ref
Rice plants	(S)-Limonene	SPME	Solid phase (SPME): divinylbenzene (DVB)/carboxen (CAR)/polydimethylsiloxane (PDMS)	Bacterial blight (*Xanthomonas oryzae* pv. *oryzae*)	[20]
Rice husk	Momilactones A, B, E, and 7-Ketostigmasterol	Repeated-column chromatography	Hexan:EtOAc; $CHCl_3$:MeOH Silica gel 60–100 mesh size in a 5 × 60 cm column followed by 200–400 mesh in a 2 × 50 cm column	Barnyardgrass (*E. crus-galli*), tall goldenrod (*S. altissima*), and Lettuce (*Lactuca sativa*)	[99]
Rice grains	Phenolics	UAE	MeOH:H_2O (80:20, *v*/*v*) At 45 °C, in 25 min, cycle 0.4 s^{-1}, ultrasound amplitude 47%	Wild grass	[132]
Rice grains	Phenolics	PLE	EtOAc:MeOH (60:40, *v*/*v*) Pressurized 200 atm and then heated 190 °C in 10 min with three cycles	Wild grass	[133]
Rice grains	Phenolics	MAE	100% MeOH Solve to sample (10:1) At 185 °C, 20 min, cycle 0.4 s^{-1}, microwave power 1000 W	Wild grass	[134]

SPME: solid-phase microextraction; UAE: ultrasound-assisted extraction; MAE: microwave-assisted extraction; PLE: pressured-liquid extraction; EtOAc: ethyl acetate; $CHCl_3$: chloroform; MeOH: methanol.

5.2.2. Isolation and Purification Techniques

Thin-layer chromatography (TLC) is a principal chromatographic technique that is widely applied in screening natural products and supporting the isolation and purification of natural compounds [135]. Its advantages are its simplicity and time- and cost-effective [135]. In order to improve the TLC technique, high-performance thin-layer chromatography (HPTLC) was developed, which is simple, rapid, and enhances the separation of compounds [135]. The detection sensitivity of HPTLC is 5 to 10 times higher compared to classical TLC [135]. Additionally, this improved TLC technique is efficient in the quantitative analysis of compounds [135].

Column chromatography (CC) is a well-known method for separating and purifying compounds from plant extracts [136]. The column contains a stationary phase with silica gel [136]. Through the column, the mobile phase separates the compounds based on their affinities from the stationary and mobile phases [136]. After that, the isolated components can be collected along with the mobile phase [136]. CC can be listed with two common types, including normal CC and flash CC [136].

Reverse phase chromatography (RPC) is based on a partitioning mechanism to induce separation effects [137]. Separation in RPC is determined through the reversible adsorption and desorption of solute molecules with different levels of hydrophobicity to the hydrophobic stationary phase [137]. Most reverse-phase separations are performed in five steps consisting of starting conditions, sample adsorption, the initiation of desorption, the termination of desorption, and generation [137]. This technique was originally developed in the 1960s to separate small organic molecules. Recently, it has been applied to purify biomolecules such as proteins [137].

5.3. Qualitative and Quantitative Analyses

5.3.1. Spectroscopic Methods

UV-visible (UV-vis) spectroscopy can be applied for the identification and quantification of specific groups of compounds in a pure form or in a mixture. Notably, aromatic compounds are strong chromophores in a wide range of UV wavelengths. Natural compounds including rice PGIs (e.g., phenolics, flavonoids, anthocyanins, tannins, etc.) have been detected by UV-vis spectroscopy [138], among which, phenolics, flavonoids, and anthocyanins can be determined with absorbances of 280, 320, and 520 nm, respectively. In addition, this technique requires a short time and low cost [139].

Infrared spectroscopy (IR) is based on the vibrational changes inside a substance under IR radiation exposure. Different kinds of bonds (e.g., C–C, C–O, O–H, N–H, etc.) in a molecule have various vibrational frequencies. These bonds can be determined by detecting the characteristic frequency absorption band in the IR spectrum [139]. Fourier transform-infrared spectroscopy (FT-IR) is an improved IR technique with a high-resolution analytical tool to determine the chemical components and clarify the compound structure [139]. In another report, near-infrared spectroscopy (NIRs) equipped with UV-vis could evaluate the degradation of thermal rice oil [140]. A review by Fang et al. showed that FT-IR has been used to elucidate the thermal deterioration mechanism of bio-oil of rice husk owing to it providing information about functional groups rapidly and accurately [141]. The models of NIRs have been developed to predict protein, amylose, crude oil, and fiber content in rice [119].

