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Development of a rice herbicide, fenquinotrione

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Fenquinotrione is a novel rice herbicide that was discovered and developed by Kumiai Chemical Industry Co., Ltd. It can control a wide range of broadleaf and sedge weeds with excellent rice selectivity at 30 g a.i./10 a and is as effective as the wild type on acetolactate synthase inhibitor-resistant weeds. Our metabolic and molecular biological studies showed that CYP81A6-mediated demethylation and subsequent glucose conjugation are responsible for the safety of fenquinotrione in rice. Fenquinotrione was registered in Japan in 2018, and various products containing fenquinotrione have been launched. With its high efficacy and excellent rice selectivity, we believe that fenquinotrione will contribute to efficient food production in the future.

Keywords: fenquinotrione, oxoquinoxaline, paddy rice, herbicide, CYP81A6, 4-hydroxyphenylpyruvate dioxygenase (HPPD).

Introduction

In the current Japanese agricultural setting, rice cultivation systems are diversifying, including direct seeding and transplant cultivation. In addition, planting of new rice varieties, that are in demand for feed and processing, has increased. From the viewpoint of weed management, the following weeds, that show resistance to acetolactate synthase (ALS)-inhibiting herbicides, have become problematic in Japanese rice paddy fields: *Schoenoplectus juncoides*, *Monochoria vaginalis*, *Monochoria korsakowii*, *Sagittaria trifolia*, and *Lindernia* spp. Under these circumstances, there is a need for herbicides that have long application periods, can be applied to various cropping systems and cultivars, and can control the growth of a wide range of weeds, including ALS-resistant weeds, at low concentrations.

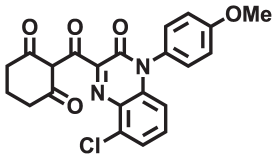

Fig. 1. Structure of fenquinotrione.

To meet the needs of such herbicides, we focused on 4-hydroxyphenylpyruvate dioxygenase (HPPD) inhibitors in this study, and succeeded in discovering a novel herbicide, fenquinotrione (trademark name: EFFEEDA®, Fig. 1). In addition, we revealed its biological properties as well as rice safety factors using molecular biology methods.

1. Discovery of fenquinotrione

1.1. Discovery of an oxoquinoxaline derivative

Following a review of commercialized HPPD-inhibiting herbicides (Fig. 2) and patents-related HPPD inhibitors, we confirmed that substituents at the 2-, 3-, and 4-positions of the benzoyl group have a significant impact on herbicidal activity, crop safety, and herbicidal spectrum. Based on this knowledge, we designed and synthesized 2-pyridone derivatives. However, although these 2-pyridone derivatives showed potent HPPD inhibitory activity as well as high herbicidal efficacy, we were unable to identify a compound with practical applications. Subsequently, we focused on the heterocyclic structure with a carbonyl group at the 2-position and identified an oxoquinoxaline derivative, which is the basic structure of fenquinotrione, and used it as a lead compound to convert the acid moiety, *N*-position, and fused benzene ring moiety (Fig. 3).[1)]

1.2. Structure and biological activity of acid site structure

The selection of compounds with promising biological activity was based on their herbicidal efficacy against *S. juncoides* at the pre-emergence application. The cyclohexadione ring was identified as the most active acid, whereas other acid structures, such

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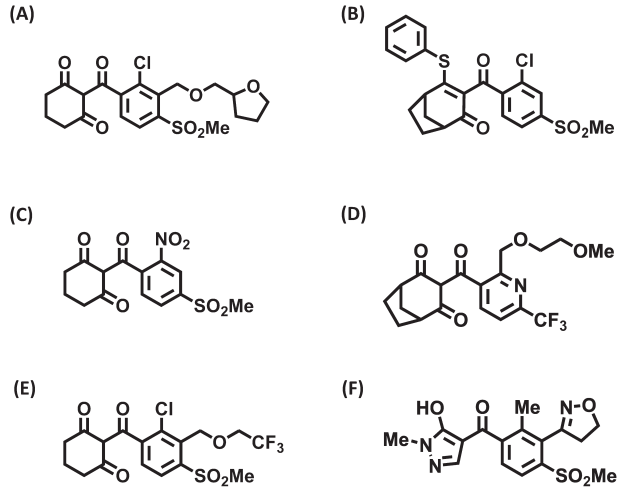


