Sakuranetin: A multifaceted study from plant resistance to pharmacological activity

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Abstract: *Sakuranetin is a 7-methoxyflavanone compound that is widely found in a variety of plants. In recent years, with the increasing research on sakuranetin, researchers have found that it plays an important function in various aspects of botany and zoology. In this paper, we used a research review to extract the research literature related to sakuranetin published from 2010-2025, and reviewed the research progress on the biosynthesis of sakuranetin, its mechanism of action in plant resistance, and its pharmacological activity. By analysing the relevant studies in recent years, the key roles of sakuranetin in rice disease and insect resistance, as well as its potential for other pharmacological activities such as anti-inflammatory and antioxidant activities, anti-tumour activities, involvement in immunomodulation and cardiovascular protection, as well as antiviral activities, were investigated in medical research. The results of this review indicate that the functions of sakuranetins from plant resistance to pharmacological activities are diverse and effective, and there is a need for more in-depth research on flavanones such as sakuranetins in the future and to promote their translation from basic research to practical applications.*

Keywords: *Sakuranetin, plant resistance, pharmacological activity*

1. Introduction

1.1 Necessity and purpose of the study

Sakuranetin, as a natural 7-methoxyflavanone compound, is widely found in a variety of plants, and it shows versatility in terms of plant resistance and pharmacological activity[18]. In recent years, in plant production research, researchers have increasingly pursued the exploration and exploitation of natural plant resistance mechanisms to breed broad-spectrum, long-lasting resistant varieties with the ability to reduce dependence on chemical pesticides. Therefore, revealing the ecological adaptation strategies of plant secondary metabolites is a way to provide new targets for crop resistance breeding, reduce the dependence on chemical pesticides and develop biopesticides based on plant natural products. On the other hand, sakuranetin, as a novel drug lead compound, especially in the field of chronic diseases, cancer or neurodegenerative diseases, has the potential to develop natural nutraceuticals or functional food additives, which can meet the needs of the health industry.

This paper reviews the latest research work on sakuranetin in biosynthesis, plant resistance and pharmacological activity at home and abroad in recent years, aiming at identifying the differences and commonalities of sakuranetin research from the literature, with the expectation of providing theoretical basis and technical support for sakuranetin's application in the fields of agriculture and medicine, and promoting its transformation from basic research to practical application.

1.2 Content of the study

The aim of this study is to summarise and explore in depth the biosynthetic modes of sakuranetins and their functions in life science research in plants and animals (including humans), and to answer the following questions:

The biosynthetic pathway of sakuranetin and its synthesis through modern biotechnology.

Elucidate its molecular mechanism of action in plant disease and insect resistance.

To elucidate the pharmacological activities of sakuranetins, including anti-inflammatory, antioxidant, antibacterial, antitumour, immunomodulatory and cardiovascular and neuroprotective effects.

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2. Research Methods

2.1 Sources of materials

In this paper, journal articles from Zhi.com, Wanfang, etc. and all over the world on the biosynthesis of sakuranetin, its involvement in the resistance process in rice and other plants, and its function in medical pharmacology from 2010-2025 were referred to, and most of them were from the latest research progress after 2020.

2.2 Data analysis process

In this paper, a large number of articles were searched, and finally 35 articles were identified to meet the experimental research method for the purpose and content of the study, and the 35 articles were analysed to extract the research content in the synthesis and function of sakuranetin, and then cluster analysis was carried out to merge and summarize the literature with the same type of content, and analyse the differences and common points.

3. Research results

3.1 Biosynthesis of sakuranetin

Sakuranetin is an antifungal plant antitoxin produced from the antimicrobial precursor naringenin catalysed by naringenin-O-methyltransferase (NOMT), which is widely found in the plant kingdom, such as rice and cherry tree [9].

In plants, the synthesis of sakuranetin is closely related to a variety of environmental factors. Ultraviolet (UV) irradiation, $CuCl_2$ treatment, jasmonic acid (JA) treatment, and infection by phytopathogenic bacteria can induce the production of sakuranetins[4][7][10]. Takafumi S et al. found that naringenin 7-O-methyltransferase encoded by the OsNOMT gene in rice was capable of converting naringenin to sakuranetins [9]. Park L H demonstrated that the synthesis of sakuranetin was significantly enhanced under stress conditions such as UV irradiation or jasmonic acid treatment, suggesting that its synthesis pathway is regulated by plant defence responses [7].

