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Systematic Description of the Content Variation of Natural Products (NPs): To Prompt the Yield of High-Value NPs and the Discovery of New Therapeutics

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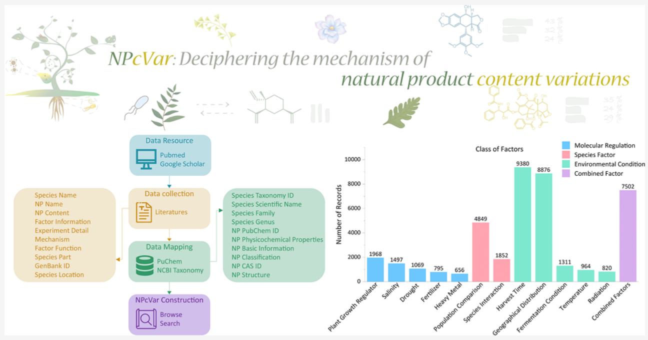
ABSTRACT: Natural products (NPs) have long been associated with human production and play a key role in the survival of species. Significant variations in NP content may severely affect the "return on investment" of NP-based industries and render ecological systems vulnerable. Thus, it is crucial to construct a platform that relates variations in NP content to their corresponding mechanisms. In this study, a publicly accessible online platform, NPcVar (http://npcvar.idrblab.net/), was developed, which systematically described the variations of NP contents and their corresponding mechanisms. The platform comprises 2201 NPs and 694 biological resources, including plants, bacteria, and fungi, curated using 126 diverse factors with 26,425 records. Each record contains information about the species, NP, and factors involved, as well as NP content data, parts of the plant that produce NPs, the location of the experiment, and reference information. All factors were manually curated and categorized into 42 classes which belong to four mechanisms (molecular regulation, species factor, environmental condition, and combined factor). Additionally, the cross-links of species and NP to well-established databases and the visualization of NP content under various experimental conditions were provided. In conclusion, NPcVar is a valuable resource for understanding the relationship between species, factors, and NP contents and is anticipated to serve as a promising tool for improving the yield of high-value NPs and facilitating the development of new therapeutics.



INTRODUCTION

Natural products (NPs) have long been valued as a rich source of pharmaceutical agents,[1−3] nutritional supplements,[4−6] and cosmetic ingredients,[7−9] among others. Their production is life-essential for originating species because of their crucial role in pollinator attraction, allelopathy effect, species defense, etc.[10−12] The rapid advances in analytical techniques (such as mass spectrometry) have prompted a clear shift from "detection" to "quantification" in current NP studies,[13−15] resulting in several quantified NP contents.[16−18] These quantified data are essential, given that specific NP content (produced by its originating species) is mainly responsible for (a) determining the yield and cost for producing the corresponding pharmaceutical/nutritional/cosmetic products[19−21] and (b) understanding the molecular mechanisms underlying the species−species cooperation/competition and species resistance to different stresses.[22−24] Therefore, studies on specific NP content have attracted significant interest from related research communities.[25−27]

However, significant NP content variation (mediated by abiotic and biotic factors)[28−30] may significantly affect the "return on investment" of NP-based industries[31] and render ecological systems severely vulnerable.[28] Therefore, many studies have been conducted to identify the mechanisms underlying variations in certain NP content.[32] These mechanisms include molecular regulation,[33] species factor,[34] environmental conditions,[35] and combined factor.[36] Some endogenous/exogenous molecules have been found to substantially increase NP production by mediating secondary metabolites.[37−39] Moreover, several species factors have been reported to extensively promote symbiosis between plants and their endophytes.[40−42] Also, many environmental conditions have been found to determine the yields of different natural products.[43−45] These mechanisms collec-

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tively and synergistically induce significant NP content variation.[46−48] Given that the variation and mechanism data accumulated in the studies mentioned are essential for prompting future NP-related "quantification" research,[49−51] a knowledge base providing these data (both content variation and regulation mechanism) is highly required.