Fig. 2. Structure of commercialized HPPD-inhibiting herbicides, tefuryltrione (A), benzobicyclone (B), mesotrione (C), bicyclopyrone (D), tembotrione (E) and topramezone (F).

as pyrazole rings, were significantly less active. Therefore, the acid moiety was fixed to the cyclohexadione ring, and the other moieties were converted.[1)]

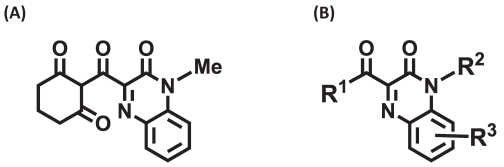
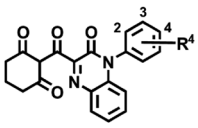


Fig. 3. Structure of lead compound (A) and oxoquinoxaline derivative (B).

1.3. N-position structure and biological activity

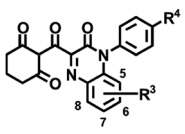
Phenyl and heterocyclic groups at the *N*-position showed high herbicidal efficacy; however, their safety against rice was low. Therefore, we introduced a substituent on the *N*-phenyl ring to improve the crop injury in rice plants. The introduction of methoxy or methyl groups at the 3- or 4-positions of the phenyl ring decreased herbicidal efficacy but improved the selectivity between rice and paddy weeds (Table 1). In particular, the 4-methoxy group was the most suitable because of the resulting excellent balance between herbicidal efficacy and safety against rice. 4-methoxyphenyl was not sufficiently safe against rice, and we continued to investigate the substituent effect on the fused benzene ring.[1)]

Table 1. Effect of substituents

	R^4	ED_{20} (g a.i./10 a)	ED_{90} (g a.i./10 a)		
		ORYSA	ECHOR	MOOVP	SCPJU
	H	0.4	6.3	1.6	1.6
	3-Me	6.3	25	6.3	25
	4-Me	6.3	25	6.3	6.3
	2-OMe	6.3	100	25	25
	3-OMe	6.3	100	6.3	6.3
	4-OMe	6.3	100	6.3	6.3

Evaluation: Herbicidal activity and crop injury were visually evaluated using a rating of 0 (no effect) to 100 (complete kill). ED20: Dosage at 20% crop inhibition. ED90: Dosage at 90% weed control. Crop and weeds tested were ORYSA, *Oryza sativa* cv. Kinmaze; ECHOR, *Echinochloa oryzicola*; MOOVP, *Monochoria vaginalis*; and SCPJU, *Schoenoplectus juncoides*.

Table 2. Effect of substituents

	R^3	R^4	ED_{20} (g a.i./10 a)	ED_{90} (g a.i./10 a)		
			ORYSA	ECHOR	MOOVP	SCPJU
	H	OMe	6.3	100	6.3	6.3
	5-Cl	OMe	6.3	25	6.3	25
	6-Cl	OMe	6.3	100	6.3	25
	7-Cl	OMe	6.3	25	1.6	25
	8-Cl	OMe	>100	>100	6.3	6.3
	8-Br	OMe	>100	>100	6.3	25
	8-Me	OMe	100	25	6.3	25
	8-Cl	H	1.6	25	1.6	1.6

Evaluation: Herbicidal activity and crop injury were visually evaluated using a rating of 0 (no effect) to 100 (complete kill). ED20: Dosage at 20% crop inhibition. ED90: Dosage at 90% weed control. Crop and weeds tested were ORYSA, *Oryza sativa* cv. Kinmaze; ECHOR, *Echinochloa oryzicola*; MOOVP, *Monochoria vaginalis*; and SCPJU, *Schoenoplectus juncoides*.

