

Review

Potential Momilactones in Rice Stress Tolerance and Health Advantages

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Abstract: The aim of this review was to provide an updated outlook on the relevance of momilactones in rice during the 50 years since their discovery. Momilactones A (MA) and B (MB) were initially extracted from rice husks in 1973 and have since been identified in various parts of the rice plant including leaves, bran, straw, roots, and root exudates. The biosynthesis of these compounds in rice initiates from geranylgeranyl diphosphate (GGDP) and progresses through several cyclization stages. The genes governing the synthesis of MA and MB are located on chromosome 4 within the rice genome. Concentrations of these compounds vary across different parts of the rice plant, ranging from 2 to 157 µg/g. Notably, Japonica rice varieties tend to have higher levels of MA and MB (157 and 83 µg/g, respectively) compared to Indica varieties (20.7 and 4.9 µg/g, respectively). There is a direct correlation between the levels of MA and MB and the increase in antioxidant activity, protein, and amylose content in rice grains. The production of these compounds is enhanced under environmental stresses such as drought, salinity, chilling, and UV exposure, indicating their potential role in rice's tolerance to these conditions. MA and MB also demonstrate allelopathic, antibacterial, and antifungal properties, potentially improving the resilience of rice plants against biotic stressors. Although their antioxidant activity is modest, they effectively inhibit leukemia cells at a concentration of 5 µM. They also show promise in diabetes management by inhibiting enzymes like α-amylase (with IC₅₀ values of 132.56 and 129.02 mg/mL, respectively) and α-glucosidase (with IC₅₀ values of 991.95 and 612.03 mg/mL, respectively). The therapeutic qualities of MA and MB suggest that cultivating rice varieties with higher concentrations of these compounds, along with developing their derivatives, could benefit the pharmaceutical industry and enhance treatments for chronic diseases. Consequently, breeding rice cultivars with increased momilactone levels could offer substantial advantages to rice farmers.

Keywords: momilactones; *Oryza sativa* L.; abiotic stress; biotic stress; antidiabetic; anticancer



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1. Introduction

Over half of the global population relies on rice as their primary dietary staple. The world's total rice production is around 740 million tons, with about 90% of this (approximately 670 million tons) grown and consumed predominantly in Asia, especially in its eastern, southern, and southeastern parts [1]. However, despite the significant rice cultivation in these regions, farmers in developing Asian countries, including Thailand, Vietnam, the Philippines, Indonesia, India, and Bangladesh, continue to face challenges with poverty.

The growth, quality, and health of rice are influenced not only by pathogens and pests but also by abiotic stresses (Figure 1). Challenges like drought, salinity, chilling, temperatures, and ultraviolet (UV) irradiation are increasingly impacting rice yield losses

due to global warming and climate change. Drought affects rice for the entire period of its growth [2]. During germination, it hampers the process by restricting water absorption, disrupting metabolic processes, and affecting adenosine triphosphate (ATP) production and respiration [3]. Drought also hinders the water flow to the phloem throughout of the plant growth, leading to reduced leaf size, stomatal closure, and impaired water conducting systems, which in turn decrease rice biomass and yield [4]. The most common toxicity of salinity is that it has inhibitory effect on enzyme activities, negatively impacts cell membrane functionality, and sodium (Na^+) excess in the cytoplasm interferes potassium (K^+) uptake [5]. The relationship between antioxidant capacity and salt tolerance has been examined in some plant species [5,6], as the level of antioxidants like malondialdehyde, and phenolic acids increased in response to salinity. UV radiation presents a significant challenge to rice cultivation. Due to the thinning of the ozone layer, more UV radiation is reaching the Earth's surface [7], and even a small increase in UV exposure can critically harm rice growth, significantly reducing yields [7]. Rice is also highly susceptible to low temperatures, a concern for crops grown in tropical and subtropical regions. Low temperatures during critical reproductive stages can adversely affect grain quality and reduce rice yield [8]. Both UV radiation and cold temperatures negatively impact rice plants at physiological, biochemical, and molecular levels, leading to lower yields and grain quality [9]. Exposure to UV radiation and cold can cause the formation of reactive oxygen species (ROS), resulting in oxidative stress [10]. This stress damages vital components of the rice plant, such as DNA, proteins, and membranes, thereby hindering growth [7]. To adopt and mitigate the adverse effects of these abiotic stresses, rice has evolved complex mechanisms and appropriate physiological and biochemical adaptations. The biochemical adoptions include the activation of signaling pathways and the synthesis of compounds such as momilactones to enhance plant's resilience to stress.

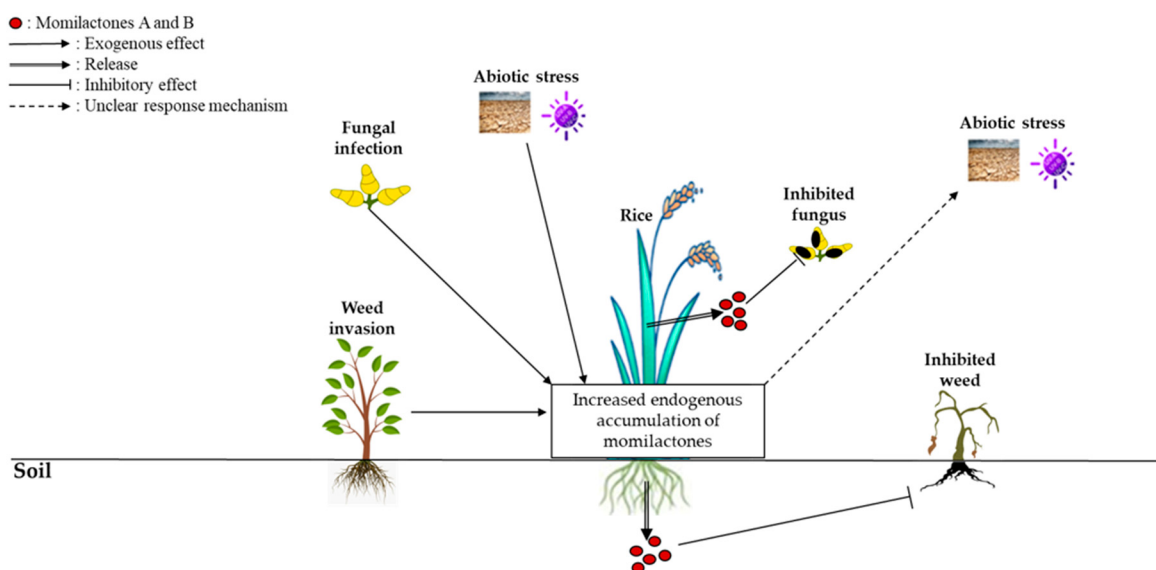


Figure 1. Potential role of momilactones in improving rice response to biotic and abiotic stresses.

Biotic stress in plants is caused by living organisms such as fungi, bacteria, viruses, and insects. In rice, the production of secondary metabolites is triggered not only by abiotic factors but also by plant infections and other biotic stressors. For instance, when rice is infected with *Pyricularia oryzae*, a highly destructive rice fungal pathogen, there is an observed increase in the plant's phenolic compounds [11,12]. The germination and growth of pathogens *Xanthomonas oryzae* pv. *Oryzae* [12] and *Magnaporthe oryzae* [13], which cause rice bacterial leaf streak, have been effectively inhibited using bio-extracts enriched with active metabolites from medicinal plants [12,13]. These bioactive compounds play crucial roles due to their antibacterial, antifungal, and antiviral properties, which com-

bat rice diseases and safeguard the plants from harm. Rice plants produce a variety of secondary metabolites including phenolic acids, flavonoids, terpenoids, and diterpenoids such as momilactones, phytocassanes, oryzalexines, and gibberellins. These compounds are crucial for several physiological functions, including antimicrobial, growth regulation, antioxidant, and allelopathic activities, aiding rice in stress resistance [14]. Rice has also developed self-defense strategies to mitigate the adverse effects of stress, involving both enzymatic defenses (like superoxide dismutase, catalase, glutathione reductase, ascorbate peroxidase, and peroxidase) and non-enzymatic defenses (such as tocopherol, ascorbic acid, and glutathione) [15,16]. These protective mechanisms can be categorized into physical and chemical responses. Physically, rice strengthens its cell walls with phenolic polymers and creates a protective cuticle layer on its leaves [17]. Chemically, it mobilizes enzymes to combat harmful microbes and accumulates secondary metabolites including phenolics, flavonoids, and momilactones [17]. In terms of biotic stress defense, rice relies on secondary metabolites like momilactones, known for their potent antifungal properties. These compounds gather around infection sites following a pathogen attack, providing a robust defense mechanism [18–23]. Utilizing plant secondary metabolites for biological treatment in rice offers a more environmentally friendly approach to disease management.