In mass spectrometry (MS), compounds can be bombarded with electrons or lasers, thereby converting them to charged ions. A mass spectrum is recorded as the relative abundance of fragmented ions against the ratio of mass/charge of these ions. Accordingly, the relative molecular mass (molecular weight) can be calculated. In addition, elucidation of the compound structure can be conducted by applying tandem mass spectrometry (MS/MS). Therefore, LC equipped with MS systems has been improved to support compound identification more rapidly and accurately in extracted samples without the use of standard substances [142–145]. Recently, LC-MS has been one of the most frequently used methods to identify and quantify some allelochemicals, such as phenolics and phenyl amides (Table 3).

Nuclear magnetic resonance (NMR) spectroscopy is based on the magnetic characteristics of atomic nuclei. By reporting differences among various magnetic nuclei, NMR can determine the positions of these nuclei in a molecule. In particular, atoms and their amounts present in neighboring groups can be indicated [138]. Based on that, the structures of isolated and purified substances applying TLC, LC, and CC can be subsequently confirmed by NMR [138]. In 2019, the structures of momilactone A, B, E, and 7-ketostigmasterol in the crude extracted rice husk were identified and confirmed by applying ^{1}H and ^{13}C NMR,

electrospray ionization (ESI), high-resolution mass spectrometry (HR-MS), and infrared spectroscopy (IR) [99].

X-ray crystallography is the most powerful technique that can identify the atomic and three-dimensional (3D) structure of target compounds from small crystals to large molecules [146]. X-ray crystallography is the only method to figure out the absolute configuration of chiral molecules, and results from crystallographic studies [146]. In this study, there are four major steps, including crystallization, data collection, structure solution, and refinement/validation [146]. The X-ray crystallography method directly indicates information on the compound structure at the atomic level with high accuracy [147].

5.3.2. Chromatography

Thin-layer chromatography (TLC) is a method for the rapid determination of the fingerprint compounds in the natural compound extraction based on the mobile phase composition and the water content of the silica stationary phase. To date, TLC has been developed to rotate planar chromatography (RPC), centrifugally accelerated thin-layer chromatography (CTLC), and overpressure layer chromatography (OPLC) to overcome the disadvantages of classical TLC. Normally, the thicknesses of the chromatography plates are 0.5–2 mm, with the maximum sample load for a 1.0 mm silica layer being about 5 $mg.cm^{-2}$. Optimization of mobile phases plays an important role in determining organic compounds in the mixtures, and n-hexane: ethyl acetate, n-hexane: acetone, and chloroform: methanol are frequently used as the mobile phases with various proportions [148]. The evidence of this technique in the isolation of allelochemicals in rice is shown in Table 3.

Pressure liquid chromatography techniques are the main form of liquid chromatography, occurring under 0.2 to 2.0 mPa. The principle of these techniques depends on the stationary-phase column, the mobile phases, and the specific samples. Other technical features which have been applied to identify natural compounds in rice are also briefly summarized in Table 3. High-pressure liquid chromatography (HPLC) is one of the mainstays in the isolation of the stage in natural products. In this technique, the particle size of the stationary phase is significant for separate processing, with its range being from 3 to 10 µm, which is smaller compared to other liquid chromatography methods, such as low- or medium-pressure liquid chromatography. Regarding the particle size, the extracted plant compounds in the mobile phase can be pushed through the system by the high pressure. The interaction between the high surface area of the solutes and the high surface area of the solvent leads to improving the purifying ability of mixtures. The diameter of the column (from 10 to 100 mm), as well as the length of the column, depends on the compounds that need to be isolated [149,150]. To date, a variety of pressure liquid chromatography techniques have been applied to determine the composition of natural compounds such as phenolic acids, flavonoids, and terpenoids owing to their structures, vapor temperature, and pressure [151]. In this section, the evidence also indicates that HPLC is the optimal method for obtaining simple phenols in rice and other plants by combining it with a spectroscopic section (Table 3) [152].