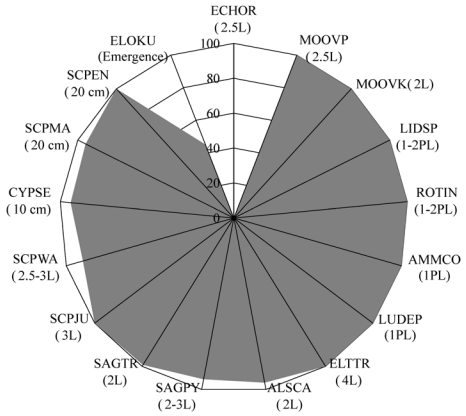


Fig. 4. Herbicidal spectrum of fenquinotrione. Herbicidal efficacy was visually evaluated using a rating of 0 (no effect) to 100 (complete kill). Tested weeds were: ECHOR, *Echinochloa oryzicola*; MOOVP, *Monochoria vaginalis*; MOOVK, *Monochoria kowsakowii*; LIDSP, *Lindernia* spp.; ROTIN, *Rotala indica*; AMMCO, *Ammannia coccinea*; LUDEP, *Ludwigia epilobioides*; ELTTR, *Elatine triandra*; ALSCA, *Alisma canaliculatum*; SAGPY, *Sagittaria pygmaea*; SAGTR, *Sagittaria trifolia*; SCPJU, *Schoenoplectus juncoides*; SCPWA, *Schoenoplectus wallichii*; CYPSE, *Cyperus serotinus*; SCPMA, *Bolboschoenus maritimus*; SCPEN, *Schoenoplectus nipponicus*; ELOKU, and *Eleocharis kuroguwai*; L and PL, Leaf stage of weeds at application.

1.4. Structure and biological activity of the fused ring moiety

The introduction of various substituents at positions 5, 6, and 7 of the fused benzene ring moiety did not improve its safety in rice plants. However, the introduction of a halogen or methyl group at the 8-position tended to improve the selectivity between rice and paddy weeds (Table 2). In particular, the 8-chloro form (fenquinotrione) was selected as the development compound because it showed sufficient crop safety and herbicidal efficacy.[1)]

2. Physicochemical properties

Common name (ISO name): Fenquinotrione
Development code: KUH-110
Chemical name (IUPAC): 2-{[8-chloro-3,4-dihydro-4-(4-methoxyphenyl)-3-oxoquinoxalin-2-yl]carbonyl}cyclohexane-1,3-dione
CAS registry number: 1342891-70-6
Molecular formula: $C_{22}H_{17}ClN_2O_5$
Molecular weight: 424.83
Appearance (physical state, form, and color): Pale yellow powder
Melting Point: 157.6°C
Solubility in water: 17.3 mg/L (20°C)
Log P_{ow}: 2.91 (pH 1.0), 1.59 (pH 4.0), 0.33 (pH 7.0)

3. Biological properties

3.1. Herbicidal spectrum

The herbicidal activity of fenquinotrione against each weed species was confirmed in the greenhouse trials. Fenquinotrione showed high herbicidal activity against paddy sedges and broadleaf weeds such as *S. juncoides* and *M. vaginalis* except for *Echinochloa oryzicola* and *Eleocharis kuroguwai*, from pre-emergence to early post-emergence application at 30 g a.i./10 a (Fig. 4),[2,3)] and was considered to have a broad spectrum of weed-killing activities.[4,5)]

3.2. Herbicidal activities at post-emergence application window

The herbicidal efficacy of fenquinotrione on *S. juncoides*, *M. vaginalis*, and *S. trifolia*, at different leaf stages, was confirmed in greenhouse trials. At a dose of 30 g a.i./10 a, fenquinotrione showed high herbicidal efficacy against these weed species, including at the high-leaf stages, such as the 4-leaf stage of *S. juncoides* and *M. vaginalis*, and the 1-arrowhead-leaf stage of *S. Trifolia* (Fig. 5).

Fenquinotrione was also effective against ALS inhibitor-resistant biotypes similar to the wild type (Fig. 6).