The discovery of momilactones was first made by Kato et al. [24]. The name “momilactone” originates from the Japanese word “momi”, translating to rice husk, and refers to any naturally occurring lactone derived from rice husks. In terms of their structure, momilactones are characterized by a (9 β -H)-pimarane framework, featuring a γ -butyrolactone ring at the 4th, 5th, and 6th carbon positions (Figure 2).

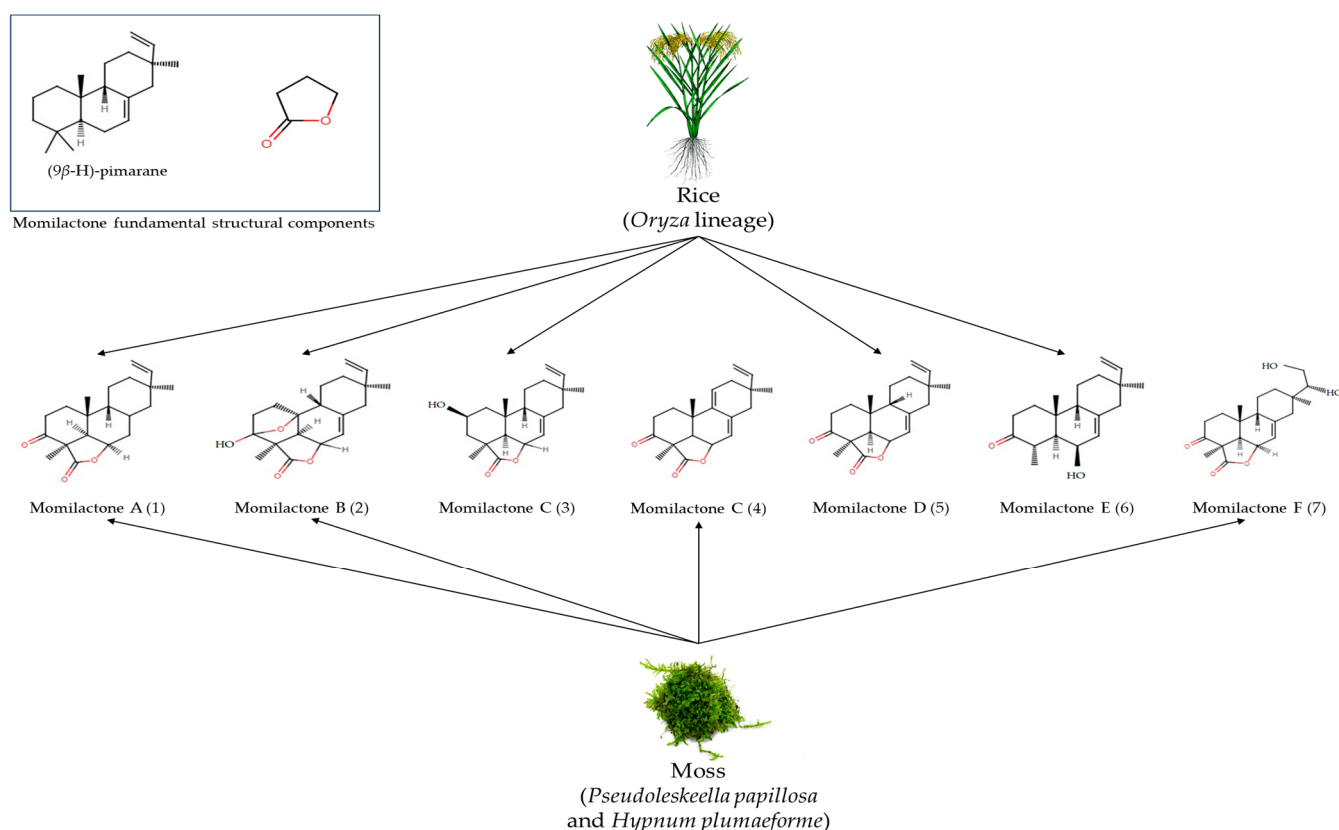


Figure 2. Momilactone structures and their plant sources. According to the literature, compounds (3) and (4) have both been identified as momilactone C. The classification of momilactone E is an erroneous categorization.

To date, seven momilactone molecules have been identified, namely momilactones A (MA), B (MB), C (MC), D (MD), E (ME), and F (MF) [24–29]. Among these, only MA (1), MB

(2), and MC (3) as shown in Figure 2 have been definitively identified in rice husks [24,26,27]. In contrast, MD (5) was extracted from rice roots [28]. The compound labeled as ME (6) was initially classified as a momilactone, but this was a misclassification since it does not contain a lactone group in its 19-nor-(9 β -H)-pimarane structure. Additionally, two compounds, (3) and (4), have been recognized as MC. However, only compound (3) was derived from rice husks [27]. The other two, compounds (4) (MC) and (7) (MF), were extracted from moss species, specifically *Pseudoleskeella papillosa* and *Hypnum plumaeforme*, respectively [29,30].

The significance of momilactones in the defense mechanisms of rice is apparent, as they have been noted for their increased accumulation in response to various stressors [25]. A number of momilactone-like substances have been identified in both rice and moss to date [31]. Although the biological activities and biosynthesis of momilactones are well-documented, their precise role in enhancing rice's tolerance to abiotic and biotic stress, as well as their potential to boost rice's health benefits, is yet to be fully understood. In this study, we present a detailed review of how rice responds to adverse conditions through the accumulation of momilactones and explore their potential health advantages for humans. We also engage in an in-depth discussion on the production of momilactones in rice plants and the factors affecting this process. Additionally, this paper aims to provide future insights, encouraging research into these unique metabolites as promising bioactive compounds for enhancing rice tolerance and aiding the pharmaceutical industry.

2. Literature Source and Search Methodology

To fulfill the objectives of this research, we conducted a comprehensive literature review focusing specifically on the role of momilactones in the growth, quality, and health of rice, particularly under abiotic and biotic stress conditions. The review process was carried out in four stages (Figure 3) and involved searching databases such as Web of Science, PubMed, and Google Scholar. During the initial identification phase, we used keywords including diterpenoids, momilactones, rice health, rice quality, biotic stress, and abiotic stress. This search yielded 350 articles in March 2023. Out of these, three hundred articles were thoroughly screened. Articles that were either duplicates or not relevant to the study's focus were excluded. In the end, a total of 255 papers were deemed suitable and were subsequently reviewed for this study.

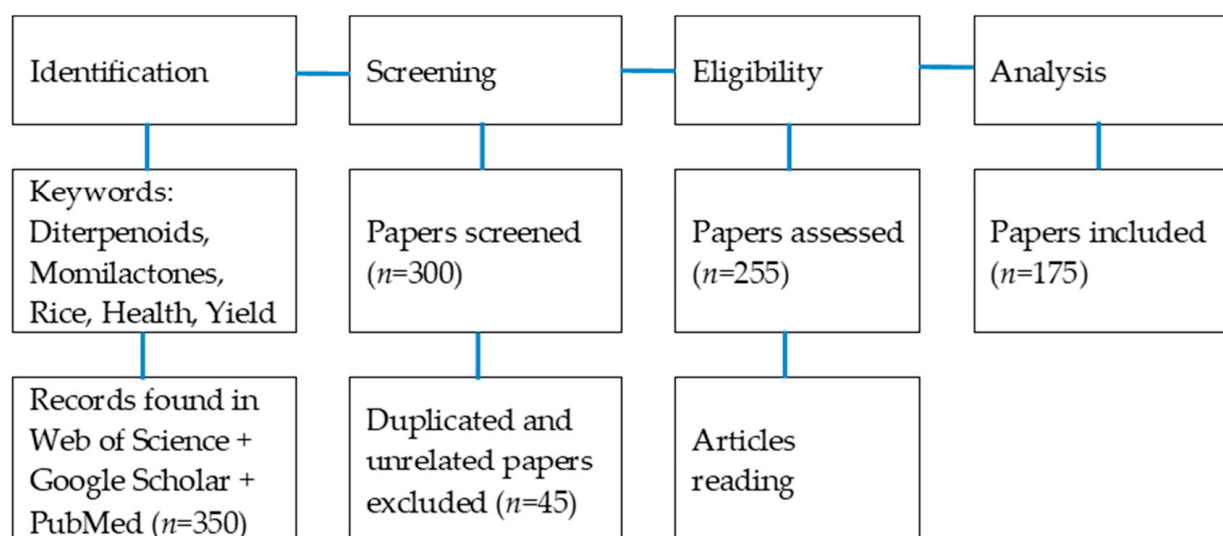


Figure 3. PRISMA flow diagram of the literature included in the review.