To date, various valuable NP-related databases have been constructed.[52−64,68] Some provide data on traditional medicines and their active or inactive ingredients (HERB,[52] SymMap,[53] TCM@taiwan,[54] ETCM,[55] TCMID,[56] and NPCDR[65]); others describe the biological activities and structural characteristics of each NP (NPASS,[57] CMAUP,[58] COCONUT,[59] HIT,[60] and NPACT[61]); and the rest provide the species taxonomies and geographic locations of NPs (StreptomeDB,[62] CMNPD,[63] SWMD,[64] etc.). Although these NP-related databases have distinctive data coverage, none of them describes the data on NP content variations nor their underlying mechanism. Thus, it is crucial to construct a platform that relates NP content variations to their corresponding mechanisms.

In this study, a platform named "NPcVar" was therefore introduced to comprehensively describe variation data for NP contents. Corresponding studies of species conducted under specific conditions were manually extracted from PubMed and systematically reviewed; next, NP content variations were thoroughly examined, and the mechanisms underlying each variation were identified. Then, the data (such as NP and species) were reserved and presented on the NPcVar platform for visualization, fullly referenced by cross-linking to well-established databases.[57,58,60,66−69,71,72] Overall, NPcVar provides a valuable resource for understanding the relationship between species, factors, and NP content, and has the potential to improve the yield of high-value NPs and facilitate the development of new therapeutics.

■ CONSTRUCTION AND CONTENT

Data Source, Collection, and Curation. All data in the NPcVar were retrieved from the literature and various web repositories, and the required information was obtained from online database resources. The NP content variation data were obtained using the following sequential steps. First, 1254 common herbs were obtained from the HIT 2.0[60] database, which was deduplicated according to their Latin names; only the botanical herbs were maintained, resulting in 772 medicinal plants. Second, the related literature was obtained from PubMed by searching keyword combinations, such as "*medicinal plant Latin name* + variation + composition", "*medicinal plant Latin name* + endophyte + natural product", "*medicinal plant Latin name* + stress + secondary metabolite", and "*medicinal plant Latin name* + stress + compound". Finally, the corresponding literature on collected NP content variation data was carefully reviewed and recorded. An overview of the methodology involved in NPcVar construction is shown in Figure 1.

Data Standardization and Platform Implementation. Basic information on the NPs, such as synonyms, chemical formula, InChIKey, and physicochemical properties were retrieved from PubChem.[66] The NP classification information was based on the chemical ontology of LOTUS,[70] MeSH, and ChEMBL.[71] Moreover, basic species information, including scientific name, family, and genus, was matched using the NCBI Taxonomy.[72] All NP content variation data in NPcVar were processed uniformly per unit, allowing the user to correctly compare the differences in NP content under varying factors. Information on NP-producing plant parts and the location of the species source was also included in NPcVar, allowing researchers to conduct more comprehensive studies regarding NP yield. For ease of use, all the specific condition names from lengthy experimental conditions were compressed into a short sentence while retaining as much essence as possible. Additionally, NPcVar is based on the Apache HTTP Server, an open-source software platform developed on MySQL to manage backend resources. The front-end and search functions of NPcVar were implemented using PHP, HTML, CSS, and JavaScript. NPcVar is freely accessible at http://npcvar.idrblab.net/.

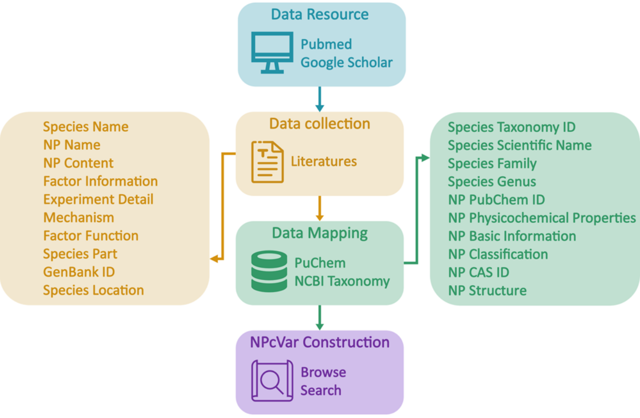

Figure 1. Workflow of NPcVar.