3.3. Residual activity

The residual activity of fenquinotrione on *S. juncoides* and *M. vaginalis* was confirmed in greenhouse trials. The weeds were seeded on the soil surface of the pots at 10, 20, 30, and 40 days

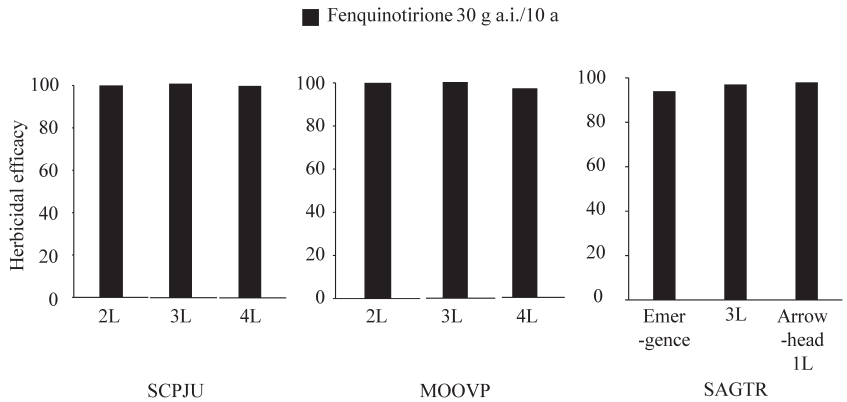


Fig. 5. Herbicidal efficacy of fenquinotrione against *Schoenoplectus juncoides* (SCPJU), *Monochoria vaginalis* (MOOVP), and *Sagittaria trifolia* (SAGTR). Herbicidal efficacy was visually evaluated using a rating of 0 (no effect) to 100 (complete kill). L, Leaf stage of weeds at application.

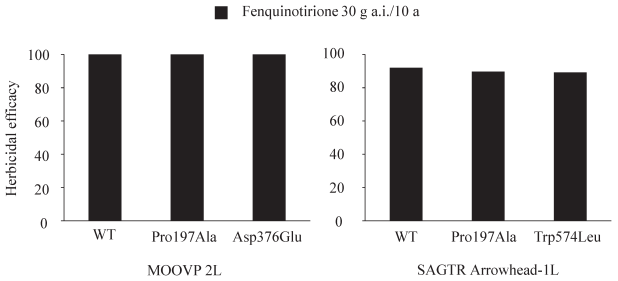


Fig. 6. Herbicidal efficacy of fenquinotrione against acetolactate synthase (ALS) inhibitor-resistant *Monochoria vaginalis* (MOOVP) and *Sagittaria trifolia* (SAGTR). Herbicidal efficacy was visually evaluated using a rating of 0 (no effect) to 100 (complete kill). WT, Wild type; Pro197Ala, Asp376Glu, and Trp574Leu, amino acid substitutions in ALS; L, Leaf stage of weeds at application.

after application, and residual activity evaluated. Fenquinotrione at a dose of 30 g a.i./10 a was as effective as, or more effective than, the control (Fig. 7).[2)]

3.4. *Influence of overflow on herbicidal efficacy*

Various environmental factors affect herbicidal efficacy such as overflow due to rainfall, temperature, weed seeding depth, rice transplanting depth, and water leaching. The effect of overflow on the herbicidal efficacy of fenquinotrione was confirmed in a greenhouse trial. At a dose of 30 g a.i./10 a, fenquinotrione showed less variation in efficacy and higher stability in herbicidal effects than the reference, under conditions assuming an overflow of 6 cm in three days (2 cm/day) (Fig. 8).[2)]

3.5. *Effect of environmental factors on rice phytotoxicity*

The phytotoxicity of transplanted paddy rice (*Oryza sativa* cv. Kinmaze) was confirmed in the greenhouse trials. In the field, water leakage conditions are assumed to have stronger herbicidal phytotoxicity. However, fenquinotrione, at a dosage of 30 g a.i./10 a, showed high paddy rice safety in a trial in which 10 cm of water leakage occurred in 10 days (1 cm/day) (Fig. 9).[2)]

In a trial under high-temperature (assuming cultivation in the western part of Japan), low-temperature (assuming cultivation in the northern part of Japan), and intermediate temperature

