Arabian Journal of Chemical and Environmental Research

Vol. 13 Issue 1 (2026) 152-169

Gramine: A Multidisciplinary Review on an Indole Alkaloid Bridging Chemistry, Biology, and Medicine

B. Akabli[1], Z. Abbaoui[1*], I. Oualdi[1], S. Ben m'barek[2], N. Bentouhami[2], A. Asehraou[2], A. Chetouani[3], W. Agerico Diño[4] and R. Touzani[1]

[1]*Mohammed first University, Laboratory of Applied Chemistry and Environment (LCAE), Department of Chemistry, Faculty of Science., 60000 Oujda, Morocco.*

[2]*Mohammed first University, Laboratory of Bio-resources, Biotechnology, Ethnopharmacology and Health (LBBES) Department of Biology, Faculty of Science., 60000 Oujda, Morocco.*

[3]*Laboratory of Innovation in Science, Technology and Edu cation (LIST), CRMEF Oriental, Oujda, Morocco.*

[4]*Osaka University, Department of Applied Physics, Suita, Osaka 565-0871, Japan*

Email: *(BA) brahim.akabli.m24@ump.ac.ma, (IO) imane.oualdi@ump.ac.ma, (SB) soufiane.benmbarek@ump.ac.ma (NB) noureddine.bentouhami@ump.ac.ma (AA) a.asehraou@ump.ac.ma (AC) Ahmed.Chetouani@gmail.com, (ADW) wilson@dyn.ap.eng.osaka-u.ac.jp, (RT) r.touzani@ump.ac.ma*

Received 21 December 2025, revised 11 Feb 2026, Accepted 14 Feb 2026

***Cited as**: B. Akabli, Z. Abbaoui, I. Oualdi, S. Ben m'barek, N. Bentouhami, A. Asehraou, A. Chetouani, W. Agerico Dino and R. Touzani (2026) Gramine: A Multidisciplinary Review on an Indole Alkaloid Bridging Chemistry, Biology, and Medicine, Arab. J. Chem. Environ. Res. 13(1), 152-169*

Abstract

The natural alkaloid gramine has attracted great interest from academia and industry due to its potential and diverse biological activities, including antiviral, antibacterial, antifungal, anti-inflammatory and antitumor activities; therapeutic application in Alzheimer's disease; serotonin receptor activity; insecticidal activity; and application as an algaecide. In this review, we highlight the progress made in the study of herb-based molecules since their discovery and provide key information on their extraction and isolation, chemical synthesis and various biological activities. Data on their mechanism of action are also presented. This comprehensive and critical review will provide guidance for the development of new drug candidates based on the grass alkaloid backbone.

Keywords: Gramine; Indole Alkaloid; Serotonin Receptor Activity; Alzheimer's Disease; Drug Development; Bibliometric analysis.

*Corresponding author
E-mail address: zakariae.abbaoui@ump.ac.ma

1. Introduction

Gramine, also known as N,N-dimethyl-*1H*-indole-3-methylamine, is an indole alkaloid initially isolated from *Arundo donax* L. and generally plays a defensive role in plants against herbivores (Orechoff and Norkina, 1935) (**Figure 1**). Recently, this alkaloid has also been isolated from various raw plants, particularly barley, and it may act as a precursor for tryptophan biosynthesis and play a vital role in amino acid metabolism (Matsuo *et al*., 2001; Omar *et al*., 2021). Gramine has attracted considerable attention due to its various antiviral, antibacterial, anti-inflammatory, antitumor, and insecticidal activities (Hanson *et al*., 1983). In traditional Chinese medicine, it is also used to control toothaches, urinary problems, and heart disease (Li *et al*., 2020). It is interesting to note that certain molecules with a structure similar to gramine, such as sumatriptan and rizatriptan, have been approved for clinical trials or for use in clinical practice.

Figure 1: *Arundo donax* L.

The rational exploitation of bioactive compounds requires a rigorous synergy between chemical synthesis and molecular modelling. The synthesis of new indole derivatives attracts more attention of researchers to numerous applications as anticancer, antibacterial, anticorrosion… (Zarrok *et al*., 2012; Tribak *et al*., 2017; Hadda *et al*., 2021; Abdelazeem *et al*., 2024; Er-ray *et al*., 2025; Kumar *et al*., 2026). As demonstrated by (Abbaoui *et al*., 2024**)** via the virtual screening of diterpenes targeting Alzheimer's disease, this *in silico* approach is decisive for elucidating ligand-receptor interactions, thus validating a predictive methodology that can be directly transposed to the pharmacological valorization of Grass. In 1935, Orechoff *et al*. discovered gramine for the first time in A. donax L. and named it donaxine **(**Orechoff and Norkina, 1935**)**. It is interesting to note that in 1959, gramine was first discovered in Acer saccharinum, with 1.1 g of prismatic crystals obtained from 3.75 kg of dried maple leaves, which are widespread in the United States and southeastern Canada (Pachter *et al*., 1959). Then, (Anderson *et al*., 1976) extracted 85 mg of gramine from 640 g of Lupinus hartwegii seeds (six weeks old) grown in vermiculite (Anderson and Martin, 1976). In 1985, Zúǹiga *et al*. reported gramine in 34 barley cultivars, in amounts ranging from 0 to 48 mmol/kg (Zúñiga *et al*., 1985).

A bibliometric analysis receives more attention of police makers to dress indicators of the most fields and domains studied as well as the prolific authors and countries having significant contributions and their collaborations (Aria and Cuccurullo, 2017; Tribak *et al*., 2017; N'diaye *et al*., 2022; Abdelazeem *et al.*, 2024; Laita *et al*., 2024; Kumar *et al*., 2025; Salghi *et al.*, 2025; Mishra, 2026). **Figure 2a** shows the geographical distribution of the number of documents published in relation to a specific field of research (not specified here). It shows that the United States largely dominates scientific output with more than 120 documents, followed by China and Japan, each with more than 60 publications. The United Kingdom, Germany, and Canada form an intermediate group, with between 30 and 40 documents. Finally, countries such as Australia, Italy, India, and France have made a more modest contribution, with around 15 to 25 publications. This distribution highlights the concentration of scientific activity in certain regions of the world, particularly North America and East Asia. This finding may be elucidated more via the VOSview map showing the countries via colored circles (node) with a diameter in relation of the number of articles (Martins *et al*., 2024; Hammouti *et al*., 2025). The largest node is attributed to the US (orange color), followed by the purple nodes of China and Japan. The fourth position via a green node (UK) and Germany by the brown node etc… (**Figure 2b**). **Figure 3** shows the distribution of scientific publications according to the most prolific authors in a given field of research. It highlights that Snyder, H.R. ranks first with a total of 11 published papers, closely followed by Corcuera, L.J. and Jasiewicz, B., each contributing to 10 publications. Other researchers such as Eto, M., Hirashima, A., and Mrówczyńska, L. also show notable productivity with 8 papers. The other authors in the ranking, including Csaba, G., Hu, H.Y., Scanlan, R.A., and Hong, Y., each have 7 to 6 publications. This distribution highlights the significant contribution of a small group of researchers in the field, illustrating their central role in advancing scientific knowledge on the subject.