3. Rice Diterpenoids and Momilactones

The majority of diterpenoids in rice belong to a chemical category known as the labdane-related superfamily. This superfamily is diverse, encompassing not only the phytohormone gibberellins but also compounds like phytocassanes, oryzalexins, and momilac-

tones. These compounds play a critical role in the rice plant's defense mechanisms against both abiotic and biotic stress factors. So far, researchers have discovered 37 diterpenoid-based phytoalexin analogues in rice, which are organized into five distinct subgroups. These classifications are based on their biosynthetic pathways and structural features. The first group, the pimaradiene type, includes MA and MB, along with 9 β -pimara-7,15-diene-3 β ,6 β ,19-triol [32]. The second group, the ent-sandaracopimaradiene type, primarily comprises oryzalexins [33]. The third, known as the stemarene type, includes oryzalexin and stemar-13-en-2 α -ol [34]. The fourth type encompasses phytocassanes. Finally, the fifth group is the casbene type, which includes compounds such as 5-deoxo-ent-10-oxodepressin, 5-dihydro-ent-10-oxodepressin, and ent-10-oxodepressin [34,35].

3.1. Biosynthesis Pathway of Rice Diterpenoids

All isoprenoids are derived from a common five-carbon building block known as isopentenyl diphosphate (IPP) and its isomeric counterpart, dimethylallyl diphosphate (DMAPP) (Figure 4). In the plant kingdom, these precursors, IPP and DMAPP, are synthesized via two distinct pathways: the mevalonate (MVA) pathway occurring in the cytosol and the methylerythritol-4-phosphate (MEP) pathway located in the chloroplasts. Certain isoprenoids, including monoterpenes, diterpenes, carotenoids, tocopherols, and chlorophyll side chains, are produced through the MEP pathway. On the other hand, isoprenoids such as phytosterols, sesquiterpenes, triterpenes, and the side chain of ubiquinone are formed via the MVA pathway [36]. There is substantial evidence to suggest the MEP pathway's involvement in diterpenoid biosynthesis [37,38], although the possibility of some interaction between the MEP and MVA pathways has not been entirely dismissed [39,40]. Microarray studies have demonstrated a clear association between gene expression in the MEP pathway and the regulation of diterpenoid phytoalexins in cells treated with elicitors [37].

Isopentenyl diphosphate Δ -isomerase (IPPI) plays a pivotal role in catalyzing the reversible conversion of IPP to DMAPP. In the cytoplasm, IPPI is crucial for this conversion, and without it, the MEP pathway is impeded. However, in plastids, where both DMAPP and IPP are produced from 4-hydroxy-3-methylbut-2-enyl diphosphate (HMBPP) by the HMBPP reductase (HDR)—the final enzyme in the MEP pathway—the presence of IPPI is not strictly required [41]. In rice, two isoforms of IPPI, named OsIPPI1 and OsIPPI2, have been identified. A study by Jin et al. [36] investigated the subcellular locations of OsIPPI1 and OsIPPI2 by tagging these enzymes with synthetic green fluorescent protein (sGFP). Both isoforms were observed in the endoplasmic reticulum (ER), mitochondria, and peroxisomes, but only OsIPPI2 was found in plastids. Interestingly, the expression of the OsIPPI2 gene did not show a correlation with the accumulation of chlorophyll or carotenoids in plastids. This finding suggests that OsIPPI2 might act as a supplementary element in the MEP pathway rather than being essential. The presence of both OsIPPI1 and OsIPPI2 in the ER implies that in rice, DMAPP could be synthesized *de novo* within this organelle [36].

3.2. Biosynthesis of Momilactones and Related Genes

Geranylgeranyl diphosphate (GGDP) serves as the foundational precursor for a range of rice diterpenoid phytoalexins, including oryzalexins, phytocassanes, and momilactones. The synthesis of GGDP involves the use of two isoprenoids, isopentenyl diphosphate and dimethylallyl diphosphate. These isoprenoids are generated from pyruvate and glyceraldehyde-3-phosphate via the methylerythritol phosphate pathway (Figure 4) [41,42].

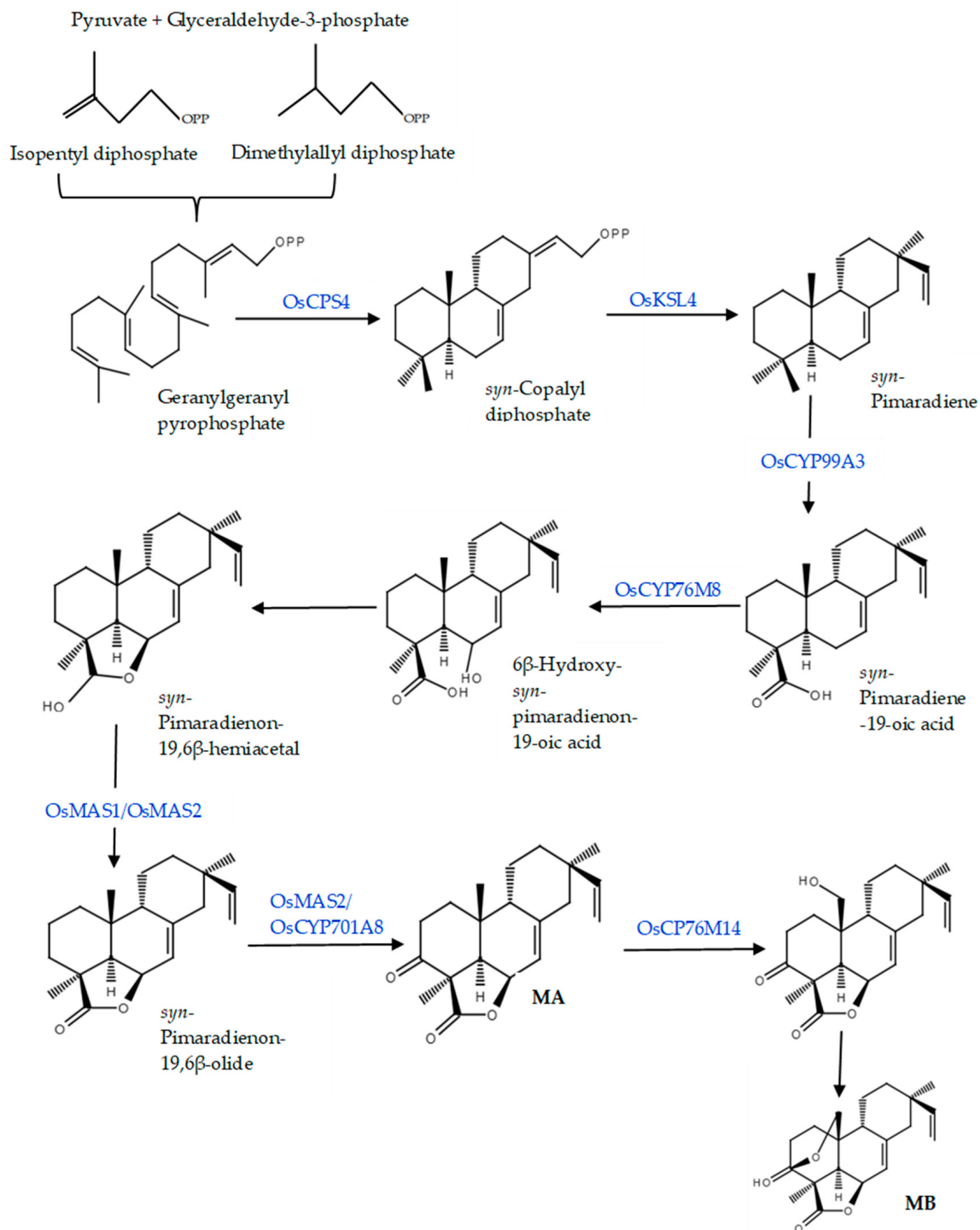


Figure 4. Biosynthetic pathway of momilactones.