Hydrophilic interaction chromatography is the solution for the analysis of polar substances (HILIC). However, the separation mechanism of HILIC needs to be clear because HILIC separation has been obtained on adsorption and partition processes owing to the intermolecular force [150,151]. Silica gel, silica-based polar bonded phases, particulate organic polymer materials, zwitterionic stationary phases, and monolithic HILIC stationary phases are the solutions used in the HILIC columns so far. Based on these mixtures, HILIC columns and the mobile phase will be chosen for suitable separation [153]. The applications of this technique in isolating allelochemicals from rice are shown in Table 3. More specifically, the revolutionary separation technique is ultra-performance liquid chromatography (UPLC), which surmounted the limitations of previous liquid chromatography methods, with high resolution, speed, and sensitivity, due to its upgraded instruments and column technologies. Indeed, Quan et al. [24] quantified MB by means of HPLC and ultra-performance liquid chromatography-electrospray ionization-mass spectrometry (UPLC-ESI-MS) in 2019.

The limit of detection (LOD) and limit of quantification (LOQ) of MB were 0.48 ng/mL and 0.46 ng/mL, respectively, by using HPLC with a 250 mm × 4.6 mm column, 10 µm, and flow rate of 0.4 mL/min. Similarly, the LOD and LOQ indexes of MB were 0.27 and 0.83 ng/mL, respectively, which were determined by UPLC-ESI-MS method with a 50 mm × 2.1 mm column, 1.7 µm, and a flow rate of 0.3 mL/min [26]. The values of LOD and LOQ demonstrate that the sensitivity of the ultrahigh-performance liquid chromatography (UHPLC) in determining MB is higher compared to the indexes with HPLC due to the length and particle size of the column. Therefore, UPLC was equipped with a triple quadrupole mass spectrometer (QqQ-MS) to obtain flavonoids and antioxidants in wild rice [154].

Gas chromatography (GC) techniques are essential solutions for the identification and quantification of substances in rice due to their heterogeneous complexations. Extracted solutions of rice contain various substances at different concentrations, including hydrophobic or hydrophilic compounds and polar or non-polar compounds. To date, gas chromatography coupled with other spectroscopies, such as MS, NMR, ESI, and HR-MS NMR, has been the main solution to determine the structural compounds in rice mixtures. Gas chromatography-mass spectrometry is approved as a sensitive method for the identification and structural elucidation of allelochemical compounds in rice. MS is a technique for identification and characterization through generated charged particles from molecules of the analyses by comparing them with the mass spectra and retention time. The MS libraries are installed in the running program. Additionally, the ionizer, ion analyzer, and detector are three specific regions for MS instrumentation [155–159]. In this section, a detailed example of GC's application to determine allelochemicals in rice is provided, namely for a volatile compound ((Z)-3-hexen-1-ol), which was published by Japanese researchers. The volatile compounds in rice leaves were collected by means of solid-phase microextraction (SPME) before being transferred to the analysis stage. The mixing was resolved using a CP-Sil 8CB column with He as the carrier gas, which was coupled with MS in a 30 to 300 m/z range. The contents of volatiles were calculated based on the peak area of the total ion chromatography. For instance, volatiles in the rice leaves were analyzed by GC-MS [160]. Other applications of gas chromatography in the isolation of allelochemicals in rice are shown in Table 3.

Table 3. Chromatography techniques for determination of PGIs in rice by LC and GC techniques.

Rice Samples	Compounds	Techniques	Conditions			Ref.
	LC Techniques		Stationary Phase	Technical Index	Mobile Phase	
Rice hulls	Diterpenoids	TLC-NMR/ESI/MS	Si-gel G 60 F254 plates		$CHCl_3$	[22]
Rice hulls	Momilactones A, B, E, and 7-Ketostigmasterol	NMR/ESI/HR/MS-HPLC	Waters Spherisorb ODS2 column	150 mm × 4.6 mm, 10 µm	0.1% Trifluoroacetic acid (TFA) in 70% ACN	[99]
Rice grains	Momilactones A and B	UPLC-ESI-MS/MS	UPLC® BEH C18 column	1.7 µm, 50 × 2.1 mm	0.1% TFA and 0.1% TFA in ACN (50:50, *v*/*v*) in a gradient program	[26]
Rice germplasm	Flavone O-glycosides	HPLC	Zorbax SB-C18 column	150 mm × 4.6 mm, 5 µm	ACN:AcOH (1%): 2:3 (*v*/*v*)	[46]
Shoots	Jasmonic acid	UPLC-MS/MS	BEHC18 column	50 mm × 2.1 mm, 1.7 µm	AcOH in H_2O (0.2%): MeOH Flow rate of 300 µL/min	[161]
Rice cultivars	2,4-Dimethoxybenzoic acid, *p*-coumaric acid, vanillic acid, salicylic acid, and cinnamic acid.	HPLC-UV/Vis	XDB-C18 column	150 mm × 4.6 mm, 5 µm equipped with 20 mm × 3.9 mm, 5 µm	A: MeOH/ B: HCOOH 0.1% A:B (30:30, *v*/*v*) or A: ACN/ B: HCOOH 0.1% A:B (20:80, *v*/*v*)	[36]
Rice leaves	Phenolics and phytoalexins	LC–MS/MS	Shiseido Capcell PaK C8 column	150 mm × 4.6 mm, 5 µm	ACN (HCOOH 0.1%):D.I.W. (80:20, *v*/*v*)	[162]