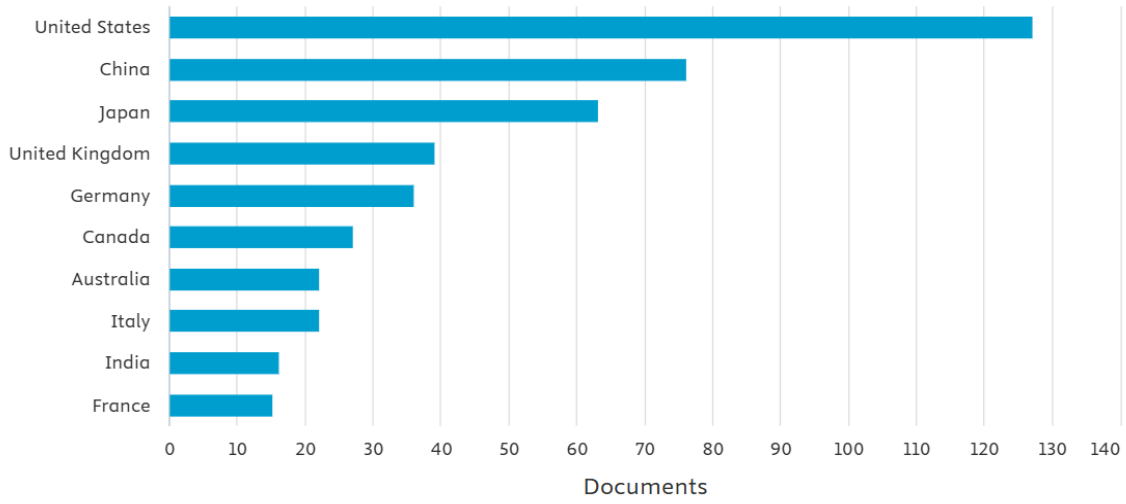


Figure 2a: The top countries working on gramine (from Elsevier Scopus)

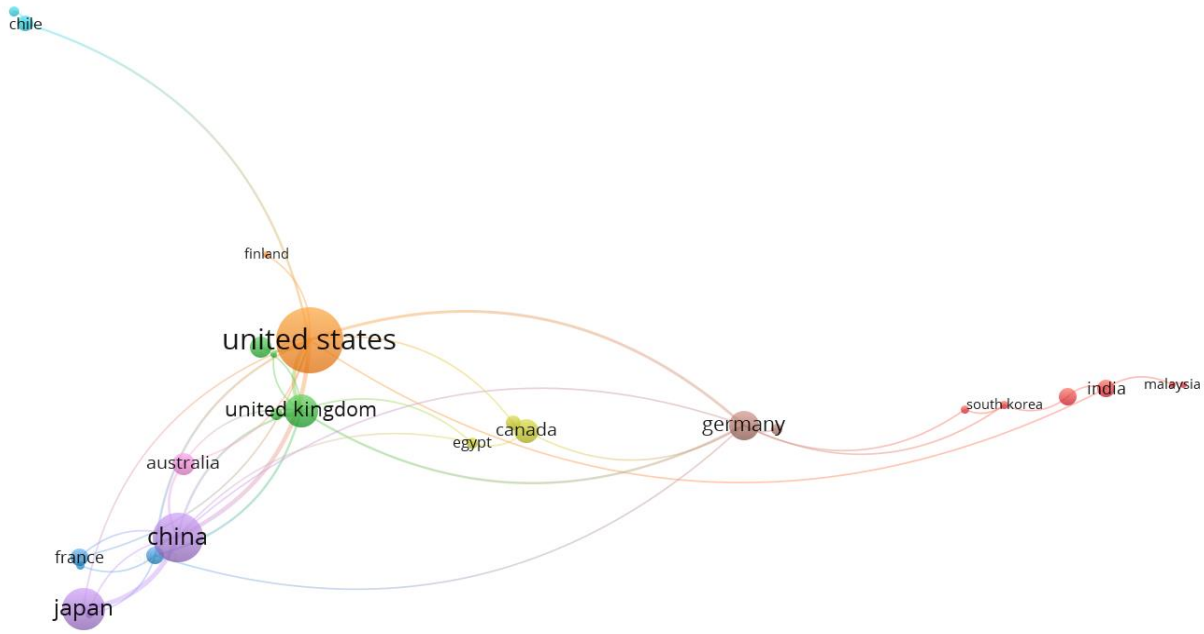


Figure 2b: VOSviewer Network visualization of 23 countries contributing on gramine

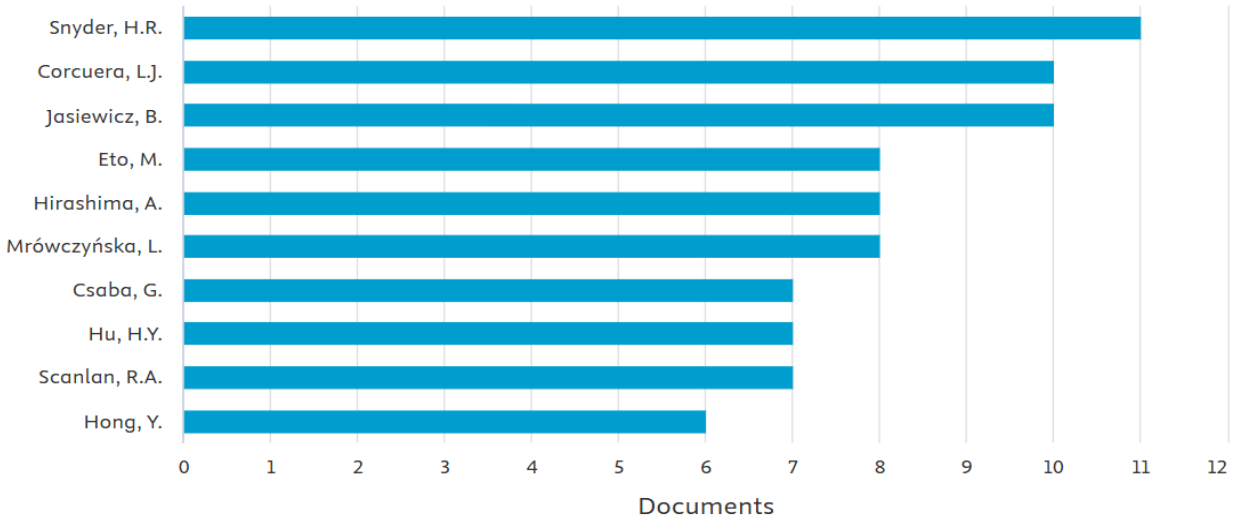


Figure 3: Top authors working on gramine (from Elsevier Scopus)

2. Physicochemical characterization and preparation of gramine

2.1. Structure and derivatives

Gramine, with the chemical formula $C_{11}H_{14}N_2$, is an indole derivative substituted in position 3 by a dimethylaminomethyl group ($-CH_2N(CH_3)_2$), forming a tertiary amine linked to a conjugated bicyclic aromatic ring. is a natural organic compound belonging to the indole alkaloid family, found in many plants, particularly grasses. Grasses can use it for defense, as the molecule is toxic to many organisms. (Semenov and Granik, 2004).

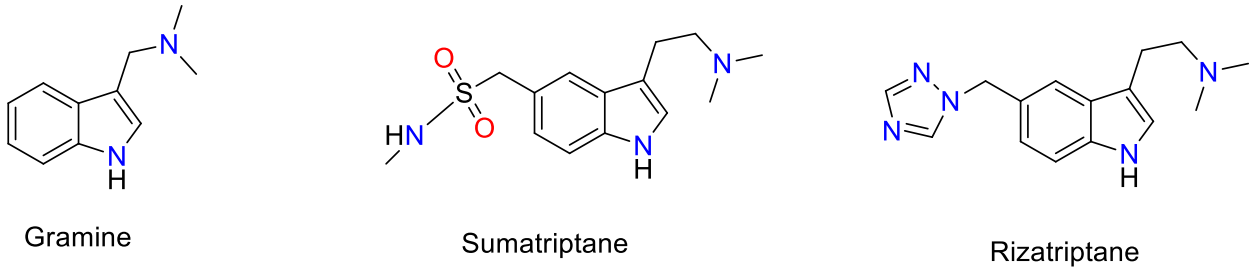


Figure 4: Chemical structures of gramine and therapeutic indole derivatives (*Sumatriptan* and *Rizatriptan*) (Lines and Visser, 2001)