This process involves converting GGDP into *syn*-copalyl diphosphate (*syn*-CDP) through the action of CDP synthases (*Os*-CPS4). Following this, *syn*-CDP is cyclized into *syn*-pimaradiene by *Os*KSL4. The cDNA for *Os*CPS4 was obtained from rice leaves subjected to UV irradiation. Both *Os*CPS4 and *Os*KSL4, which are located close to each other on chromosome 4, have been identified as having a sequential mechanism to produce *syn*-CDP and *syn*-pimaradiene [43,44]. Further metabolism of *syn*-pimaradiene is carried out by cytochrome P450 enzymes (CYPs). *Os*CYP99A3 oxidizes the C19 methyl group of *syn*-pimaradiene, resulting in *syn*-pimaradien-19-oic acid. Subsequently, *Os*CPY76M8 adds a hydroxyl group at the C6 position to produce 6β-hydroxysyn-pimaradienon-19-oic

acid. This is followed by the spontaneous closure of the ring between C19 and C6, forming *syn*-pimaradienon-19,6 β -hemiacet [39]. OsMS1 or OsMS2, also known as momilactone synthase, then converts the C19 hydroxyl group into a ketone, yielding *syn*-pimaradienon-19,6 β -olide [39]. This is further catalyzed by OsMS2 (or OsCPY701A8) to transform the C3 hydroxyl group into a ketone, leading to the formation of MA [22,24]. MB is synthesized through the spontaneous closure of the hemiacetal ring following the C20 hydroxylation of MA, a reaction conducted by OsCP76M14 [45,46].

According to earlier studies, the genes OsCPS4, OsKSL4, CYP99A2, CYP99A3, OsMS1, and OsMS2, which are instrumental in the synthesis of MA and MB, are located on chromosome 4 within the callus cells of rice [47,48]. However, there are still unidentified enzymes within the momilactones biosynthetic pathway that require further exploration. Notably, the principal enzymes responsible for the synthesis of MB have yet to be discovered, despite the compound being known for over five decades. Although many genes related to momilactone biosynthesis are grouped together in the genome, there are additional genes outside this cluster that are vital, yet their identification poses a more intricate challenge. Gaining a deeper understanding of the momilactones biosynthesis pathway, including the functions of the associated enzymes and genes, is essential for furthering research into the natural production of momilactones in plants. Specifically, the application of genetic modification techniques, such as marker-assisted selection (MAS) and marker-assisted backcrossing (MABC), could be pivotal in enhancing host plants to accumulate higher levels of these target compounds.

4. Distribution of Momilactones in Rice and Their Correlation with Rice Growth and Quality

4.1. Distribution of Momilactones in Rice Plant Organs

Rice plants produce allelochemicals and phytoalexins, like MA and MB, in varying amounts across different stages of growth, influencing plant growth and physiological responses to environmental stresses. The internal concentrations of MA and MB in various rice organs have been quantified under a range of experimental settings, including different rice varieties, treatments, and growth conditions (Table 1). It has been noted that japonica rice varieties accumulate more momilactones than indica varieties. In japonica varieties, the levels of MA and MB were found to be 157 and 83 $\mu\text{g/g}$, respectively, whereas in indica varieties, these levels ranged from 20.7 to 4.9 $\mu\text{g/g}$ for MA and MB, respectively [17]. The concentration of MA and MB peaks up to the flowering stage and then begins to decline during the reproductive phase. Research indicates that a single rice plant can emit 2.1 μg of MB daily [49]. In 80-day-old rice plants, MB concentrations were recorded at 74.3 $\mu\text{g/g}$ in shoots and 21.2 $\mu\text{g/g}$ in roots, with the shoot concentration being 3.5 times higher than that in the roots [50]. Rice varieties with higher levels of MA and MB are more adept at handling stress [24,25,34,49]. Additionally, variations in allelopathic capabilities among different rice types have been observed, potentially linked to differences in the amounts of momilactones released into the environment [24,42].

Table 1. Concentration of MA and MB in different parts of rice.

Compound	Plant Part	Concentration ($\mu\text{g/g}$)	Reference
MA	Root	8.06	[47,50]
	Leaf	4.28	[17,44,51]
	Husk	16.44	[44,52]
	Bran	6.65	[53]
	Grain	2.07	[54]
	Root	5.69	[48,50,55]
MB	Leaf	12.73	[44,50,51]
	Husk	9.24	[44,52]
	Bran	6.24	[53]
	Grain	1.06	[54]

Gaining a thorough understanding of how momilactones are distributed in various plant sources is crucial for developing effective methods and strategies to utilize them beneficially. Initially, momilactones were identified in cultivated rice varieties (*Oryza sativa* L.). In a notable study in 2015, Cho et al. [28] isolated MD and ME from rice roots [28]. Recent improvements in detection and quantification technologies have enabled the identification of momilactones in different rice parts, including the grain and bran [53]. Momilactone contents were analyzed in 99 rice varieties, revealing that the highest concentrations were found in Korean rice types, especially those characterized by awns and a late maturity [25].

Beyond cultivated varieties, momilactones have also been found in wild rice species [17]. Notably, species possessing the AA genome, such as *Oryza sativa*, *Oryza rufipogon*, *Oryza barthii*, *Oryza glaberrima*, *Oryza glumaepatula*, and *Oryza meridionalis*, as well as those with the BB genome, like *Oryza punctata*, have been identified to contain momilactones. In contrast, species with the FF genome, such as *Oryza brachyantha*, have not shown the presence of these compounds [17].

4.2. Momilactones and Rice Quality

Rice quality is determined not just by genetic factors but also by the interactions between starch, proteins, and lipids under varying environmental conditions. Additionally, the chemical composition of rice grains, including both primary and secondary metabolites with low molecular weight, plays a significant role in determining rice quality through their biological activities [56]. There is a notable relationship between rice quality and specific metabolites, particularly those involved in amino acid, lipid, and citrate cycle metabolism [52]. A range of other phytochemicals such as flavonoids, phenolic acids, carotenoids, polyunsaturated fatty acids, and glucosinolates are important nutrients that contribute to human health, with their benefits extending to the effective prevention of clinical diseases [57,58]. Therefore, researching and examining the changes in metabolites that enhance rice quality is valuable for understanding the metabolic processes that can improve the quality of rice.

Kakar et al. [59] reported that MA and MB in rice grain, husk, and straw showed a positive correlation with grain amylose content and antioxidant activity. However, they observed a negative correlation between these compounds and both taste score and yield. This suggests the need for further research to accurately determine the relationship between MA and MB and the overall quality of rice grains. Studies have shown that mutant rice lines with higher protein and lower amylose levels contain greater amounts of MA and MB compared to their original cultivars [59]. While it is known that amylose affects protein content through down-regulating starch enzyme (ISA2), the specific link between momilactones and protein content has been relatively unexplored. The mechanisms of this interaction remain unclear. Considering the correlation of momilactones with grain amylose content, more in-depth research is needed to understand the interactions between protein, amylose, and other micronutrients like calcium (Ca), magnesium (Mg), iron (Fe), and zinc (Zn) in relation to momilactones for improving rice varieties with high quality and bioactive compounds. This should include genetic analysis for a more complete comprehension of these relationships.