Table 3. *Cont.*

Rice Samples	Compounds	Techniques	Conditions			Ref.
	LC Techniques		**Stationary Phase**	**Technical Index**	**Mobile Phase**	
Rice leaves	Phenylamides	LC-MS/MS-NMR	Acquity UPLC BEH C18 column	50 mm × 2.1 mm, 1.7 µm	A: HCOOH 0.1% aqueous B: HCOOH 0.1% ACN	[108]
Rice bran	Phenolics	HPLC-DAD	Kinetex C18 column	150 mm × 4.6 mm, 5 µm	A: D.I.W (HCOOH 0.1%). B: ACN (HCOOH 0.1%). gradient 5–70% A/(A + B)	[163]
Non-glutinous purple rice	Phenolics	HPLC-ESI-MS/MS	Zorbax Eclipse XDB C18 column	150 mm × 4.6 mm, 5 µm	• For bound phenolic acids A: 50 mM H_3PO_4 at pH 2.5 B: ACN • Free phenolic acids A: MeOH 2.5% + HCOOH 2.5% B: MeOH	[152]
	GC Techniques		**Conditions**			**Ref.**
Rice plants	(S)-Limonene	SPME- GC/MS	• Column: HP-5MS capillary: 30 m × 0.25 mm, 0.25 µm • Oven program: 80 °C for 3 min, heated to 150 °C at 5 °C/min, heated to 250 °C for 10 min, then 20 °C/min until 300 °C (3 min hold). Flow rate of helium gas is 1 mL/min; m/z range: 50–350			[20]
Rice leaves	Oryzalides and oryzalic acids	GC-SIM	• Column: Quadrex-methyl silicon capillary: 15 m × 0.53 mm, 1 µm • Oven program: Temperatures of the injection port, interface, and FID are 230 °C, 200 °C, and 200 °C, respectively. Flow rate of helium gas is 25 mL/ min			[157]
Rice plants	Flavone *O*-glycoside	GC-FID	• Column: Hewlett–Packard 6890 gas chromatograph with a 25 m HP-5 column • Oven program: 60 to 170 °C at 2 °C/min, and from 170 to 250 °C at 1 °C/min. Flow rate of hydrogen gas is 1.5 mL/s			[158]
Japanese rice	Momilactones A and B	GC/MS	• Column: DB-5MS capillary: 30 m × 0.25 mm, 0.25 µm • Oven program: 50 °C for 6 min, heated to 280 °C at 5 °C/min (5 min hold). The carrier gas is helium • m/z range: 20–900			[32]
Black and purple rice bran	Flavonoids	UAE-GC/MS/FID	• Column: WCOT capillary: 30 m × 0.25 mm, 0.25 µm • Oven program: 40 °C for 2 min, heated to 280 °C at 5 °C/min The carrier gas is helium • m/z range: 35–600			[160]

D.I.W: deionized water; TFA: trifluoroacetic acid; ACN: acetonitrile; AcOH: acetic acid; MeOH: methanol; SIM: selective ion monitoring; FID: flame ionization detector; WCOT: wall-coated open tubular; TLC: thin-layer chromatography; NMR: nuclear magnetic resonance; ESI: electrospray ionization; MS: mass spectrometry; HPLC: high-pressure liquid chromatography; UPLC: ultrahigh-performance liquid chromatography; DAD: diode-array detector; GC: gas chromatography; SPME: solid phase microextraction; UAE: ultrasound-assisted extraction; LC: liquid chromatography; Ref., references.