■ UTILITY AND DISCUSSION

Composition and Statistics of Species in NPcVar. NP content variations affect extensive biological sources. Currently, NPcVar comprises 694 distinct species, including plants, fungi, and bacteria (Figure 2a). Out of the 6763 species families in nature, 144 are drug-productive, contributing to the 933 approved and 363 clinical trial drugs.[73] The top five viridiplantae families created over 64.3% of the NPs (Figure 3b). The *Lamiaceae* family is the largest source in NPcVar, containing many medicinal plants, including thyme, mint, savory, and rosemary, among others; it is highly valued in the pharmaceutical and cosmetic fields.[74,75] The *Asteraceae* family is one of the largest plant families distributed worldwide,[76] which possesses potent antioxidant, anti-inflammatory, and antimicrobial activity, and has been used for traditional medicine.[77] The *Fabaceae* family is a prolific constituent of clinical trial drugs that primarily targets the nervous system.[73] As shown in Figure 3c, *Streptomyces* is a top-rank genus in NPcVar. It belongs to *Streptomycetaceae*, the most crucial drug-prolific family; various anti-infection, antitumor, anti-immunity, and circulation drugs are primarily from *Streptomycetaceae*.[73] *Aspergillus* and *Penicillium* are common fungal genera[78,79] of the *Aspergillaceae* family. Their secondary metabolites have been reported to exhibit enriched chemical diversity and diverse biological activities, including anticancer, antiviral, anti-inflammatory, cytotoxic, and antiparasitic activities.[80,81]

Category Distribution and Analysis of NPs in NPcVar. *Explicitly Classification of NPs by Their Biosynthetic Pathway.* NPs in NPcVar were classified into its corresponding chemical classes based on the biosynthetic pathway of LOTUS.[70] Terpenoids, fatty acids, shikimate,

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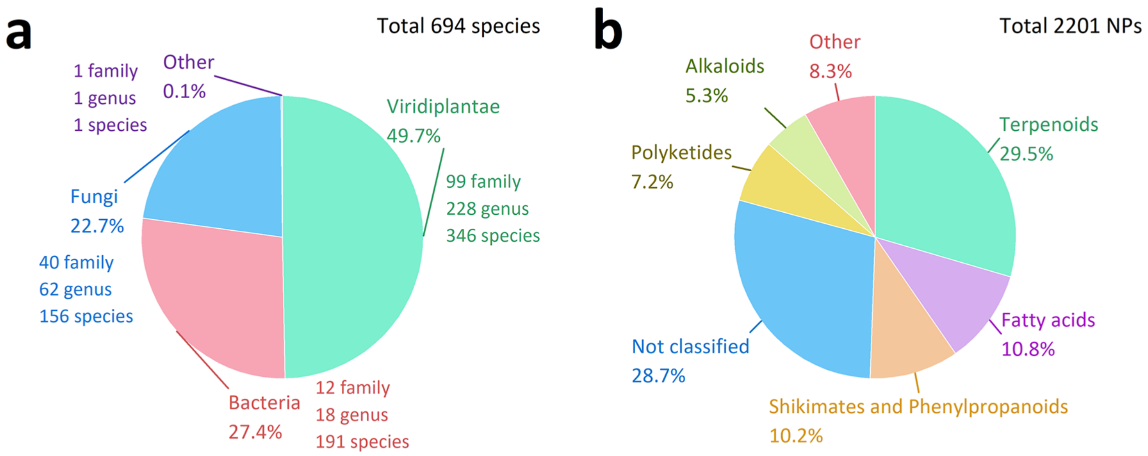

Figure 2. Pie charts illustrating the composition of NPcVar in species and natural products. (a) Composition of biological sources and their corresponding family, genus, and species number. (b) Distribution of NP categories based on the biosynthetic pathways.