2.2 Physical and chemical properties

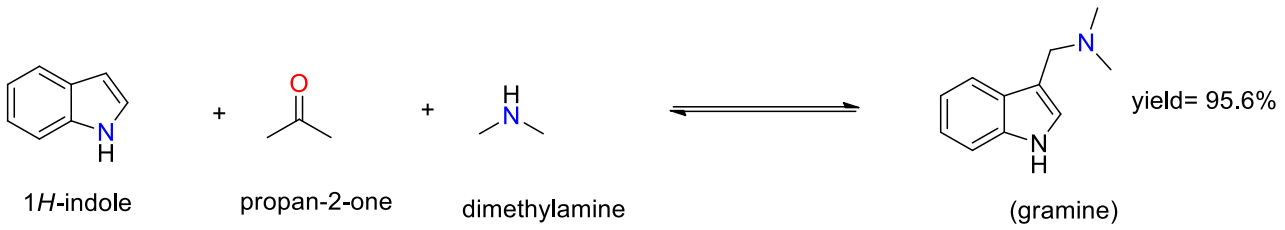
In the table below (**Table 1**) we summarize the physical and chemical of gramine:

Table 1: Physicochemical Properties of Gramine (NCBI, 2025)

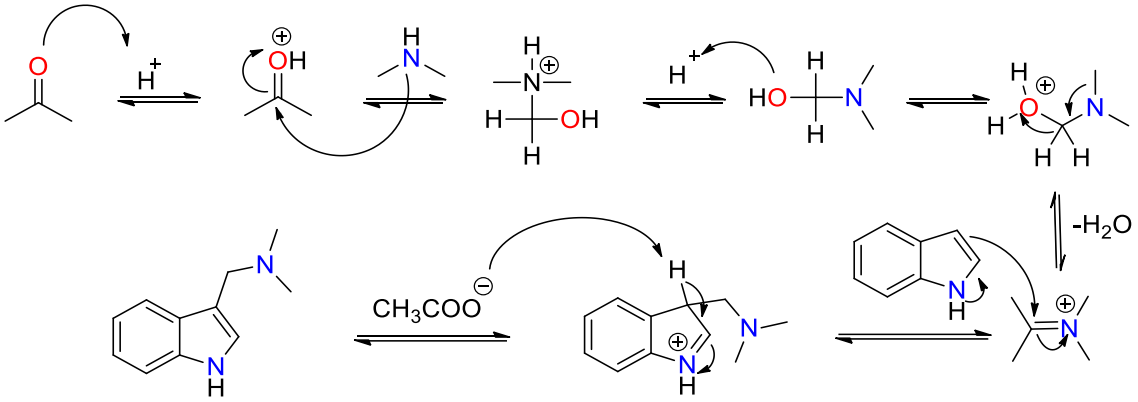
Molar Mass	175.23 g/mol
Physical state	Crystalline solid
Density	1.2 g/cm³ (approx.)
Boiling point	315 °C
Melting point	165-167 °C

2.3 Chemical synthesis and mechanism

Gramine and its derivatives have been synthesized by various methods by the scientific community due to their attractive function and biological activities. For the sake of clarity, we have summarized these classic and effective synthesis methods according to their key reaction type. The Mannich reaction (**Scheme 1**) is widely used in the synthesis of gramine and its derivatives, with indole, propan-2-one (formaldehyde), and dimethylamine as raw materials. (Xu *et al*., 2004) synthesized gramine using acetic acid as a catalyst, with a total yield optimized to 95.6% (Xu and Wei, 2004). (Zhang *et al*., 2020) demonstrated the synthesis of gramine which were substituted with methyl, nitro, and methoxy groups, with yields ranging from 70.5% to 95%. In 2014, microwave-assisted technology was introduced into the acetic acid-catalyzed Mannich reaction, with a high yield of 98.1% (Yin *et al*., 2014). In particular, the response time is only 5 minutes. The development of efficient synthetic pathways is crucial for accessing these bioactive indole scaffolds. In the field of catalysis, (Mezinae *et al*., 2024), (Abbaoui *et al*., 2025), (Ridal *et al*., 2026) and (Titi *et al*., 2023) have reported advanced catalytic methodologies regarding N-heterocyclic compounds, offering sustainable routes that could be applied to the synthesis of gramine derivatives.



Scheme 1: the synthesis method based on the Mannich reaction.



Scheme 2: Mechanism of the Gramine synthesis reaction

2.4 Extraction and separation

Ultrasonic extraction of gramine is based on the principle of sonication, which uses high-frequency ultrasonic waves (generally between 20 and 40 kHz) to cause acoustic cavitation in the extraction solvent (**Figure 5**). This phenomenon creates microbubbles that implode near the cell walls of plant matrices (such as barley or reed), causing them to rupture and thus promoting the efficient release of intracellular compounds, including gramine. This technique is considered fast, efficient, and environmentally friendly, as it allows for more complete extraction in less time while using less solvent compared to conventional methods (such as maceration or percolation) (Vinatoru, 2001). In 2020, an ultrasonic method was used to extract gramine (Li *et al*., 2020). The extraction rate of A. donax L. gramine was 1% under the following conditions: ultrasonic power: 600 W, duration: 50 min, temperature: 50°C, liquid/material ratio: 40 mL/g, and pH: 5.

3. Biological activities

3.1. Antiviral activity

Enterovirus 71, widely reported in the Asia-Pacific region, is a classic RNA virus that can infect the hands, feet, and mouth of humans (Dan *et al*., 2023). Prevention of this disease has so far relied mainly on alerts and public health management (Batista *et al*., 2019). Furthermore, no specific drugs for enterovirus 71 infections have been used in clinical practice to date. Usually, certain broad-spectrum antiviral drugs, such as type I interferon, ribavirin, and pleconaril, are used to treat enterovirus 71 infection (Han *et al*., 2021). In 2014, certain gramine derivatives synthesized by Wei *et al*. showed

potential inhibitory activity on the cytopathic effects induced by enterovirus 71. Beyond viral infections, the pharmacological scope of these scaffolds encompasses significant antiproliferative properties. Recently, (Abbaoui *et al*., 2025) and (Qorri *et al*., 2025) synthesized and characterized novel N-heterocyclic entities, demonstrating their potential through anticancer evaluation and comprehensive ADME profiling (**Figure 6**).

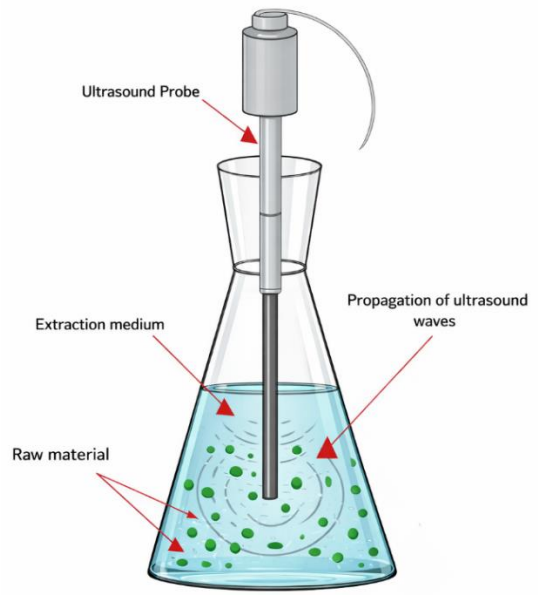
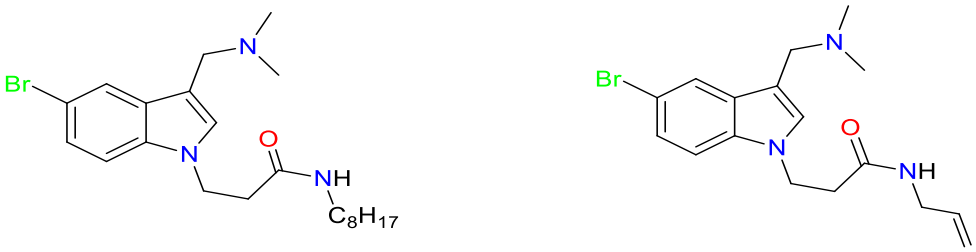