6. Current Status, Existing Limitations, and Future Perspectives

To date, a broad range of identification and isolation techniques for evaluating the fundamental mechanism and overall effect of allelochemicals in rice have been developed. Each methodology exhibits different levels of efficacy and limitations [61]. There is no standard or defined protocol for the extraction, separation, purification, and identification of PGIs in rice. Even though allelopathy research has been undertaken since the 1960s, it has been difficult to identify and isolate these compounds in rice because of their complicated features, such as solubility, volatility, and stability. The absence of a robust and effective approach for determining PGIs remains a major obstacle. Therefore, studies on PGI extraction, separation, purification, and identification are critical for future studies and applications. As a result, determining efficient and effective techniques and developing a comprehensive understanding of these extraction, separation, purification, and identification techniques are essential for further research and applications in the large-scale industrial production of PGIs. This review article provides an in-depth understanding of the conventional and modern methodologies for the isolation and identification of PGIs from rice.

6.1. Current Status and Existing Limitations

6.1.1. Extraction and Separation Techniques

Extraction is a key initial step in the analysis of rice PGIs. For many years, rice PGIs have been extracted and isolated by using conventional extraction methods such as sonification, percolation, Soxhlet extraction, and maceration [164]. However, the limitations of conventional techniques include their ineffectiveness, time and money consumption, and pollution caused by a large amount of used organic solvents. Due to these reasons, more sophisticated green approach techniques have been studied and introduced, such as ultrasonication-assisted extraction (UAE), microwave-assisted extraction (MAE), solid-phase microextraction (SPME), and pressurized liquid extraction (PLE or PSE) [165]. Some of these methods are referred to as "green methods" because they adhere to the requirements established by the United States Environmental Protection Agency, such as a reduction in organic solvent consumption, especially the dangerous chemicals used for synthesis, a designation for energy conservation, the elimination of derivatives, catalysis, improvement in extraction efficiency and selectivity, a design to prevent sample degradation, as well as naturally safer chemistry for accident prevention [164]. Pressurized liquid extraction (PLE) is performed at elevated temperatures and pressures to enable the extraction solvent to quickly penetrate the plant cells while preventing the compounds from degrading. This technique is a promising candidate method for extracting compounds which are stable under high temperatures [166]. However, it was not possible to optimize the extraction process by implementing a greater PLE temperature, since applying too much heat might destroy the phenolic compound. Lindquist [167] discovered that phenolic compounds became less stable and showed mild degradation at 150 °C and severe degradation at 200 °C. By testing the stability of individual phenolic compounds, various PLE temperatures are considered, and the ideal extraction temperature was determined. The validated method was successfully applied for the analysis of a wide variety of rice grains [133]. On the other hand, various groups of compounds with various characteristics require different ideal extraction temperatures, which need further comprehensive investigation.

Similar to PLE, microwave-assisted extraction (MAE) efficiency depends on extraction duration, temperature, and the type and ratio of the solvent. In terms of extraction efficiency, the amount of time, and solvent used, MAE and PLE outperformed other extraction techniques including Soxhlet, reflux, and ultrasonic extraction. A study on the extraction of a total of fifteen phenolic contents in various rice grains proved that MAE is a powerful tool for the determination of phenolic compounds from a wide variety of rice grains [134]. The advantages of MAE were introduced by [168], such as higher extract yield, minimal equipment size, and rapid heating for the extraction of bioactive compounds from plant sources. MAE is also considered a green technique because of its reduced use of organic solvents. However, the biggest limitation of MAE, unfortunately, is also the probability of the degradation of temperature-sensitive compounds under higher temperatures. The use of UAE, which breaks down the cell structure with sonic energy and quickly releases bioactive chemicals, might prevent these issues. In addition, small samples can be extracted by using ultrasound-assisted extraction, which would provide an increase in yield while significantly reducing extraction time and solvent usage. However, it is challenging to replicate this procedure, because using a lot of energy might cause the phytochemical to degrade by creating free radicals.

In addition, a solvent-free modern technique was introduced recently which is advanced in many aspects. Solid-phase extraction (SPE), or SPME (an optimized type of SPE), is a sophisticated, accurate, economical, non-exhaustive, and robust technique. This can reduce labor requirements for extraction by combining all steps of extraction into one. Additionally, it has been demonstrated as a highly efficient technique by means of its direct integration with separation and analysis systems such as chromatography systems. Despite the numerous advantages and extensive applications of SPME in both agriculture and medicine fields, this technique still has some limitations. For instance, although SPME seems to be the most effective tool for analyzing volatile and semi-volatile organic com-

pounds, for non-volatile and high-molecular-weight compounds, it is less effective, which remains a major concern that needs to be tackled.