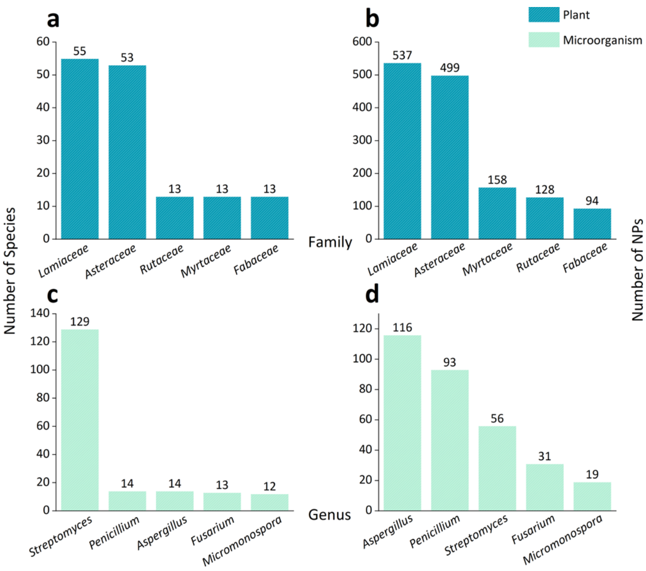

Figure 3. Statistics analysis of the top five plant families and microorganism genera of biological sources in NPcVar. (a) Top five plant families and their species number. (b) Number of natural products from the top five plant families. (c) Top five microorganism genera and their species number. (d) Number of natural products from the top five microorganism genera.

phenylpropanoids, polyketides, and alkaloids are the major constituents (63%) of the 2201 NPs (Figure 2b). Secondary metabolites are essential for thriving under different environmental conditions.[82] Terpenoids are the most diverse class of NPs in plants, representing approximately 60% of the known NPs, and are essential in plant growth and development.[83] Fatty acids are structural components of membranes in species and play a crucial role in protecting cells from abiotic stress through membrane fatty acid composition changes.[84] The shikimate and phenylpropanoid pathways comprise many crucial secondary metabolites, such as lignans, salicylic acid, shikimic acid, and flavonoids, which have essential functions in response to biotic and abiotic stresses, including plant defense, structural support, and survival.[85] Polyketides are remarkably diverse in structure and biological activity.[86,87] In NPcVar, these molecules are mainly isolated from endophytic fungi by different polyketide synthases (PKSs).[88] Their structural and functional diversity has attracted significant attention regarding the discovery of new drugs.[89−91]

Chemical Space of NPcVar Depicted by Physiochemical Properties. Six physicochemical properties were used to describe the chemical space of the 1840 NPs in NPcVar, which included the number of hydrogen bond acceptors (HBA) and donors (HBD), topological polar surface area (TPSA), octanol−water partition coefficient (log *P*), molecular weight (MW), and the number of rotatable bonds (RB). As shown in Figure 4a, 92% of the NP MWs were below 500 g/mol, which was mainly concentrated in 100−200 and 200−300 g/mol. TPSA is a parameter for predicting the ability to permeate drug cells, in which compounds with TPSA < 60 Å^2 are considered completely