In terms of microbial synthesis, researchers have genetically engineered the ab initio synthesis of sakuranetin using microorganisms such as Escherichia coli (E. coli) and Saccharomyces cerevisiae (Saccharomyces cerevisiae).For example, by overexpressing the relevant genes in Escherichia coli, sakuranetins were produced up to 40.1 mg/L [8],whereas in Saccharomyces cerevisiae, a multimodular metabolic engineering strategy was used to produce sakuranetins up to 50.62 mg/L in shake flasks and up to 158.65 mg/L in a 1L bioreactor [3].Similarly, a modular co-culture engineering approach was applied to the synthesis of sakuranetin, where the production of sakuranetin from glucose was significantly increased by optimising the co-culture system up to 79.0 mg/L [6].Furthermore, by means of genetic engineering, Álvaro V P et al. have successfully achieved the heterologous biosynthesis of sakuranetin in Streptomyces albidoflavus (yellow and white Streptomyces).By optimising gene expression and culture conditions, the yield of sakurantin was significantly increased, which opens up the possibility of large-scale production of sakuranetin [1].

3.2 Role of sakuranetins in plant resistance

3.2.1 Disease resistance in rice

Sakuranetin, as a plant antitoxin, plays an important role in rice disease resistance.It inhibits the spore germination and growth of rice blast fungus. The content of sakuranetin was significantly increased in rice leaves infected with B. oryzae, especially in inoculated with B. oryzae in unaffiliated areas of the pathogen-infected area, and was significantly increased in disease-resistant rice varieties, while it was lower in susceptible varieties[11]. In addition to rice blast, sakuranetin is also involved in the resistance to rice bacterial streak disease as well as leaf blight. Rice plants overexpressing the OsWRKY45 gene contained significantly higher levels of sakuranetin and exhibited greater resistance to rice blast, leaf blight, and bacterial streak, suggesting that the OsWRKY45 gene may enhance broad-spectrum disease resistance in rice by regulating the synthesis of sakuranetin [16].

In addition, exogenous application of sakuranetin was also able to significantly inhibit the growth of

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rice blast fungus. In in vitro experiments, sakuranetin inhibited B. oryzae better than other plant antitoxins, such as momilactone A (Momilactone A) [15][17].Transcriptome analysis showed that 1525 genes were up-regulated and 428 genes were down-regulated in rice blast fungus after sakuranetin treatment, suggesting that sakuranetin inhibits the growth of the pathogen through a variety of mechanisms [14][17].

Further studies showed that sakuranetin was also able to enhance disease resistance by inhibiting endocytosis in rice cells. The accumulation of Sakuranetin in disease-resistant rice lines was correlated with the attenuation of intracellular endocytosis after infection with M. oryzae. Sakuranetin reduces the endocytosis of pathogen effectors by targeting the cadherin-mediated endocytosis (CME) pathway, thereby preventing pathogen infection [12]. This mechanism provides a new perspective on rice disease resistance. Sakuranetin has an important role in rice resistance to rice blast.

3.2.2 Insect resistance in rice

In addition to disease resistance, sakuranetin also showed significant activity in rice insect resistance[5]. Sakuranetin was found to be able to resist the attack of brown planthopper (BPH)[2].In mutant lines, increased sakuranetin content was associated with elevated expression levels of the naringenin 7-O-methyltransferase gene Os12g13800, and these mutants were significantly more resistant to brown planthopper and rice grasshopper [9].In addition, knockdown of the Os07g32020 gene by gene editing resulted in increased accumulation of sakuranetin in rice and significant resistance to brown planthopper and rice grasshopper [19].

In addition, silica fertiliser treatment was also found to induce sakuranetin accumulation, thereby enhancing rice resistance to rice blast fungus. Sakuranetin content was significantly increased in silica fertiliser-treated rice plants, suggesting that exogenous inducers are able to enhance resistance in rice by activating the sakuranetin synthesis pathway [15].

3.2.3 Resistance effects in other plants

Sakuranetins have not only shown significant resistance effects in rice, but have also been extensively studied in other plants.For example, in pea, UV treatment induced the synthesis of sakuranetin, which enhanced pea resistance to grey mould.In addition, Sakuranetins isolated from plants such as white sand beach and cypress-like proposed Brachystegia have also shown similar resistance [13].