Figure 5: The Ultrasonic Device



(**a**) (**b**)

Figure 6: Chemical structures of gramine derivatives (**a**–**b**) exhibiting antibacterial activity

3.2. Antibacterial activity

In 2014, Yang *et al*. reported the antibacterial activity of gramine, which could effectively inhibit the growth of Escherichia coli and Staphylococcus aureus with minimum inhibitory concentrations (MIC) of 16.92 and 6.26 μg/mL (Shklar, 1999). In addition, it may also slightly inhibit the growth of methicillin-resistant Staphylococcus aureus (MRSA) with an inhibition rate of 82% at 400 μg/Ml (Kumar and Suresh, 2014). In 2018, Feng *et al*. reported the antibacterial activity of gramine derivatives associated with the acylamino group (Feng *et al*., 2018). It is interesting to note that compounds (**a**) and (**b**) showed moderate antibacterial activity against S. aureus with an MIC of 30 μg/mL. The rhizosphere microbiota can reflect the growth and development status of plants, which is valuable for sustainable agriculture. In 2021, Maver *et al*. discovered that gramine could regulate prokaryotic communities in the

rhizosphere microbiota of barley (Maver *et al*., 2021). In the same year, these results were also validated by Schütz *et al* (Schütz *et al*., 2021). They discovered that gramine could promote the proliferation of beneficial strains, such as ASV Novosphingobium and Massilia. Further expanding on this antimicrobial potential, (Abbaoui *et al*., 2025) conducted a dual in silico and in vitro evaluation of N-heterocyclic derivatives. Their study combined molecular docking, SAR analysis, and ADMET profiling to confirm the efficacy of these compounds as promising antimicrobial agents (**Figure 6**).

3.3. Antifungal activity

In 2001, Matsuo *et al*. discovered that gramine content increased significantly in the leaves of barley seedlings after infection with Blumeria graminis, indicating its potential antifungal activity (Matsuo *et al*., 2001). In 2011, Schreiber *et al*. reported that gramine 1 could effectively reduce the severity of Fusarium graminearum infection in wheat (Schreiber *et al*., 2011). In 2011, Wollein *et al*. studied the antifungal activity of gramine derivative (**a**) against Candida glabris and Aspergillus Niger (Wollein and Bracher, 2011). Unfortunately, no inhibitory activity was found. However, its cyclization product (**b**) showed antifungal activity against C. glabris and A. Niger with inhibition zone diameters of 11 and 10 mm, respectively (Zhang *et al*., 2013). In 2019, Lu *et al*. discovered that compounds (**f**) and (**e**) exhibited an inhibitory effect of more than 90% in vitro against the plant pathogen Phytophthora piricola at 50 μg/mL via the mycelial growth method (Lu *et al*., 2019) (**Figure 7**).

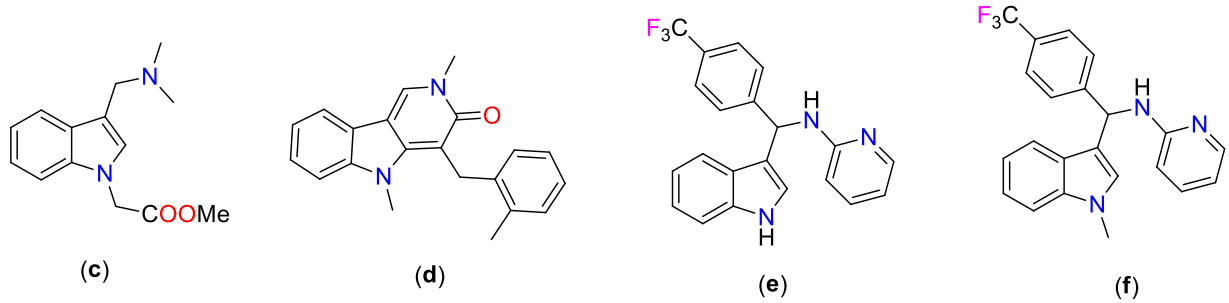


Figure 7: Chemical structures of indole derivatives evaluated for antifungal activity (**c**–**f**)

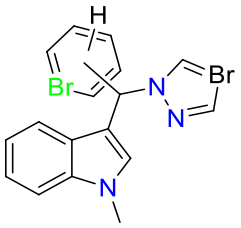
3.4. Anti-inflammatory activity

Inflammation is loosely defined as a response to invading pathogens or endogenous signals, which plays a vital role in many diseases, particularly certain chronic diseases (Dan *et al*., 2023). 5-lipoxygenase (LOX) enzymes, which are involved in the biosynthesis of leukotrienes with arachidonic acid, may mediate inflammatory reactions (Batista *et al*., 2019). Inhibition of the inflammatory factor nitric oxide (NO) has also been considered as an anti-inflammatory strategy (Han *et al*., 2021). In 2017, Magalhães *et al*. reported that gramine 1 can inhibit LOX activity, with an IC_{25} value of 119 μg/mL. In addition, it can effectively trap 34% of nitric oxide radicals at 1 mg/mL (Magalhães *et al*., 2017). In 2021, Lu *et al*. discovered that gramine could inhibit the release of pro-inflammatory mediators, including interleukin-

1β (IL-1β), IL-6, tumor necrosis factor (TNF)-α, and NO secreted by lipopolysaccharide (LPS)-induced microglia. In addition, it was found to reduce the expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2). In vivo behavioral and histological experiments indicated that gramine could attenuate microglial activation and promote motor functional recovery via the NF-κB pathway (Lu *et al*., 2021) (**Figure 8**).

3.5. Antitumor activity

Oral squamous cell carcinoma (OSCC), one of the deadliest tumors, is one of the six leading human malignancies (Torre *et al*., 2015). 7.12 Dimethylbenz[a]anthracene (DMBA) induced OSCC in a hamster buccal pouch (HBP), which is widely used as an animal model (Shklar, 1999). In 2014, Kumar *et al*. reported that gramine had a potential chemopreventive effect on DMBA-induced BPH, which could be attributed to its lipid anti-peroxidative potential, antioxidant potential, and recovery effects, as well as its detoxifying potential (Kumar and Suresh, 2014). In 2017, they discovered that gramine reduced angiogenesis and induced apoptosis in BPH by regulating transforming growth factor (TGF)-β signaling (Ramu *et al*., 2017). In 2018, they further demonstrated that gramine could activate the function of key cancer-suppressing proteins p21, p53, and Gsk-3β, which explained its anti-proliferative effects (Ramu *et al*., 2018). In 2012, Ke *et al*. reported the anti-proliferative activity of compound (**g**) against human gastric cancer, human lung cancer, and human hepatocellular liver cancer cell lines.