5. Involvement of Momilactones in Rice Response to Stresses

5.1. Involvement of Momilactones in Rice Resistance against Abiotic Stress

In research conducted by Xuan et al. [60], they observed that the accumulation of secondary metabolites, such as MA and MB, could potentially contribute to enhancing the tolerance of rice to abiotic stresses. The scientists investigated the effects of drought and salinity on various types of rice, including commercial hybrid, sticky, indica, and japonica varieties. They noted a significant increase in the levels of rice MA and MB in response to drought and salinity, ranging from 81.6 to 108.1 µg/g dry weight (DW) depending on the rice type and origin. The study's correlation analysis indicated a strong relationship between drought and salinity tolerance and the accumulation of MA (with correlation

coefficients of 0.65 and 0.16, respectively) and MB (with correlation coefficients of 0.11 and 0.27, respectively). Another study reported that mutant rice lines (TBRI, M2, and M3) exhibited higher MB levels (46.3, 34.9, and 20.5 ng/g DW, respectively) in response to salinity stress compared to their original cultivars [53]. This observation suggests that MA and MB may indeed play a role in enhancing rice tolerance to drought and salinity stresses, although further confirmation is required.

Anh et al. [61] conducted a study to examine the changes in the internal concentrations of MA and MB in response to chilling and UV stresses. They observed that, after 4 h of treatment, MA and MB levels were significantly reduced (approximately 3.5 and 2.2 times lower, respectively) compared to the control group, suggesting that MA and MB may not contribute significantly to rice's cold resistance (Table 2). However, when the duration of chilling treatment was extended to 8 h, the amount of MB increased. On the contrary, when rice leaves were exposed to UV stress, both MA and MB contents significantly increased, ranging from 3.6 to 6.4 times higher than in the control group [61]. These findings suggest that MA and MB may play a role in the physiological responses of rice to UV stress and low temperatures. Gene analysis revealed that under UV stress, the expression levels of CYP99A3, Os-MAS, OsMAS2, OsKSL4, and OsCPS4 genes increased, while these genes showed decreased expression under chilling stress (Table 2).

In the extracts of rice seedlings subjected to FeCl₂ treatment, the level of MB exhibited a 1.9-fold increase compared to the control. Additionally, the concentration of MB in the extracts of rice seedlings treated with CuCl₂ increased by 3.7 times when compared to the control, as reported by Kato-Noguchi [62] (Table 2). These results suggest that heavy metal treatments, specifically FeCl₂ and CuCl₂, lead to an elevated production of MB in rice seedlings. Researchers have implied that the heightened production and release of MB in response to heavy metal exposure in rice could potentially enhance the allelopathic activity of rice, given its potent phytotoxic effects.

Table 2. Variation of MA and MB in rice under different stresses.

Rice Type	Stress	MA Content (% Increase/Decrease over Control)	MB Content (% Increase/Decrease over Control)	Relevant Gene Expression	References
Japonica and Indica	Drought (4–7 days)	68%	30%	nd	[60]
Japonica	Salinity (5–12 dSm ^{−1} NaCl)	15.4%	90%	nd	[51,60]
Japonica (Koshihikari)	Chilling (6 °C)	−78%	−44%	Decreased expression of OsCPS4, OsKSL4, CYP99A3, OsMAS, and OsMAS2	[61]
Japonica (Koshihikari)	UV (2–8 h)	75%	80%	Increased expression of CYP99A3, OsMAS, OsMAS2, OsKSL4, OsCPS4	[61,63,64]
Japonica (Koshihikari)	Heavy metals (FeCl ₂ , CuCl ₂)	nd	50–72%	nd	[62]

—decrease over control; (nd), further study.

While there has been extensive research on the changes in the internal levels of MA and MB in response to drought, salinity, and heavy metals, there has been a limited investigation into the regulation of momilactone biosynthetic genes in rice under these stress conditions. Furthermore, the combination of genetic engineering techniques with advanced methods and a comprehensive rice genome database presents a highly efficient approach to bolster rice's resilience to various stresses. This approach is specifically geared towards enhancing the production of stress-tolerant secondary metabolites, such as phenolics and momilactones. Addressing these areas of uncertainty has the potential to open up new

avenues for innovative research strategies aimed at improving rice tolerance in adverse conditions. Additionally, expanding research into the abundance of secondary compounds and the corresponding gene expressions holds promise for safeguarding rice production from the impacts of environmental stresses.

5.2. Involvement of Momilactones in Rice Resistance against Biotic Stress

5.2.1. Antifungal Activity

Plants have evolved a range of mechanisms to protect themselves from pathogens, which can be broadly classified into two categories: physical defenses and chemical defenses. Physical defenses encompass strengthening cell walls with phenolic polymers when under pathogenic attack, along with the presence of a protective cuticle layer on the surfaces of leaves. In contrast, chemical defenses involve the synthesis of antimicrobial enzymes and the accumulation of specific toxic compounds, which may include momilactones that were isolated later from rice leaves as phytoalexins [26,42,63].

Rice blast, a highly destructive disease affecting rice crops worldwide, is caused by the infection of *Magnaporthe oryzae* (also known as *Magnaporthe grisea* and *Pyricularia grisea/oryzae*). Researchers have investigated the antifungal properties of MA and MB using inhibition assays targeting the germination of conidia and the elongation of germ tubes in rice blast (Table 3). Prior studies have demonstrated that MA and MB exhibit potent anti-*M. oryzae* properties, displaying the most robust effectiveness against both spore germination and germ tube growth in the fungus [31]. In the case of *P. oryzae*, the germination of conidia was inhibited by 30% and 50% when MA was applied at concentrations of 300 and 1000 µM, respectively [17]. In another study, MB displayed the strongest inhibitory effect on the growth of *Botrytis cinerea*, with an IC₅₀ value of 1.2 mg, while MA had a considerably higher IC₅₀ value of 78.1 mg against this fungus [65]. It has been observed that the phytotoxic activities of both MA and MB vary depending on the type of fungus. These findings suggest that increasing the production of MA and MB following a pathogenic infection could potentially aid in inhibiting the growth and dissemination of fungal infections.

Table 3. Antifungal and allelopathic activities of momilactones.

Compound	Rice Type/Variety	Plant Part Used for Isolation	Activity and Model Organism	Observations *	References
MA	Japonica, (Koshihikari, and Akitakomachi)	Coleoptiles and, Husk	Antifungal (<i>P. oryzae</i> , <i>M. oryzae</i> , <i>B. cinerea</i> , <i>F. solani</i> , <i>C. gloeosporioide</i> , and <i>F. oxysporum</i>)	IC ₅₀ (µg/mL): 78 to 198	[17,31,63,65,66]
MB	Japonica (Koshihikari and, Nipponebare)	Seedlings	Allelopathic (<i>E. galli</i> , <i>Lepidum sativum</i> L. and <i>Arabidopsis thaliana</i>)	Inhibition (%): 2 to 9	[49,67–72]
	Japonica, (Koshihikari, and Akitakomachi)	Husk and, Bran	Antifungal (<i>P. oryzae</i> , <i>M. oryzae</i> , <i>B. cinerea</i> , <i>F. solani</i> , <i>C. gloeosporioide</i> , and <i>F. oxysporum</i>)	IC ₅₀ (µg/mL): 53.4 to 137.4	[17,31,63,65,67]
	Japonica (Koshihikari and, Nipponebare)	Seedlings	Allelopathic (<i>E. galli</i> , <i>Lepidum sativum</i> L. and <i>Arabidopsis thaliana</i>)	Inhibition (%): 14 to 40	[49,66,68–72]
MC	Koshihikari	Seeds	Allelopathic (<i>L. sativa</i>)	IC ₅₀ (mg/mL): 1.0	[27,73]

* The value varied depending on method.