3.3 Pharmacological activities of sakuranetin

3.3.1 Anti-inflammatory and antioxidant activities of sakuranetin

3.3.1.1 Anti-inflammatory activity

Sakuranetin possesses significant anti-inflammatory activity and is able to inhibit the inflammatory response through a variety of mechanisms. In a lipopolysaccharide (LPS)-induced acute lung injury (ALI) model in mice, sakuranetin significantly reduced the number of neutrophils in peripheral blood and bronchoalveolar lavage fluid, lowered the levels of macrophages (especially M1-type macrophages), and inhibited the production of keratinocyte-derived chemokines (IL-8 homologues)[32] . In addition, sakuranetin reduced collagen fibre formation, matrix metalloproteinase-9 (MMP-9) and tissue inhibitor of metalloproteinase-1 (TIMP-1)-positive cells, and lowered the level of oxidative stress in lung tissue. These results suggest that sakuranetin prevents and attenuates lipopolysaccharide-induced lung inflammation by modulating oxidative stress and lung function, and is expected to be a novel drug candidate for the treatment of acute lung injury in mice [32].

In a mouse model of Crohn's disease-like colitis, sakuranetin attenuated colitis symptoms by antagonising apoptosis of intestinal epithelial cells. It was found that sakuranetin significantly reduced the levels of inflammatory factors (e.g., TNF-α, IL-6, IL-17A, and IL-1β) in colonic tissues, decreased the translocation of intestinal bacteria, and exerted its anti-inflammatory effects by inhibiting the activation of the Toll-like receptor 4 (TLR4) signalling pathway [30].Furthermore, in allergic asthma and Alzheimer's disease models, sakuranetin significantly improved disease symptoms by inhibiting the expression of inflammatory factors such as TNF-α and IL-6 [34].

Sakuranetin has shown significant potential in arthritis treatment. In a mouse model of osteoarthritis (OA), sakuranetin significantly reduced inflammation and metabolic disturbances in chondrocytes by inhibiting the activation of the PI3K/Akt/NF-κB signalling pathway.In addition, sakuranetin promotes chondrocyte repair by up-regulating the expression of chondrogenic markers, such as Acan and Col2a1

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[23][28].

3.3.1.2 Antioxidant Activity

The antioxidant activity of sakuranetin is mainly mediated by scavenging free radicals, inhibiting oxidative stress and modulating the expression of antioxidant enzymes. In several studies, sakuranetin has been shown to significantly reduce the levels of oxidative stress markers (e.g., malondialdehyde [MDA]) while increasing the activities of antioxidant enzymes such as glutathione (GSH) and superoxide dismutase (SOD).For example, in a model of nephrotoxicity induced by polyethylene microplastics (PEMPs), sakuranetin significantly attenuated renal injury by modulating the Nrf2/Keap1 signalling pathway [25].Furthermore, in a mouse model of spinal cord injury (SCI), sakuranetin ameliorated histopathological damage after SCI by inhibiting oxidative stress [24].

3.3.2 Immunomodulatory and cardioprotective effects of sakuranetin

3.3.2.1 Immunomodulation

Sakuranetin showed significant activity in immunomodulation. In a cyclophosphamide-induced immunodeficiency mouse model, sakuranetin significantly improved immunosuppression by modulating the levels of immune factors such as IFN-γ, TNF-α, IgG and IgM [20]. In addition, sakuranetin enhanced the immune function of the organism by increasing lymphocyte proliferation and immunoglobulin production.

3.3.2.2 Cardiovascular protection

Sakuranetin has also shown significant potential in cardiovascular protection. In a PEMPs-induced cardiotoxicity model, sakuranetins significantly attenuated cardiac injury by modulating oxidative stress and inflammatory responses[22]. In addition, sakuranetin showed hypotensive and vasodilatory activity by inhibiting calcium channels and reducing systolic and diastolic blood pressure [29].