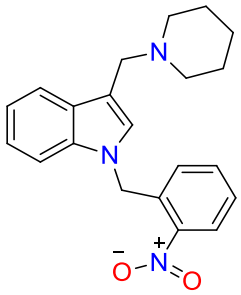
(**g**)

Figure 8: Chemical structure of the hybrid N-heterocyclic entity (g) evaluated for antitumor activity

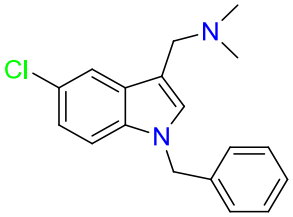
3.6. Treatment of Alzheimer's disease

Alzheimer's disease (AD), as a neurodegenerative disease, represents an enormous burden on society (Cousins *et al*., 2021). The physiological characteristics of AD, including β-amyloid (Aβ) peptide and neurofibrillary tangles (NFTs) caused by the aggregation of τ protein, are important therapeutic targets (Iqbal *et al*., 2016). The increasing amount of phosphorylated τ protein causes its self-aggregation into NTT, depending on kinase and phosphatase activity. Specifically, Ser/Thr phosphatase plays an important role in the dephosphorylation of τ protein (Zhang *et al*., 2013). Furthermore, reducing cytosolic Ca^{2+} in neurons can block the development of AD, as demonstrated by the successful commercialization of memantine (Anand *et al*., 2014). In 2016, Lajarín-Cuesta *et al*. reported that compound 80 could reduce Ca^{2+} influx via voltage-gated calcium channels (VGCCs) and maintain the

action of Ser/Thr phosphatase 2A (PP2A), thereby decreasing τ hyperphosphorylation (Lajarin-Cuesta *et al*., 2016). In 2018, their group reported the activity of N-benzylated gramines 81 that dissipate neuronal Ca^{2+} overload (Gonzalez *et al*., 2018). The introduction of a nitro group into benzyl could greatly improve the VGCC blocking effect with an IC_{50} of 1.8 μM for compound (**h**). Furthermore, Lajarín-Cuesta *et al*. synthesized a derivative of (**i**), which could restore 78% of PP2A activity and block 40% of VGCC (Zhang *et al*., 2023). Previous research has indicated that neuroinflammation is a therapeutic target in neurodegenerative diseases, such as AD (Dan *et al*., 2023). English Activation of NF-κB in neurons will promote their survival (**Figure 9**). In 2021, Yang *et al*. reported that gramine prevented apoptosis of PC12 cells, inhibited neuroinflammation via the NF-κB signaling pathway, and ultimately promoted the treatment of associated central nervous system diseases such as AD (Lu *et al*., 2021). In 2023, Jadhav *et al*. found that gramine remarkably restored memory in a scopolamine-induced amnesia model, indicating its potential in the treatment of AD (Jadhav and Sable, 2023).



(**h**)

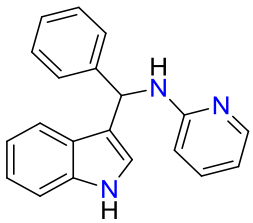


(**i**)

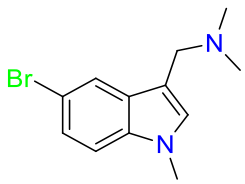
Figure 9: Chemical structures of N-benzyl indole derivatives (**h**–**i**) evaluated for anti-Alzheimer potential

3.7. Insecticidal activity

Gramine, as an important defensive toxin in plants, exhibits broad-spectrum insecticidal activity against herbivorous insects (**Figure 10**), including aphids, cotton bollworms, brown planthoppers, and beetles (Yang *et al*., 2021). In addition, gramine also exhibits toxicity to Daphnia magna with an EC_{50} value of 6.03 μg/mL (Griffiths *et al*., 2021). In 2019, Lu *et al*. explored the insecticidal activities of compounds (**j**–**k**) against *Helicoverpa armigera*, *Culex pipiens pallens*, *Ostrinia nubilalis*, and *Mythimna separe*. Notably, the insecticidal rate of (**j**) against *C. pipiens pallens* can reach 80% at a concentration of 10 μg/mL (Lu *et al*., 2019).



(**j**)



(**k**)

Figure 10: Chemical structures of indole derivatives (**j**–**k**) evaluated for insecticidal activity

4. Result and discussion

4.1. Applications

The figure below is a pie chart illustrating the distribution of scientific publications by discipline. It highlights the fields most represented in scientific output. It can be seen that life and material sciences occupy a predominant place, particularly biochemistry, genetics, and molecular biology (22.9%), closely followed by chemistry (21.5%) and agriculture and biological sciences (15.9%). Other disciplines such as pharmacology, medicine, and chemical engineering are also well represented, while fields such as computer science, materials science, and engineering are present in smaller proportions. This graph thus allows us to visualize the thematic distribution of published research, highlighting the importance given to certain fields in the current scientific landscape (**Figure 11**).

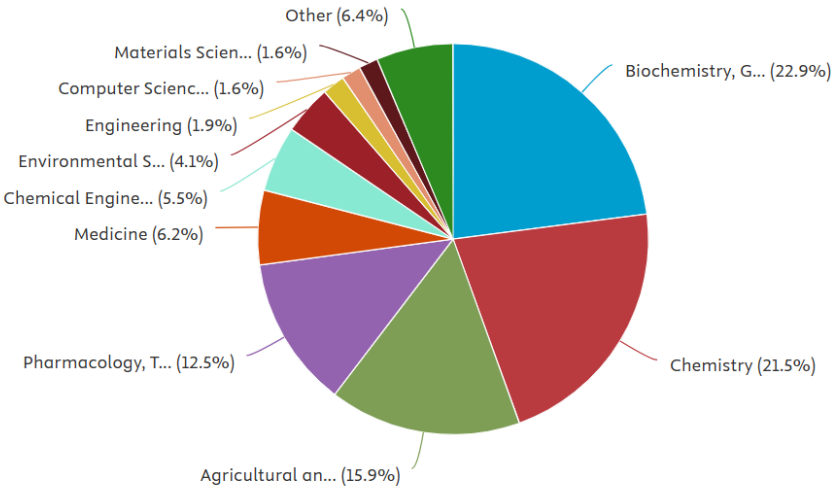


Figure 11: The areas of application of gramine

4.1.1. Natural plant defense

Gramine is a secondary metabolite produced by certain grasses (such as barley, reed, or rye) in response to stress or insect attack. It has antifeedant (prevents insects from feeding) and toxic properties, particularly against aphids, Colorado potato beetles, and grasshoppers. It works by disrupting the insects' nervous system, which drives them away from the plant. This property is used naturally by the plant as a chemical defense barrier. (Leszczynski *et al*., 1989)

4.1.2. Model molecules in pharmacology

Thanks to its indole structure and tertiary amine function, gramine is used in laboratories to model interactions between natural alkaloids and biological receptors, particularly biogenic amine receptors (such as serotonin). It serves as a basis for designing new neuroactive compounds and better understanding the behavior of alkaloids in biological environments, particularly at the synaptic level. (Glennon *et al*., 1980)

4.1.3. Phytotoxic effect (potential natural herbicide)

Gramine, when accumulated in the soil or on the surface of leaves, can inhibit germination or slow the growth of competing plants, particularly certain weeds. It acts by disrupting the cellular metabolism of sensitive seedlings. This natural phytotoxicity could be exploited in sustainable agriculture as an environmentally friendly alternative to synthetic herbicides. (González-Coloma *et al*., 2002)

4.1.4. Application of gramine in the cosmetics industry

Gramine is sometimes explored in cosmetics for its antioxidant and anti-inflammatory properties, derived from its indole structure. It can inhibit lipid peroxidation and reduce oxidative stress in skin cells, making it potentially useful in anti-aging and soothing formulations, or to prevent UV-induced damage. In addition, certain extracts rich in gramine (from plants such as Arundo donax) are incorporated into natural cosmetic products for their protective effects and their role in strengthening the skin barrier (Zhang *et al*., 2014).

4.2. Results

The figure below illustrates the evolution of the number of documents published per year over a period from 1937 to 2025 in a given field of research. There is a general upward trend, marked by low activity before the 1970s, followed by gradual growth between 1980 and 2010. From 2015 onwards, the curve shows a sharp and rapid increase in the number of publications, peaking in 2025 with more than 25 documents. This increase reflects a growing interest in the subject among the scientific community, particularly over the last two decades (**Figure 12**).