5.2.2. Allelopathic Activity

An effective approach for mitigating the impact of weeds on crop cultivation involves bolstering the innate competitive abilities of crops in their proximity. Over time, plants

have evolved diverse strategies for competing with their environment. One noteworthy strategy amid these environmental challenges is the production and release of specific chemicals by certain plant species, which can exert control over the growth or germination of neighboring plants. This phenomenon is termed allelopathy and can be thought of as a form of chemical defense. To assess the contribution of MA and MB to allelopathic activity, researchers have utilized various rice extracts and purified momilactones to assess their inhibitory effects on weed species (Table 3). According to Kato et al. [66], the IC_{50} values for MA against *Echinochloa crus-galli* shoots and roots were estimated at 146 and 91 $\mu\text{M/L}$, respectively, while for MB, these values were 6.5 and 6.9 $\mu\text{M/L}$, respectively. This implies that MB had a significantly stronger inhibitory effect compared to MA, being 22 times more potent on *E. crus-galli* shoots and 13 times more effective on roots. Moreover, rice extracts obtained from a single-incubation assay inhibited the growth of *E. crus-galli* roots and shoots by 15% and 12%, respectively. In contrast, extracts from a mixed-incubation assay involving rice and *E. crus-galli* significantly suppressed the growth of *E. crus-galli* roots and shoots, resulting in reductions of 79% and 75%, respectively. Additionally, MC was reported to inhibit the germination rate of *Lactuca sativa* by 50%. These findings suggest that rice allelopathy could be one of the defense mechanisms triggered through chemical interactions between rice and weed plants. This induced allelopathy holds the potential to provide rice with a competitive advantage by restraining weed growth. Although momilactones potential on weed management have been extensively studied, their environmental degradation has not been thoroughly investigated. Only one study conducted in 2006 provided information on momilactone concentrations in the soil at various stages of rice straw decomposition. This research found that MB was not detected in the soil after 90 days of decomposition, indicating that it could potentially undergo soil degradation within a 90-day period, although the specific mechanism of degradation remained unclear [25].

6. Contribution of Momilactones to Human Health Benefits

Momilactones exhibit a broad spectrum of biological effects. In addition to comprehensive investigations into their allelopathic properties, we also emphasize their potential applications in the treatment of particular chronic illnesses and cancer. We conduct a comparative analysis of momilactones' effectiveness when compared to commonly used medications. Furthermore, we delve into the mechanisms underlying their actions. Based on this information, we provide a comprehensive overview of the current achievements, constraints, and hurdles. The multifaceted medicinal and pharmaceutical potential of momilactones is summarized in Figure 5

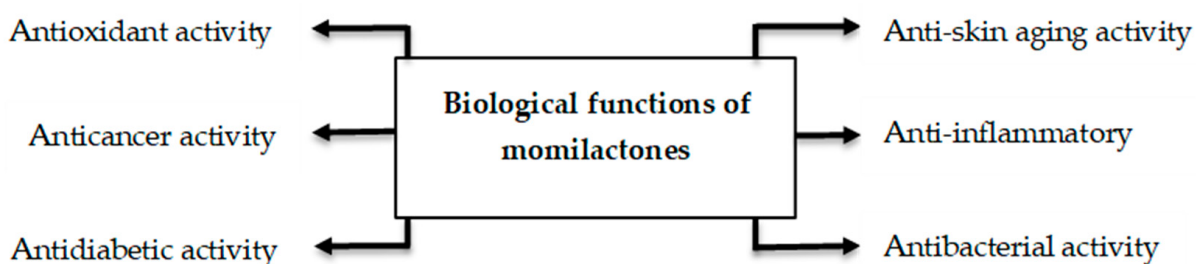


Figure 5. Biological functions of MA and MB.

6.1. Antioxidant Activity

The antioxidant properties of MA and MB have been assessed using both the reducing power and 2,2'-azino-bis radical cation (ABTS) assays [53,54,65]. According to the ABTS assay results, it was noted that both MA and MB exhibited comparatively lower activity, with IC_{50} values of 2.8 and 1.3 mg/mL, respectively, in contrast to the standard antioxidant, butylated hydroxytoluene (BHT, IC_{50} 0.08 mg/mL) [53,54] (Table 4). In the reducing power assay, these compounds also displayed a weaker antioxidant activity when compared to

other secondary metabolites found in rice, such as benzoic acid, *p*-hydroxy-benzoic acid, *p*-coumaric acid, vanillic acid, caffeic acid, syringic acid, and protocatechuic acid [65]. The antioxidant potential of MA and MB, as assessed through the aforementioned methods, was found to be less potent than the established standards. As a result, for obtaining more precise measurements of the anti-radical capabilities of MA and MB, it is advisable to conduct antioxidant capacity assays using alternative reference standards such as 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (trolox), ascorbic acid, and butylated hydroxyanisole (BHA). The use of these standards would offer a more dependable basis for comparing and evaluating the antioxidant potential of MA and MB.

Table 4. Pharmacological activities of MA and MB.

Compound	Rice Variety	Plant Part Used for Isolation	Activity	Assay	Inhibitory Effects *	References
MA	Japonica/Koshihikari	Husk, grain	Antioxidant	ABTS, Reducing Power	IC ₅₀ (mg/mL): 2.8 EC ₅₀ (μg): 783	[54,65]
	Koshihikari	Husk, bran	Anti-leukemia Anti-lymphoma	HL-60 U-937	- -	[74–78]
	Koshihikari	Husk, bran	Antidiabetic	α-Amylase α-Glucosidase	IC ₅₀ (μg/mL): 133 IC ₅₀ (μg/mL): 182	[53,58,76]
	Koshihikari, Shinnosuke	Grain	Anti-skin aging	Elastase Tyrosinase	Inhibition (%): 30.9 Inhibition (%): 37.6	[79]
	Japonica	Roots	Anti-inflammatory	LPS-stimulated NO production	IC ₅₀ (μg/mL): 0.53	[28]
	Japonica, (Koshihikari, and Akitakomachi)	Husk	Antibacterial	<i>E. coli</i> <i>P. ovalis</i> <i>B. cereus</i> B. <i>pumilus</i> <i>M. aeruginosa</i>	Inhibition (mm): 11 to 17	[31,63,65,80,81]
MB	Japonica/Koshihikari	Husk, grain	Antioxidant	DPPH ABTS	IC ₅₀ (mg/mL): 1.3 EC ₅₀ (μg): 790	[54,65]
	Koshihikari	Husk, Bran	Anti-leukemia Anti-lymphoma	HL-60 U-266	IC ₅₀ (μM): 4.49 IC ₅₀ (μM): 5.09	[74,78]
	Koshihikari	Husk, Bran	Antidiabetic	α-Amylase α-Glucosidase	IC ₅₀ (μg/mL): 129.02 to 146.85 IC ₅₀ (μg/mL): 612.03	[53,58,76]
	Koshihikari, Shinnosuke	Grain	Anti-skin aging	Pancreatic elastase Tyrosinase	Inhibition (%): 18.5 Inhibition (%): 12.6	[54,79]
	Japonica, (Koshihikari, and Akitakomachi)	Coleoptiles and, Husk	Antibacterial	<i>E. coli</i> <i>P. ovalis</i> <i>B. cereus</i> B. <i>pumilus</i> <i>M. aeruginosa</i>	Inhibition (mm): 14.2 to 17.2	[31,63,65,80,81]

* The value varied depending on method.

6.2. Anticancer Potential

Research findings have unveiled the potential of MA and MB as agents against cancer. MA exhibited the least potent impact on normal, leukemia, and multiple myeloma cell lines, whereas MB and MAB (a mixture of MA and MB in a 1:1 ratio) exhibited significant suppression of these cell lines at concentrations of 5 μM [68,69]. The inhibition of leukemia cell viability by MA was 30.25% [74,75], whereas MB achieved inhibition rates ranging from 40% to 80% [70,74,76] at a concentration of 10 μM. Moreover, MB and MAB induced apoptosis in leukemia cells while having a minimal effect on non-cancerous (MeT-5A) cells at 5 μM [74]. In the quest for suitable candidates for the development of new anticancer medications, it is crucial to identify compounds capable of effectively eliminating cancer cells with an IC₅₀ value equal to or less than 5 μM [77,78]. In this regard, both MB and MAB, with their IC₅₀ values hovering around 5 μM, hold promise as potential substances for the advancement of anti-leukemia and anti-myeloma drugs.

6.3. Antidiabetic Potential

MA and MB have displayed potential for antidiabetic activity by inhibiting enzymes relevant to type 2 diabetes, including α -amylase and α -glucosidase. Both MA and MB exhibited inhibitory effects against porcine pancreatic α -amylase, with IC₅₀ values of 132.56 and 129.02 mg/mL, respectively, as well as against α -glucosidase, with IC₅₀ values of 991.95 and 612.03 mg/mL, respectively [48,53,58]. Results from in vitro assays indicate that MA and MB exerted a stronger inhibitory effect on α -amylase and α -glucosidase compared to γ -oryzanol, a standard inhibitor against α -amylase and α -glucosidase found in rice bran [80].