3.3.3 Other pharmacological activities of sakuranetin

3.3.3.1 Anti-tumour activity of sakuranetin

Sakuranetin has shown remarkable potential in anti-tumour activity. It has been found that sakuranetin is able to inhibit the proliferation and metastasis of tumour cells through a variety of mechanisms. For example, in breast cancer treatment, sakuranetin exhibited significant inhibitory activity against aromatase (CYP19A1) with an IC50 value of 5.77 ± 1.50 μM . Molecular docking analysis showed that sakuranetin was able to bind tightly to the binding site of aromatase, displaying good selectivity. In addition, sakuranetin inhibited the proliferation and migration of tumour cells by suppressing the activation of the PI3K/Akt signalling pathway [27].

In melanoma cells, sakuranetin significantly stimulated melanogenesis, increased tyrosinase activity, and upregulated the expression of tyrosinase-related proteins (TRP1 and TRP2). In addition, sakuranetin reduced cell proliferation by inhibiting the phosphorylation of ERK1/2, while having no significant effect on cell activity.These results suggest that sakuranetin has potential applications in melanoma treatment [33].

3.3.3.2 Neuroprotective effects of sakuranetin

Sakuranetin showed significant activity in neuroprotection.In a mouse model of spinal cord injury (SCI), sakuranetin significantly reduced microglia-mediated inflammatory responses, ameliorated histopathological damage after SCI, and promoted the recovery of motor function by inhibiting the activation of the PI3K/Akt signalling pathway [24].

3.3.3.3 Antiviral activity

Sakuranetin has also shown significant activity in antiviral activity.For example, in hepatitis B virus (HBV) infection models, sakuranetin was able to significantly inhibit the expression of HBsAg and HBeAg in a dose-dependent manner. In addition, sakuranetin inhibits viral replication by binding to HBV polymerase and coat protein [31].

3.3.3.4 Anti-gastric ulcer activity

Sakuranetin showed significant activity against gastric ulcer. In a gastric ulcer model, sakuranetin significantly ameliorated gastric mucosal damage by inhibiting inflammatory responses and oxidative stress. In addition, sakuranetin promotes the repair of gastric mucosa by upregulating the expression of eNOS and iNOS genes [26].

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3.3.3.5 Regulation of intestinal microbiota

The regulatory effects of sakuranetin on the intestinal microbiota have also received attention. In a mouse model of enteritis induced by Dextran Sulfate Sodium Salt (DSS), sakuranetin improved the structure of the intestinal microbiota by increasing the abundance of increased short-chain fatty acid (SCFA)-producing bacteria, and exerted its protective effects through the GPR41/43 signalling pathway.In addition, sakuranetin improved the intestinal barrier function by regulating the Treg/Th17 balance [21].

4. Conclusion and Outlook

Sakuranetin, as a natural flavanone compound, has attracted much attention due to its remarkable properties in plant resistance and pharmacological activities.

In terms of plant resistance, the synthesis of sakuranetin is regulated by a variety of environmental stresses, and its mechanism of action in plant defence mechanisms is becoming clear. The biosynthetic pathway of sakuranetin has been successfully introduced into the microbial system by means of genetic engineering and metabolic engineering, providing the possibility of large-scale production. In addition, studies on the mechanism of action of sakuranetin in plant disease and insect resistance have provided a theoretical basis for the development of new biopesticides.

In terms of pharmacological activities, the anti-inflammatory, antioxidant, antitumour, immunomodulatory and neuroprotective properties of sakuranetins make them highly promising natural drug candidates. Especially in the field of anti-inflammatory and antioxidant, sakuranetin shows therapeutic potential for a wide range of diseases by modulating multiple signalling pathways and targets. In addition, studies on sakuranetins in modulating the gut microbiota, antiviral and anti-gastric ulcer have provided further evidence of their versatility.

Despite the remarkable progress in sakuranetin research, many challenges remain. Future studies need to further explore in depth the specific mechanism of action of Sakuranetins in plant defence mechanisms, as well as their molecular targets and signalling pathways for biomedical applications. In addition, optimising the biosynthetic pathway of sakuranetin and improving its yield and bioavailability are also important directions for future research. Meanwhile, conducting clinical trials to verify the safety and efficacy of sakuranetin will help to promote it from the laboratory to clinical applications.

In conclusion, sakuranetin, as a multifaceted natural compound, its research in the field of plant resistance and biomedicine not only enriches our understanding of plant defence mechanisms, but also provides new ideas and directions for the development of novel drugs and biopesticides. With the deepening of research, sakuranetin is expected to achieve breakthroughs in many fields and make important contributions to human health and sustainable agricultural development.

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