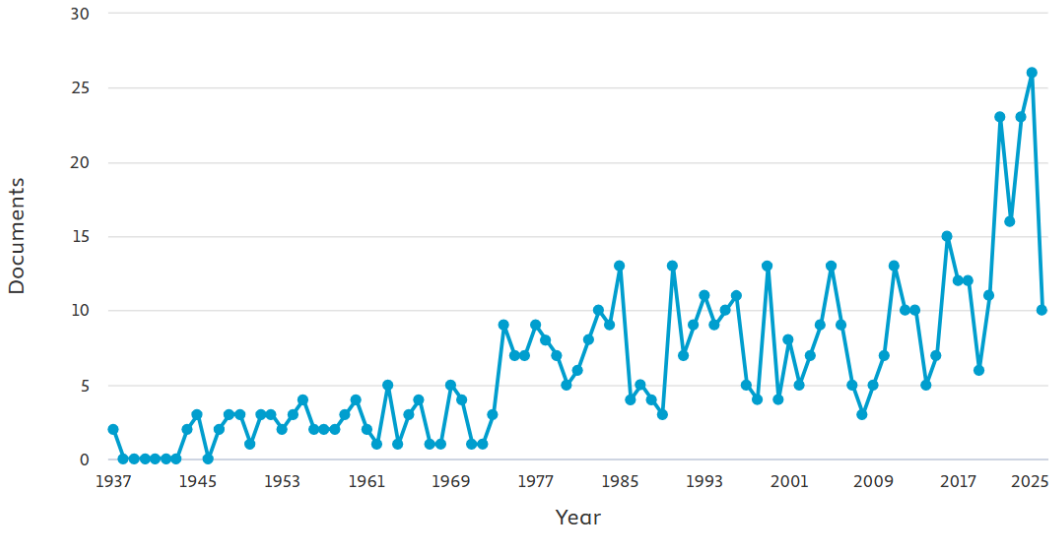


Figure 12 : Scientific production of gramine (1937-2025) (from Elsevier Scopus)

5. Conclusion and Perspectives

This review presents a wealth of information on gramine alkaloids, including their extraction, chemical synthesis, and various biological activities that have been discovered since their first isolation in 1935. First, the source, distribution, and extraction technology of gramine are briefly summarized. Next, their chemical synthesis methods are described according to their key reaction type. Clearly, gramine skeletons can be easily obtained. Modifications with various bioactive moieties provide many potential molecules. Indeed, some drugs with a structure similar to gramine have been successfully commercialized, such as sumatriptan and rizatriptan. In addition, a literature search revealed that their mechanisms of biological activity have also been thoroughly discussed. Of course, there is still much unreported information regarding the pharmacological activity of gramine skeletons. For medicinal chemists, gramine-based drugs will be used in the long term due to their simple structures and desirable activities. New research perspectives in gramine-based medicinal chemistry can be divided into the following themes: (**a**) introduction of key pharmacophores via hybrid molecule design; (**b**) structural optimization for defects such as poor pharmacokinetics and bioavailability; (**c**) elucidation of structure-activity relationships; (**d**) research on drug combinations and drug resistance; (**e**) in-depth exploration of various molecular mechanisms and targets, such as the application of multi-omic analysis; (**f**) effective forms of administration of drug molecules based on gramine skeletons; and (**g**) discovery and expansion of diverse pharmacological activity.

Acknowledgments: The authors would like to thank for their support ANPMA/CNRST/UMP/VPMA347/20 project. The authors gratefully acknowledge the support from the MHESRI/DHRSR-Morocco and MIT-Hungary (Convention 2023, no. 1 & 2).

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

Abbaoui, Z., Merzouki M., Oualdi I., Bitari A., Oussaid A., Challioui A., Touzani R., Hammouti B., Agerico Dino W. (2024) Alzheimer's disease: In silico study of rosemary diterpenes activities. *Current Research in Toxicology*. (6) 100159. https://doi.org/10.1016/j.crtox.2024.100159

Abbaoui, Z., Khibech, O., Karci, H., Dündar, M., Özdemir, İ., Gürbüz, N., Koç, A., Agerico Dino, W., Özdemir, İ., Alenazi, N., Touzani, R., Alghibiwi, H. (2025). Synthesis, Characterization, and Anticancer Evaluation of N-Heterocyclic Entities: ADME Profiling and In Silico Predictions. *Toxicology Reports*, 102184. https://doi.org/10.1016/j.toxrep.2025.102184

Abbaoui Z., Khibech, O., Oulous, A., Karci, H., Dündar, M., Özdemir, İ., Gürbüz, N., Koç, A., Özdemir, İ., Touzani, R. (2025). In Silico and In Vitro Evaluation of N-Heterocyclic Derivatives as Antimicrobials: ADMET Analysis, SAR, and Molecular Docking. *In Silico Pharmacology*. 13, article number 163, https://doi.org/10.1007/s40203-025-00445-y

Abbaoui, Z., Arrass, H., Touzani, R., Moussa, S. B., Alzahrani, A. Y. A., & Hammouti, B., (2025). Combined Pyrazole and Cu (II), Co (II) Metals: An Excellent Catalyst for Catecholase, Tyrosinase, Phenoxazinone Synthase, and Laccase for Oxygen Activation. *ASEAN Journal of Science and Engineering*, 5(2), 417-446. https://doi.org/10.17509/ajse.v5i2.88662

Abdelazeem, N.M., Gouhar, S.A., Fahmy, C.A. *et al.* (2024). Evaluation of newly synthesized 2-(thiophen-2-yl)-1H-indole derivatives as anticancer agents against HCT-116 cell proliferation via cell cycle arrest and down regulation of miR-25. *Scintific Reports*, 14, 20045, https://doi.org/10.1038/s41598-024-68815-8

Anand, R., Gill, K. D., & Mahdi, A. A. (2014). Therapeutics of Alzheimer's disease: Past, present and future. *Neuropharmacology*, 76, 27–50. https://doi.org/10.1016/j.neuropharm.2013.07.004

Anderson, J. N., & Martin, R. O. (1976). Aphylline, epiaphylline, 10,17-dioxosparteine, gramine, and other unexpected alkaloids from Lupinus hartwegii. *Journal of Organic Chemistry*, 41, 3441–3444. https://doi.org/10.1021/jo00883a026

Anson, A.D., Ditz K.M., Singletary G.W., Leland T.J. (1983). Accumulation of gramine in barley leaves grown under heat stress. Plant Physiology, 71, 896–904. https://doi.org/10.1104/pp.71.4.896

Aria, M., Cuccurullo C. (2017). Bibliometrix: An R-tool for comprehensive science mapping analysis, *Journal of Informetrics*, 11(4), 959–975

Batista, C. R. A., Gomes, G. F., Candelario-Jalil, E., Fiebich, B. L., & Oliveira, A. C. P. (2019). Lipopolysaccharide-induced neuroinflammation as a bridge to understand neurodegeneration. *International Journal of Molecular Sciences*, 20, 2293. https://doi.org/10.3390/ijms20092293

Cousins, K. A. Q., Bove, J., Giannini, L. A. A., *et al*. (2021). Longitudinal naming and repetition relate to Alzheimer's disease pathology and primary progressive aphasia burden confirmed at autopsy. *Alzheimer's & Dementia: Translational Research & Clinical Interventions,* 7, e12188. https://doi.org/10.1002/trc2.12188

Dan, W., Cao, Y., Sun, Y., *et al*. (2023). Novel N1- or N9-modified α-carboline analogues as potential ligands for Alzheimer's disease treatment: Synthesis and neurobiological activity evaluation. *Bioorganic Chemistry*, 133, 106378. https://doi.org/10.1016/j.bioorg.2023.106378

Dan, W.; *et al*. Novel N1- or N9-modified α-carboline analogues as potential ligands for Alzheimer's disease: synthesis and neurobiological evaluation. *Bioorganic Chemistry* 2023, 133, 106378. https://doi.org/10.1016/j.bioorg.2023.106378