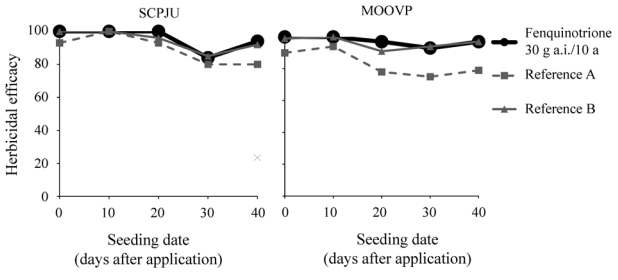


Fig. 7. Residual activity of fenquinotrione against *Schoenoplectus juncoides* (SCPJU) and *Monochoria vaginalis* (MOOVP). SCPJU and MOOVP were sown at 0, 10, 20, 30, and 40 days after application, and herbicidal efficacy was scored at about 30 days after sowing. Herbicidal efficacy was visually evaluated using a rating of 0 (no effect) to 100 (complete kill).

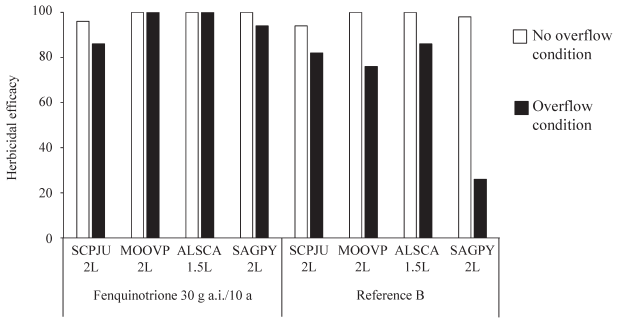


Fig. 8. Herbicidal efficacy of fenquinotrione in the overflow condition. A total of 2 cm depth of flooded water was removed from a depth of 4 cm once per day for three consecutive days beginning the day after the application. In the no-overflow condition, water depth was maintained at 4 cm. Herbicidal efficacy was visually evaluated using a rating of 0 (no effect) to 100 (complete kill). Tested weeds were: SCPJU, *Schoenoplectus juncoides*; MOOVP, *Monochoria vaginalis*; ALSCA, *Alisma canaliculatum*; SAGPY, and *Sagittaria pygmaea*. L, Leaf stage of weeds at application.

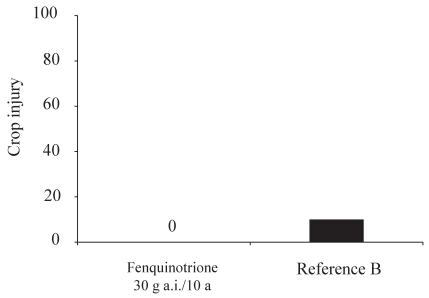


Fig. 9. Fenquinotrione crop injury in transplanted rice under the water-leakage condition. Planting depth was 2 cm. A total of 1 cm depth of water leakage occurred per day for 10 consecutive days beginning the day after application. Crop injury was visually evaluated using a rating of 0 (no injury) to 100 (complete kill).

conditions, the phytotoxicity of fenquinotrione varied depending on the temperature. However, the safety of fenquinotrione was as good as, or better than that of the control at all temperatures (Fig. 10).[3)]

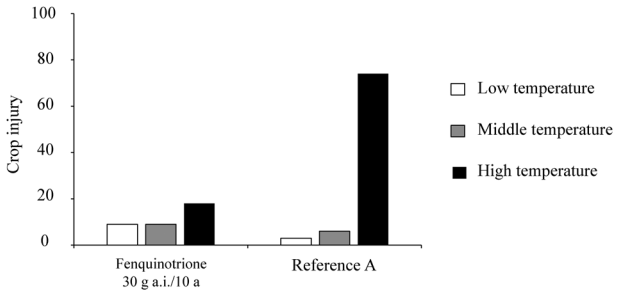


Fig. 10. Fenquinotrione crop injury in transplanted rice under various temperature conditions. Average temperatures were 16°C, 22°C, and 28°C under low, middle, and high temperature conditions, respectively. Crop injury was visually evaluated using a rating of 0 (no injury) to 100 (complete kill).