6.4. Anti-Skin Aging Potential

In laboratory tests, MA and MB displayed noteworthy inhibition of elastase and tyrosinase, two enzymes linked to skin wrinkles and freckles. At a concentration of 2 mg/mL, MA inhibited 30.9% of pancreatic elastase activity and 37.6% of tyrosinase activity, whereas MB exhibited lower inhibition, suppressing only 18.5% of elastase activity and 12.6% of tyrosinase activity [79]. Due to these valuable therapeutic attributes, MA and MB hold potential as viable candidates for the development of skin-enhancing supplements.

6.5. Anti-Inflammatory Potential

MA, MD, and ME were identified as agents that reduce the production of nitric oxide (NO) induced by LPS, with respective IC₅₀ values of 1.7, 46.5, and 30.3 μ M [25,28]. However, it is important to note that MA exhibited considerable cytotoxicity against RAW264.7 cells, with an IC₅₀ of 9.6 μ M. In contrast, MD and ME displayed moderate inhibitory effects on the growth of RAW264.7 cells, with IC₅₀ values surpassing 100 μ M. According to the findings of Cho et al. [28], MA, MD, and ME effectively suppressed inflammatory responses in macrophages by inhibiting NO production.

6.6. Antibacterial Activity

Both MA and MB possess antibacterial properties, although their effectiveness varies depending on the bacterial strain. MB exhibits stronger antibacterial capabilities compared to MA, except when it comes to *Escherichia coli*, where MA effectively inhibits its growth (17 mm). Specifically, MB effectively suppresses and reduces the growth of three bacteria: *Pseudomonas ovalis* (17.2 mm), *Bacillus cereus* (15.5 mm), and *Bacillus pumilus* (14.2 mm) [65]. In addition to its antibacterial properties, MA also displayed inhibitory effects on the mycelia growth of cyanobacteria *Microcystis aeruginosa* (*M. aeruginosa*) [81], and the mushroom species *Coprinus cinereus* (5 μ g/disc) [82]. The above-mentioned bacteria are involved in various diseases in humans. For instance, *Bacillus cereus* is a type of rod-shaped and gram-positive that can thrive in different temperatures and pH levels. When this bacterium contaminates food, it can cause two kinds of illnesses: one that leads to vomiting (emetic) and another causing diarrhea [83]. *Bacillus pumilus* has toxic properties; it has cytopathic effects in Vero cells, haemolytic activity, and proteolytic action on casein [84]. Also, it is associated with food poisoning incidents [84].

7. Future Research

7.1. Momilactones Distribution in Rice

Momilactones are recognized as natural defense mechanisms that have evolved in both rice and moss [24,25,27,31,49]. These compounds have been identified in various parts of rice plants. However, there is a need for further research to assess the natural variation in momilactone levels across different growth stages in a wide range of rice genotypes. Additionally, investigating the expression of relevant biosynthetic genes is essential to comprehend how these compounds vary among different rice varieties. Although there may be a modest correlation between the levels of MA and MB and certain indicators of rice grain quality, further investigations are required to fully elucidate this relationship. It has been observed that MA and MB contents are correlated with amylose content [59].

Moreover, rice mutant lines with high protein levels have shown elevated MA and MB levels [51]. Nevertheless, establishing the exact correlation between MA and MB and rice quality parameters (such as protein, amylose, and lipid contents) as well as the genes associated with these parameters is a task that needs further identification and exploration. Alternatively, based on the distinctive traits (such as color, whiteness, stickiness, aroma, etc.) of the studied rice cultivars, researchers can propose markers for rapidly identifying rice varieties with high momilactone contents. For instance, Chung et al. [81] observed that rice varieties with awns and late maturity tend to exhibit increased levels of MA and MB, although many of these varieties are not commercially available. Only a handful of commercial rice varieties, like eight well-known Japanese cultivars, have had their MB levels quantified [85]. However, these experiments have primarily focused on rice varieties with similar backgrounds. To fully harness the potential health benefits of momilactones, it is crucial to conduct comprehensive investigations into their presence across various commercially available rice varieties. This not only aids in identifying rice cultivars rich in momilactones for production purposes but also expands their potential applications. As of now, the correlations between momilactone accumulation and rice quality, along with other bioactive compounds such as phenolics and flavonoids in commercially available rice, remain unclear.

7.2. Potential Contribution of Momilactones in Rice to Stress Tolerance

Momilactones, categorized as labdane-related diterpenoids, utilize GGDP as their common starting material, in conjunction with gibberellic acid (GA), during their biosynthesis. More specifically, their formation involves a sequential process that employs two distinct sets of diterpene synthases and cyclases [86]. GA has been identified as a significant factor contributing to a plant's ability to withstand various abiotic stresses, including cold, salt, osmotic, and submergence conditions [87]. Moreover, momilactones have been validated as responsive agents against environmental stressors, such as weed invasion [62], salinity [51,62,88,89], drought [60], chilling [61], nutrient deficit [90], and exposure to cantharidin [90].

The biosynthesis of momilactones can be influenced by both jasmonic acid (JA)-dependent and JA-independent pathways [42]. Rakwal et al. [91] reported that when CuCl_2 was applied, the presence of inhibitors targeting JA biosynthesis (e.g., quinacrine, nordihydroguaiaretic acid, and salicyl hydroxamic acid) resulted in a decrease in the accumulation of MA in rice. Conversely, the exogenous application of JA was found to increase the production of endogenous MA in rice [92], indicating that JA plays a role in triggering the biosynthesis of MA. In addition to JA, the exogenous application of salicylic acid also enhanced momilactone production in rice, although the precise mechanism behind this effect remains uncertain [92]. Xuan et al. [60] reported that MA and MB were involved in rice's response to environmental stresses, such as drought and salinity, rather than primarily contributing to weed resistance. Under saline conditions, the exogenous application of fulvic acid and magnesium sulfate (MgSO_4) led to an increased accumulation of MA and MB in rice, suggesting an enhanced capacity of rice plants to withstand salt stress [88,89]. These observations suggest that momilactones may have significant roles in a plant's defense mechanisms against unfavorable growth conditions. However, the exact nature of their contribution remains unclear. In another study, the biosynthesis of momilactones in rice, when co-cultivated with barnyard grass, exhibited a biosynthesis pattern parallel to that of GA [93]. Consequently, there is a hypothesis suggesting that momilactones might function as signaling molecules in rice's physiological responses to adverse conditions. Following these studies, questions arise about whether momilactones act as phytohormones in rice and moss. Further exploration is needed to investigate this question and uncover the relationship between momilactones and phytohormones associated with resistance in rice under biotic and abiotic stress conditions.

7.3. Improving Momilactone-Based Products for Pharmaceutical Purposes

Momilactones, specifically MA and MB, have garnered recent attention for their potential applications in the fields of medicine and pharmaceuticals. Conversely, the use of anti-cancer drugs like doxorubicin has been known to induce oxidative stress by generating free radicals [94], with a heightened risk of causing various chronic disorders such as diabetes, obesity, and skin diseases [95]. A recognized approach to address these concerns involves the utilization of antioxidant compounds to manage chronic conditions. However, most clinical studies conducted on patients have yielded unfavorable outcomes, possibly due to the limited efficacy of potent antioxidant compounds in preventing specific diseases [96]. Consequently, momilactones, with their potential to simultaneously counteract oxidative stress, chronic illnesses, and cancer, may emerge as viable candidates for advancing effective treatments for individuals affected by these conditions [69]. However, it is important to note that nearly all investigations into the pharmacological effects of momilactones have been confined to laboratory-based methods. To unlock their full potential for medical, pharmaceutical, and practical applications, rigorous validation processes are essential. Additionally, the safety aspects of these products must undergo thorough evaluation and assessment [97]. Furthermore, it is crucial to underscore that determining optimal dosages is critical to maximize their beneficial effects while mitigating potential risks, such as neurotoxicity and hepatotoxicity [98]. Another aspect to consider is that the interactions among these compounds may hold greater significance than their individual effects. Such interactions could potentially enhance therapeutic effectiveness by targeting multiple mechanisms, reducing adverse effects, and overcoming drug resistance [99–101]. Quan et al. [58] reported that the combination of MA and MB exhibited higher antioxidant capacity compared to each compound individually. Therefore, exploring the potential of using momilactones in conjunction with other bioactive substances for the treatment of human diseases represents a promising avenue for future research (Figure 6).