Er-rajy M., El fadili M., Alnajjar R., Zarougui S., Mujwar S., Azzaoui K., Abueleiz HA. Hammouti B., Elhallaoui M. (2025) An in-depth study of indolone derivatives as potential lung cancer treatment. *Scientific Reports*, 15, 2199. https://doi.org/10.1038/s41598-025-85707-7

Feng, K., Li, X., & Yu, L. (2018). Synthesis, antibacterial activity, and antifouling marine coating application of novel acylamino compounds containing gramine groups. *Progress in Organic Coatings*, 118, 141–147. https://doi.org/10.1016/j.porgcoat.2017.10.027

Glennon, R. A., *et al*. (1980). Serotonin receptor binding affinities of tryptamine analogues. *Journal of Medicinal Chemistry*, 23(3), 294–299. https://doi.org/10.1021/jm00177a017

Gonzalez, D., Arribas, R. L., Viejo, L., Lajarin-Cuesta, R., & Rios, C. L. (2018). Substituent effects of N-benzylated gramine derivatives preventing PP2A inhibition and dissipating neuronal calcium overload as a multitarget strategy for Alzheimer's disease. *Bioorganic & Medicinal Chemistry*, 26, 2551–2560. https://doi.org/10.1016/j.bmc.2018.04.019

González-Coloma, A., *et al*. (2002). Bioactive indole alkaloids from Arundo donax. *Journal of Agricultural and Food Chemistry*, 50(3), 563–568. https://doi.org/10.1021/jf010924p

Griffiths, M.R., Strobel B.W., Hama J.R., *et al*. (2021). Toxicity and risk of plant alkaloids to Daphnia magna. *Environmental Sciences Europe*, 33, 10. https://doi.org/10.1186/s12302-020-00452-0

Hadda T.B., Rastija V., AlMalki F., Titi A., Touzani R., Mabkhot Y.N., Khalid S., *et al*. (2021). Petra/Osiris/Molinspiration and molecular docking analyses of 3-hydroxy-indolin-2-one derivatives as potential antiviral agents Current Computer-Aided, *Drug Design* 17 (1), 123-133, https://doi.org/10.2174/1573409916666191226110029

Hammouti B., Aichouch I., Kachbou Y., Azzaoui K., Touzani R. (2025) Bibliometric analysis of global research trends on UMI using Scopus database and VOS viewer from 1987–2024, *J. Mater. Environ. Sci.*, 16(4), 548-561

Han, R., Yuan, T., Yang, Z., *et al*. (2021). Ulmoidol, an unusual nortriterpenoid from Eucommia ulmoides leaves, prevents neuroinflammation by targeting the PU.1 transcriptional signaling pathway. *Bioorganic Chemistry*, 116, 105345. https://doi.org/10.1016/j.bioorg.2021.105345

Iqbal, K., Liu, F., & Gong, C. X. (2016). Tau and neurodegenerative disease: The story so far. *Nature Reviews Neurology*, 12, 15–27. https://doi.org/10.1038/nrneurol.2015.225

Jadhav, G. B., Sable, R. R. (2023). Neuroprotective impact of zingerone and gramine in a scopolamine-induced amnesia model. *Journal of Pharmaceutical Negative Results*, 14, 775–784.

Kumar, R. A., Suresh, K. (2014). Chemopreventive potential of gramine against 7,12-dimethylbenz [a]anthracene-induced hamster buccal pouch carcinogenesis. *International Journal of Modern Research and Reviews*, 2, 188–194.

Kumar R.A., Suresh K. (2014). Chemopreventive potential of gramine against DMBA-induced hamster buccal pouch carcinogenesis. *International Journal of Modern Research and Reviews*, 2, 188–194

Kumar A., Dapkekar A.B., Satyanarayana G. (2025). Recent synthetic advances in the preparation of 1,3-thiazole compounds and their therapeutic applications in degenerative diseases, *Org. Biomol. Chem.*, 23, 9222-9256 https://doi.org/10.1039/D5OB01302J

Laita M., Sabbahi R., Elbouzidi A., Hammouti B., Messaoudi Z., Benkirane R., Aithaddou H. (2024) Effects of Sustained Deficit Irrigation on Vegetative Growth and Yield of Plum Trees Under the Semi-Arid Conditions: Experiments and Review with Bibliometric Analysis, *ASEAN Journal of Science and Engineering*, 4(2), 167-190

Lajarin-Cuesta, R., Nanclares C., Arranz-Tagarro J. A., Gonzalez-Lafuente L., Arribas R.L., Brito M.A., Gandía L., Ríos C. I. (2016). Gramine derivatives targeting Ca^{2+} channels and serine/threonine phosphatases: A novel dual strategy for the treatment of neurodegenerative diseases. *Journal of Medicinal Chemistry*, 59, 6265–6280. https://doi.org/10.1021/acs.jmedchem.6b00478

Leszczynski, B., *et al*. (1989). Role of gramine in the resistance of barley to aphids. *Entomologia Experimentalis et Applicata*, 51(3), 279–285. https://doi.org/10.1111/j.1570-7458.1989.tb01276.x

Li, L., Yang, P., Li, X., Pan, F., & Yan, H. (2020). Optimization of gramine extraction from Arundo donax using response surface methodology. *Food Industry*, 41, 47–51.

Lines C.R., Visser W.H. (2001). Rizatriptan: Pharmacological differences from sumatriptan and clinical results. *Current Medical Research and Opinion*, 17, S54–S58. https://doi.org/10.1185/0300799039117015

Lu, A., Wang, T., Hui, H., *et al*. (2019). Natural products for drug discovery: Discovery of gramines as novel agents against a plant virus. *Journal of Agricultural and Food Chemistry*, 67, 2148–2156. https://doi.org/10.1021/acs.jafc.8b06859

Lu, X.; *et al*. (2021). Gramine promotes functional recovery after spinal cord injury by enhancing microglial activation.*Journal of Cellular and Molecular Medicine*, 25, 7980–7992. https://doi.org/10.1111/jcmm.16728

Magalhães, S.C.Q., Fernandes, F., *et al*. (2017). Alkaloids in Lupinus spp. seed valorization. *Industrial Crops and Products*, 95, 286–295. https://doi.org/10.1016/j.indcrop.2016.10.033

Martins J., Gonçalves R., Branco F. (2024). A bibliometric analysis and visualization of e-learning adoption using VOSviewer. *Univ Access Inf Soc* 23, 1177–1191, https://doi.org/10.1007/s10209-022-00953-0

Matsuo, H., Taniguchi, K., Hiramoto, T., *et al*. (2001). Increase in gramine associated with rapid and transient systemic resistance induced by mechanical and biological stress in barley seedlings. *Plant & Cell Physiology*, 42, 1103–1111. https://doi.org/10.1093/pcp/pce139

Maver, M., Escudero-Martinez, C., *et al*. (2021). Applications of the indole alkaloid gramine modulate rhizosphere microbiota assembly in barley. *PeerJ*, 9, e12498. https://doi.org/10.7717/peerj.12498

Meziane, H., Abbaoui, Z., Ouabane, M., Djedouani A., *et al*. (2024). Exploring Phenoxazinone Synthase Activities: Experimental and Theoretical Analyses of Symmetrical Azine Ligands. *Physical Chemistry Research*. 12(4) 859-868. https://doi.org/10.22036/pcr.2024.420037.2433

Mishra, P. (2026). Carbon market mechanisms and biodiversity co-benefits for sustainable development: a bibliometric analysis of global research trends and policy integration. *Environ Syst Res* 15, 2, https://doi.org/10.1186/s40068-025-00452-0

National Center for Biotechnology Information (NCBI). (2025). PubChem compound summary for CID 6890, Gramine. Retrieved 2025, from https://pubchem.ncbi.nlm.nih.gov/compound/Gramine