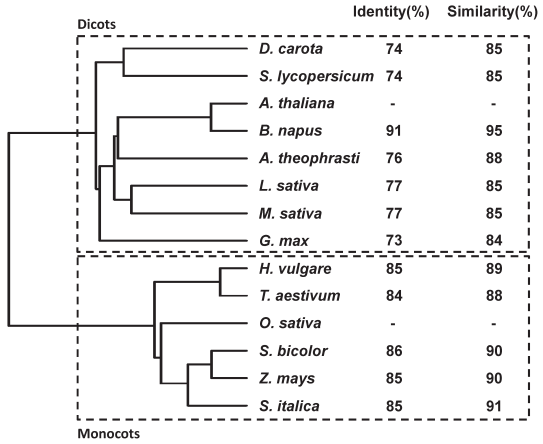


Fig. 11. Phylogenetic tree of plant HPPDs based on amino acid sequences. Phylogenetic trees were constructed using the ClustalW algorithm. The percentage indicates the amino acid identity with rice or Arabidopsis. HPPD proteins along with their GenBank (https://www.ncbi.nlm.nih.gov/genbank/) accession numbers are as follows: *Oryza sativa* (XP_015626163), *Zea mays* (NP_001105782), *Sorghum bicolor* (XP_002453359), *Triticum aestivum* (AAZ67144), *Hordeum vulgare* (CAA04245), *Setaria italica* (XP_004951787), *Arabidopsis thaliana* (NP_001154311), *Brassica napus* (AFB74218), *Glycine max* (ABQ96868), *Daucus carota* (AAC49815), *Solanum lycopersicum* (XP_004243609), *Abutilon theophrasti* (XP_004243609), *Lactuca sativa* (XP_023753058), and *Medicago sativa* (AQN69278). The identity and similarity of monocotyledons and dicotyledons were calculated based on rice and Arabidopsis HPPD, respectively.

4. Mechanism of rice safety

4.1. Elucidation of safety factors of fenquinotrione in paddy rice

To estimate the safety factors of fenquinotrione in paddy rice, we first assessed the difference in the susceptibility of the target enzymes of *Arabidopsis* and rice to fenquinotrione. Fenquinotrione potently inhibits 4-hydroxyphenylpyruvate dioxygenase (HPPD) activity in *Arabidopsis* (IC_{50}=44.7 nM) and rice (IC_{50}=27.2 nM).[6] In addition, the high similarity in the amino acid sequence of HPPD among plants (Fig. 11) as well as the high conservation of fenquinotrione-binding sites of the HPPD protein (Fig. 12) suggest that the selectivity between rice and weeds was not due to differences in affinity for the HPPD protein. Therefore, it was assumed that the high safety of fenquinotrione in rice was due to its metabolism in rice.

To determine the metabolic mechanism of fenquinotrione, we examined the metabolites of fenquinotrione in rice. The major metabolites of fenquinotrione were M-1, M-2, and their glucose conjugates (Fig. 13). M-2 is a hydrolysis product of the triketone moiety; such metabolites are commonly found in existing HPPD inhibitors.[7–10] M-1 is a demethylated form of methoxybenzene on the oxoquinoxaline ring, which is unique to fenquinotrione. Cytochrome P450 is known to be involved in oxidation reactions such as demethylation. Therefore, we focused on CYP81A6,