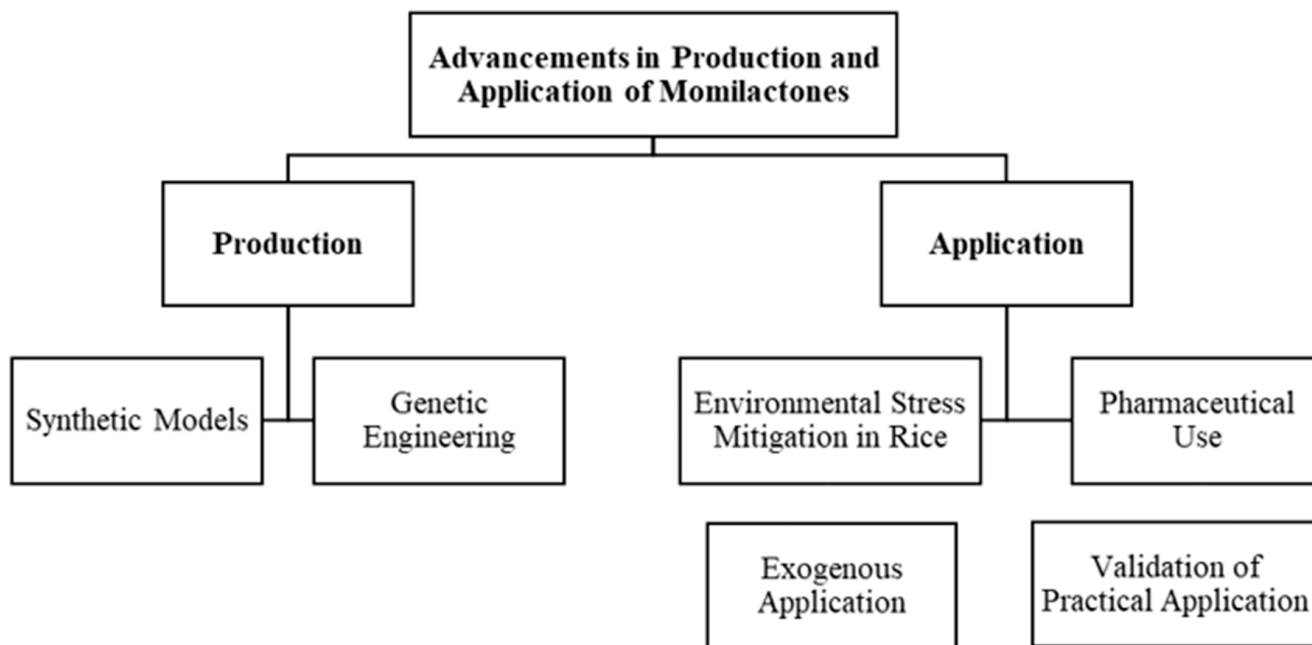


Figure 6. Future research directions for momilactones.

7.4. Promising Approaches in Exploiting Beneficial Properties of Momilactones

Extracting momilactones from plant sources poses a considerable challenge given their limited presence in small quantities [52,53]. Furthermore, these compounds are not commercially available, which has resulted in restrictions on research regarding their

utilization and practical applications. As a response to these challenges, this section introduces promising strategies aimed at overcoming these limitations.

7.4.1. Synthetic Models

The challenging task of isolating momilactones from natural sources may find a hopeful solution through synthetic models. Notably, significant efforts have been directed towards producing a fundamental component of the momilactone structure, namely, the 9 β -H pimarane skeleton [102]. Additionally, various promising intermediate compounds essential for MA biosynthesis, including ($\pm$)-4,4-Dinor-(9 β H)-pimara-7,15-diene [103,104], (9 β -H)-Pimara-7,15-diene [105], and 3 β -hydroxy-(9 β -H)-pimara-7,15-diene [106], have been successfully synthesized using straightforward methods. However, it is worth noting that there are no documented reports indicating the conversion of these intermediates into MA. Furthermore, there is currently no synthetic method available for producing MB and other momilactones. From another perspective, the synthesis and structural modification of these compounds hold the potential to enhance their biological activities and stability [107,108].

7.4.2. Genetic Engineering

Genetic manipulation represents an additional viable approach that can aid in harnessing the potential of momilactones. More specifically, techniques such as induced gene expression, metabolic engineering, and genetic modification could potentially be employed to enhance the natural production of momilactones within plant sources, thereby augmenting their associated biological activities [109].

As substantiated by evidence, the upregulated expression of transcription factors such as OsTGAP1 [110], CIPK15 [111], ACDR1 [112], RAC1 GTPase [113], SBP [114], and the Spl18 mutant [115] has led to the rapid synthesis of momilactones in rice. Furthermore, Kakar et al. [59] observed that N-methyl-N-nitroso-urea-induced mutations resulted in increased accumulation of MA and MB in mutant rice lines. Therefore, gaining a comprehensive understanding of the biosynthetic pathways driven by enzymes and the relevant gene expression can facilitate the production of larger quantities of momilactones in rice plants [25].

To date, momilactone biosynthetic genes (MBGs) have been validated, and their functions have been confirmed through knockdown assays [116,117]. Notably, an online-accessible database containing essential genes involved in the momilactone biosynthetic pathway (MBP) can be found in the National Center for Biotechnology Information (NCBI) GenBank [118]. This database provides valuable resources for sequence analysis and primer design [116]. However, there are still enzymes within the MBP that have not been fully elucidated and require further investigation. Specifically, the key enzymes associated with MB biosynthesis have remained elusive despite the compound being known for quite some time. Conversely, while many MBGs have been clustered within the genome, identifying genes beyond this cluster poses challenges [119]. Expanding our comprehension of the MBP, including the functions of associated enzymes and genes, can support research aimed at enhancing the natural production of momilactones in plants. In particular, the implementation of genetic modification techniques like MAS and MABC may prove beneficial in improving host plants to yield higher quantities of these compounds.

8. Conclusions

In this paper, an in-depth exploration is conducted to thoroughly examine the potential impacts of momilactones on various aspects of rice, encompassing growth, quality, and defense mechanisms against both abiotic and biotic stresses. Furthermore, this study offers valuable insights into the potential health benefits of momilactones for humans, which encompass their roles as antioxidants, anti-cancer agents, inhibitors of skin aging, and mitigators of inflammation.

While the accumulation of momilactones in rice has been linked to responses to salinity, drought, chilling, and UV stress, their precise functions within the rice defense

system and the mechanisms involved necessitate further clarification. Additionally, their potential medicinal and pharmaceutical properties hold promise as viable sources for the development of treatments targeting cancer, diabetes, and skin aging.

Although momilactones from rice sources possess advantageous properties, their utilization faces substantial challenges due to their limited extractable quantities. Moreover, momilactones are not commercially available, further complicating their widespread use. Consequently, potential future strategies may involve the development of artificial synthesis models for momilactones and the enhancement of their natural accumulation in rice sources through genetic techniques.

Based on the insights gathered from momilactone research discussed in this paper, the suggested research directions to fully leverage the health benefits of momilactones in rice include: (i) Identifying therapeutic properties: Researching and identifying the specific health benefits of momilactones, such as anti-inflammatory, antioxidant, and anticancer properties; (ii) Enhancing momilactone content in rice: Developing rice strains with higher levels of momilactones through genetic engineering or selective breeding; (iii) Extracting and purifying momilactones: Developing efficient methods for extracting and purifying momilactones from rice for use in supplements or pharmaceuticals; (iv) Clinical research and trials: Conducting clinical trials to verify the efficacy and safety of momilactone-based treatments for various health conditions; and (v) Formulating dietary supplements or medications: Creating supplements or medications that harness the health benefits of momilactones for public consumption.

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