N'diaye A.D., Kankou M.S.A., Hammouti B., Nandiyanto A.B.D., Al Husaeni D.F. (2022). A review of biomaterial as an adsorbent: From the bibliometric literature review, the definition of dyes and adsorbent, the adsorption phenomena and isotherm models, factors affecting the adsorption process, to the use of typha species waste as adsorbent. *Communications in Science and Technology*, 7(2), 140-153. https://doi.org/10.21924/cst.7.2.2022.977

Omar F, Tareq AM, Alqahtani AM, Dhama K, Sayeed MA, Emran TB, Simal-Gandara J. Plant-Based Indole Alkaloids: A Comprehensive Overview from a Pharmacological Perspective. Molecules. 2021; 26(8):2297. https://doi.org/10.3390/molecules26082297

Orechoff, A., & Norkina, S. (1935). On the alkaloids of Arundo donax L. *Berichte der Deutschen Chemischen Gesellschaft*, 68, 436–437. https://doi.org/10.1002/cber.19350680312

Pachter, I. J., Zacharias, D. E., & Ribeiro, O. (1959). Indole alkaloids from Acer saccharinum, Dictyoloma incanescens, Piptadenia colubrina, and Mimosa hostilis. *Journal of Organic Chemistry*, 24, 1285–1287. https://doi.org/10.1021/jo01091a032

Qorri, I., Haily EM., Abbaoui Z., Boulouiz A., Touzani R., Karci H., Özdemir İ., Gürbüz N., Ozdomir I. (2025). Synthesis, characterization, and dual applications of novel pyrazole-based ligands and their copper (II) complexes: Anticancer, Antimicrobial, and catalytic properties. *Discovery Chemistry*, 2, article number 355. https://doi.org/10.1007/s44371-025-00443-1

Ramu, A., Kathiresan, S., & Ahmed, B. A. (2017). Gramine inhibits angiogenesis and induces apoptosis via modulation of TGF-β signaling in DMBA-induced hamster buccal pouch carcinoma.

Phytomedicine, 33, 69–76. https://doi.org/10.1016/j.phymed.2017.05.008

Ramu, A., Kathiresan, S., Ramadoss, H., *et al*. (2018). Gramine attenuates EGFR-mediated inflammation and cell proliferation in oral carcinogenesis via NF-κB and STAT3 regulation. *Biomedicine & Pharmacotherapy*, 98, 523–530. https://doi.org/10.1016/j.biopha.2017.12.049

Ridal, Z., Abbaoui, Z., Elmsellem, H., Aouniti A., Yousfi, El B., El Kodadi, M., *et al*. (2026). Multifaceted Applications of Pyrazole-Based Tetradentate Ligand Coordinated with Transition Metals (Fe, Zn, Co, Cu): Synthesis, Characterization, Catalysis, Antimicrobial Activity, ADMET, and Molecular Docking Insights. *ASEAN Journal of Science and Engineering*, 6(2), 149-172. https://doi.org/10.17509/ajse.v6i1.89885

Salghi R., Alaoui M.M., Kadda S., Azzaoui K., Hammouti B. (2025). Azerbaijan: Bibliometric analysis using Scopus, VOSviewer and AD Scientific Index, *J. Mater. Environ. Sci.*, 16(12), 2261-2278

Schreiber, K. J., Nasmith, C.G., Allard, G., *et al*. (2011). Found in translation: High-throughput chemical screening in Arabidopsis thaliana identifies small molecules that reduce Fusarium head blight of wheat. *Molecular Plant-Microbe Interactions*, 24, 640–648. https://doi.org/10.1094/MPMI-09-10-0210

Schütz, V., Frindte, K., Cui, J., *et al*. (2021). Differential impact of plant secondary metabolites on soil microbiota, *Frontiers in Microbiology*, 12, 666010. https://doi.org/10.3389/fmicb.2021.666010

Semenov, B. B., & Granik, V. G. (2004). Chemistry of N-(1H-indol-3-ylmethyl)-N,N-dimethylamine (gramine): A review. *Pharmaceutical Chemistry Journal*, 38, 287–310. https://doi.org/10.1023/B:PHAC.0000048140.06266.63

Shklar, G. (1999). Experimental oral carcinogenesis development and its impact on current oral cancer research. *J. Dental Res.*, 78, 1768–1772. https://doi.org/10.1177/00220345990780120101

Titi A., Dahmani, M., Abbaoui, Z., El Kodadi, M., ET-Touhami, A., Yahyi, A., Yousfi, E., Touzani, R., Siaj, M. (2023). New catalysts based on carboxylate Sn(IV) complexes used in the oxidation reaction of 3,5-di-tert-butylcatechol to 3,5-di-tert-butyl-o-benzoquinone. *Reaction Kinetics, Mechanisms and Catalysis*. 137 133-148. https://doi.org/10.1007/s11144-023-02525-6

Torre, L. A., Bray, F., Siegel R.L., Ferlay J., Lortet-Tieulent J., Jemal A. (2015). Global cancer statistics, (2012). *CA: A Cancer Journal for Clinicians*, 65, 87–108. https://doi.org/10.3322/caac.21262

Tribak Z., Ghibate R., Skalli M.K., Kandri Rodi Y., Mrani D., A. Aouniti, B. Hammouti, O. Senhaji (2017). Int Synthesis and Characterization of a New Cationic Surfactant Derived from 5-Chloro-1H-indole-2,3-dione In Aqueous Systems, *Journal of Engineering Research and Application*, 7(4) (Part -1), 04-08, https://doi.org/10.9790/9622-0704010408

Vinatoru M. (2001). An overview of the ultrasonically assisted extraction of bioactive principles from herbs. *Ultrasonics Sonochemistry*, 8, 303–313. https://doi.org/10.1016/S1350-4177(01)00071-2

Wollein U., Bracher F. (2011). The gramine pathway to pyrido[4,3-b]indol-3-ones: Identification of a new cytotoxic compound. *Scientia Pharmaceutica*, 79, 59–68. https://doi.org/10.3797/scipharm.1011-11

Xu, Q., & Wei, P. (2004). Synthesis and application of gramine as a novel plant-derived pesticide. *Chinese Journal of Pesticide Science*, 43, 76–77.

Yang, J., *et al*. Key glutathione S-transferase family genes involved in rice gramine detoxification in the brown planthopper Nilaparvata lugens. (2021). *Insects*, 12, 1055. https://doi.org/10.3390/insects12121055

Yin, X., Wu, W., Wu, J., Qin, S. H., Chen, Z. (2014). Microwave-assisted synthesis of gramine. *Agrochemicals*, 53, 176–178.

Zarrok H., Al Mamari K., Zarrouk A., Salghi R., Hammouti B., Al-Deyab S. S., *et al*. (2012), Gravimetric and Electrochemical Evaluation of 1-allyl-1H-indole-2,3-dione of Carbon Steel Corrosion in Hydrochloric Acid, *Int. J. Electrochem. Sci.*, 7 N°10, 10338-10357.

Zhang, J., Meng, G.Study on the synthesis of gramine and its derivatives. (2020). *Journal of Dali University*, 5, 21–26.

Zhang, M., *et al*.Serine/threonine protein phosphatases from a drug discovery perspective (2013). *FEBS Journal*, 280, 4739–4760. https://doi.org/10.1111/febs.12481

Zhang, X., *et al*. Evaluation of antioxidant and anti-inflammatory properties of Arundo donax extracts for cosmetic applications. (2014). *Industrial Crops and Products*, 56, 65–73. https://doi.org/10.1016/j.indcrop.2014.02.036

Zhang, J., Jia, Q., Li, N., Gu, L., Dan, W., & Dai, J. (2023). Recent developments of gramine: chemistry and biological activity. *Molecules*, *28*(15), 5695.

Zúñiga G.E., Salgado M.S., Corcuera L.J. (1985). Role of an indole alkaloid in barley seedling *resistance* to aphids. *Phytochemistry*, 24, 945–947. https://doi.org/10.1016/S0031-9422(00)83158-1