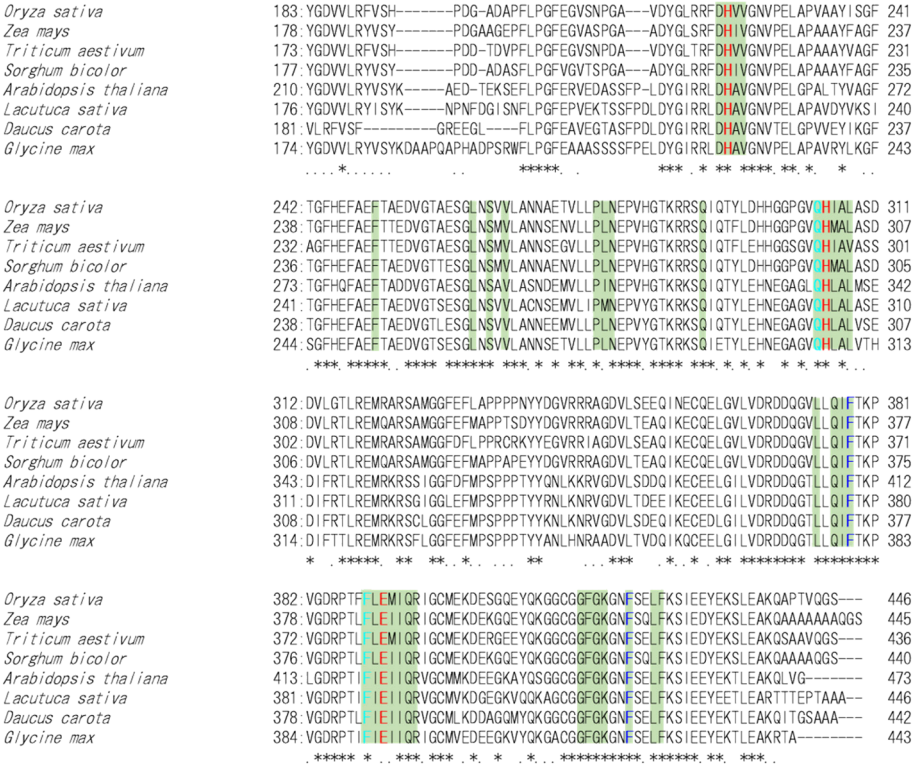


Fig. 12. Alignment of HPPD amino acid sequences in each crop and comparison of active sites in the secondary structure. The amino acid sequence of the HPPD protein is shown in Fig. 12; alignment was performed using the ClustalW algorithm. Amino acid residues located in the active site were identified based on the results of the docking study and the study by Fritze *et al.* (2004).[19] Green-highlighted regions indicate active sites, red symbols indicate iron-coordination amino acid residues, blue symbols indicate phenylalanine residues forming the π–π conjugate, and light blue symbols indicate amino acid residues forming interactions unique to fenquinotrione.

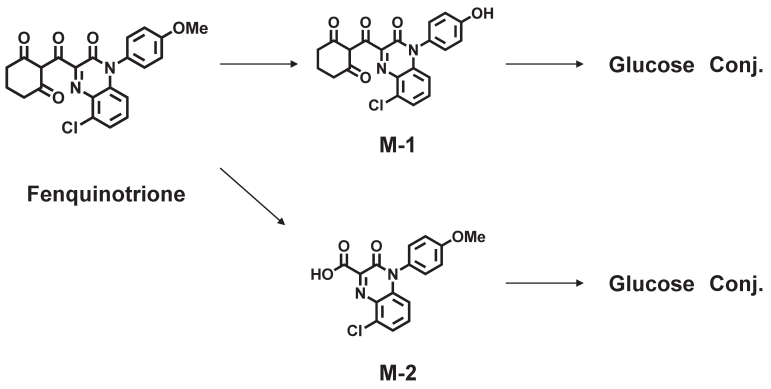


Fig. 13. Metabolites of fenquinotrione detected in rice seedlings and presumed metabolic pathways.

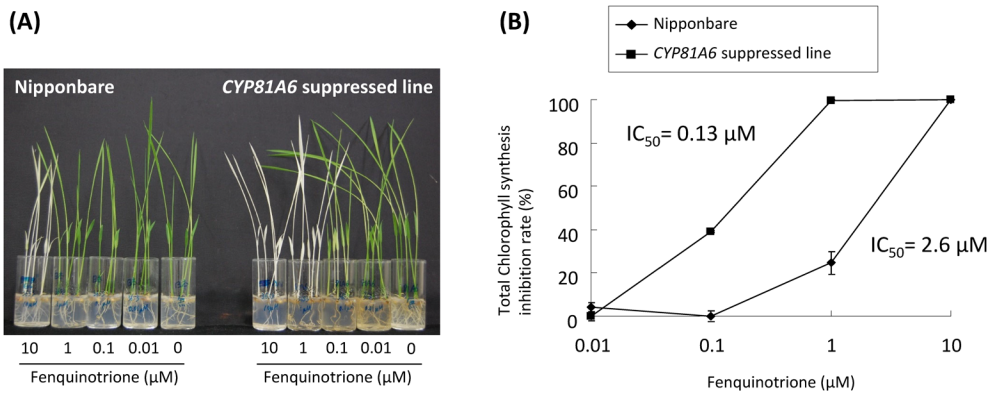


Fig. 14. Evaluation of the involvement of CYP81A6 in fenquinotrione metabolism. (A) Comparison of fenquinotrione susceptibility between wild type (*Oryza sativa* cv. Nipponbare) and a *CYP81A6*-suppressed line grown in Hogland's No. 2 medium. (B) Determination of total chlorophyll content in wild type (*Oryza sativa* cv. Nipponbare) and a *CYP81A6*-suppressed line treated with fenquinotrione.