6.1.2. Identification, Qualitative and Quantitative Analyses

After the extraction steps, the identification and quantification steps of rice allelochemicals are characterized by the use of a variety of techniques including spectroscopic techniques (UV-Vis, IR, NMR, X-ray crystallography, MS) and chromatography techniques (TLC, CC, HPLC, UPLC, HILIC). UV-vis spectroscopy is a commonly used method for not only polyphenols and flavonoids, but also other various biologically active compounds due to their wide range of wavelengths, short duration, and economical nature. However, the PGIs in the rice plant extract usually remain as an integration of a mixture of bioactive compounds with different types of extract solvent, and the use of spectroscopic analysis is not selective and sensitive for the qualification and quantification of individual PGI compounds. As a result, these factors cause the separation, identification, and characterization provided by UV-vis spectroscopy to become a significant issue. To address this issue, mass spectrometry was developed as a widely used and reliable technique. In addition, the combination of MS with chromatography techniques such as LC or GC has become one of the most powerful options for the identification and quantification of PGIs in rice due to its sensitive and selective nature. Specifically, even if the pure standard is unavailable, the application of LC with tandem mass spectrometry can provide abundant information for the elucidation of the compound structure. However, the requirement for the sample preparation to be in a gas or liquid form for the ionization sources is one of the MS drawbacks. Furthermore, mass spectrometric equipment is expensive and requires highly competent operators. Among the chromatography techniques, HPLC is the most frequently used technique for the isolation and analysis of polyphenols and organic acids found in rice, since it is the most high-resolution, efficient, high-precision, and robust technique, with no derivatization and no restrictions on the sample volatility technique when compared to other methods. Currently, the demand for environmentally friendly and robust techniques is significantly increasing. This led to the development of ultrahigh-performance liquid chromatography (UHPLC). Results from UHPLC show that it produces higher peak efficiency and chromatographic resolution than traditional HPLC. Additionally, since UHPLC techniques usually require 80% less chemical solvent than traditional HPLC techniques, they may be considered more economical. Both HPLC and UHPLC can be conveniently connected to a range of detectors, such as UV-Vis, DAD, and MS. On the other hand, a limitation of the LC system is that it requires a high-cost strategy. In addition, a large amount of organics is needed for LC operation. Muddled situations can occur in investigating issues or developing new methods that need multiple replicated confirmations. In addition, the UV-vis detector is able to identify only chromophoric compounds. In the case of LC-MS, the matrix's complexity entering the MS ion source cannot be controlled by the operators. Therefore, fluctuations in the matrix composition can lead to a reduction in ion yield. Accordingly, matrix complexities are important determinants in LC-MS analysis since they may occur in individual samples and can consequently lead to inaccurate results in these specimens. Therefore, validation of their occurrence and absence must be indicated in applying relevant assays. The obtained results should also be carefully confirmed. Further strategies should focus on minimizing their occurrence through appropriate solutions.

6.2. Future Perspectives

The ongoing investigation of innovative techniques for the isolation and identification of PGIs in rice is driven by the rising economical and allelochemical effect value in rice. The evolution of chromatography and environmental consciousness are two significant factors in the development of these approaches. The combination and development of hybrid techniques should also be considered in order to achieve the highest efficiency in the isolation and identification PGIs in rice. In addition, the biosynthesis of phenolic allelochemicals can be regulated by modifying the genetic factors. Generating strong

allelopathic plants containing high levels of phenolic allelochemicals could be considered a promising approach in the future. In addition, enhancing the interdisciplinary knowledge of soil, chemistry, ecology, genetics, molecular biology, and other subjects can help us to interpret the activities of phenolic allelochemicals in natural conditions.

The information provided in this study could be employed to generate a helpful database for manufacturing natural herbicides with the use of artificial intelligence (AI) and the Internet of Things (IoT), which can help with efficient weed management and the development of smart and sustainable agriculture. In the future, comprehensive investigations should concentrate on the identification and isolation of PGIs in rice, as well as the description of these compounds' mechanisms and allelopathic effects in biological systems. As a result, PGIs derived from rice plants might be produced and applied on an industrial scale. Currently, despite the enormous potential of the application of these PGIs as natural herbicides, there are no phenolic allelochemicals that have been successfully and effectively developed on both commercial and industrial scales [61]. Therefore, prospective studies should carefully consider the feasibility of the application of PGIs in digital farming. A circular farming model should be studied based on both simulation and reality that will help us to obtain a comprehensive view and achieve this sustainable goal. In other words, selecting proper identification and isolation methods for target rice PGIs will be an important step in deciding the most suitable rice production model for different conditions, which helps to minimize the impact of weeds, reduce costs, and increase productivity while ensuring safety and sustainability.

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