which has been reported to be involved in herbicide metabolism in rice[11] and assessed whether this enzyme metabolizes fenquinotrione using a *CYP81A6* gene expression-suppressed line. The results showed a 20-fold increase in susceptibility to fenquinotrione in the *CYP81A6*-suppressed line as compared to that in the wild-type (Fig. 14).[12] These results indicated that the demethylating metabolism by CYP81A6, followed by glucose conjugation in rice, was responsible for the safety of fenquinotrione.

4.2. *Crop safety and CYP81A6 relationship in triketone HPPD inhibitor highly sensitive varieties*

It has been reported that some new rice varieties, such as forage rice, are highly susceptible to triketone HPPD inhibitors.[13,14] Therefore, we assessed the safety of fenquinotrione, which has a triketone structure, in these rice varieties, and examined its relationship with the function of CYP81A6. The correlation between *CYP81A6* transcript levels in each cultivar and susceptibility to fenquinotrione was examined using real-time RT-PCR. *CYP81A6* gene was expressed in all cultivars, including the cultivar highly susceptible to triketone HPPD inhibitors as well as the indica variety Kasalath (Fig. 15). The safety of fenquinotrione in these varieties correlated with the expression level of the *CYP81A6* gene (Fig. 16). Furthermore, the *CYP81A6* gene sequences of these cultivars are identical to those of Nipponbare.[15]

These results suggest that CYP81A6, which is involved in the safety of fenquinotrione in rice, is ubiquitous in rice, and that fenquinotrione has sufficient crop safety potential in many rice cultivars.

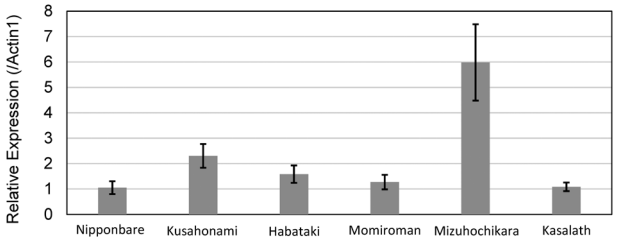


Fig. 15. *CYP81A6* transcript levels in each rice variety. Total RNA was extracted from individual rice plants one week after seeding on solid medium, and *CYP81A6* transcript levels were measured by real-time PCR (n=5) and normalized to Actin1. Nipponbare and Kusahonami were used as existing HPPD-inhibitor non-susceptible varieties, and Habataki, Momiroman, and Mizuhochikara were used as susceptible varieties. Kasalath was used as the representative indica variety.

Fig. 16. Fenquinotrione susceptibility test for each rice variety. Photos were taken one week after seeding on Hogland's No.2 medium containing fenquinotrione. The fenquinotrione concentrations were, from left to right, 10, 1, 0.1, 0.01, and 0 μM.

Concluding remarks

Fenquinotrione was registered in Japan in 2018, launched in 2019, and many fenquinotrione mixture products have been developed since then.[16–18] In Japan, the need for cultivation technology that contributes towards cost reduction, labor savings, and diversification of cultivation systems, is expected to increase. Fenquinotrione meets the needs of the current agricultural scene, as it can control a wide range of weeds, including ALS inhibitor-resistant weeds, and has a wide application window. Thus, fenquinotrione is expected to contribute to stable food production in the future.

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We would like to thank everyone involved in the practical evaluation tests as well as those who offered advice regarding the development of fenquinotrione from the Japan Association for Advancement of Phyto-regulators and multiple prefectural agricultural experimental stations. We are deeply grateful to the members of Kumiai Chemical Industry Co., Ltd., for their kind support and for providing opportunities to develop fenquinotrione.

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