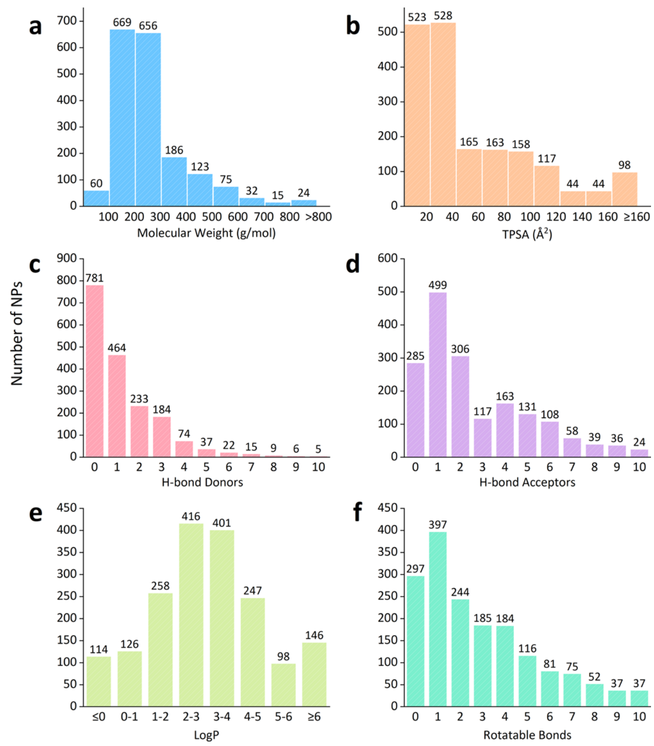

Figure 4. Distribution of the properties of compounds in NPcVar. (a) Molecular weight, (b) topological polar surface area, (c) H-bond donors, (d) H-bond acceptors, (e) log *P*, and (f) rotatable bonds.

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absorbed, and those with TPSA > 140 Å^2 have poor absorption characteristics.[92] For the distribution of TPSA in NPcVar, 66% and 92.7% of the NPs ranged between 0 and 60 Å^2 and between 0 and 140 Å^2, respectively (Figure 4b). Notably, 96.0% of the NPs had more than 10 HBA, and 96.3% had more than 5 HBD in the platform (Figure 5c,d).

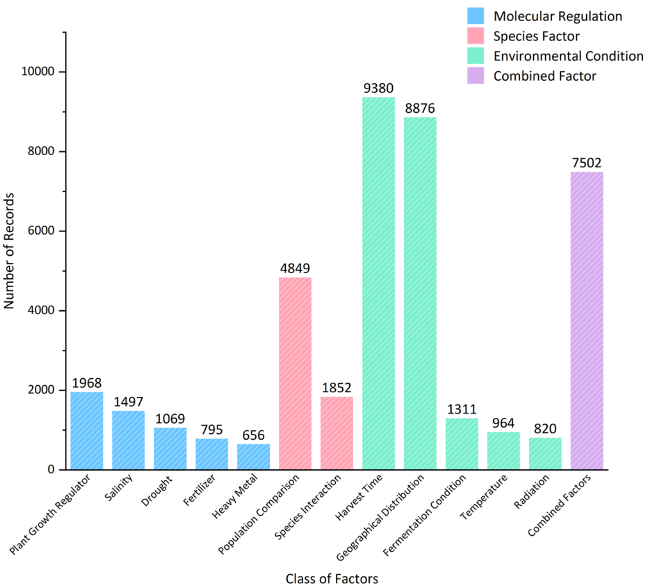

Figure 5. Composition of the factor classes in the four mechanisms and their corresponding record number. Of the 42 factor classes, 30 are combined factors such as "Heavy Metal Treatment + Species Interaction" and "Salinity Treatment + Plant Growth Regulator". For presentation purposes, all combined factors are placed in one column.

Additionally, 80.2% of NPs had log *P* values between 0 and 5, whereas only 13.5% of NPs had log *P* values > 5 (Figure 4e). Most (92.6%) of NPcVar compounds had RB values within 10 (Figure 4f). According to Lipinski's "Rule of Five",[93] 78.5% (1446) of NPs in NPcVar exhibited drug-likeness to satisfy all five rules.

Systematic Classification of Mechanisms and Statistics of Their Corresponding Factors. NP production by species under external conditions is not static but rather varies and changes over time. NPcVar provides the correspondence between species and NPs and includes 26,425 records on NP content produced by species under specific conditions. Consequently, users can easily compare and analyze NP contents under various situations. For instance, NPcVar includes 1494 diverse conditions, which were manually curated from 126 various factors and categorized into 42 classes based on four mechanisms: molecular regulation, species factor, environmental condition, and combined factors. The most significant advantage of NPcVar is that it allows users to easily observe and compare different factors in the same species or among the same NPs, which helps in understanding their mechanisms and patterns.

Molecular Regulation. NPcVar includes extensive records of exogenous small molecules that induce NP production from species (shown in Figure 5). Some small molecule compounds, such as methyl jasmonate,[94] jasmonic acid,[95] and glycine betaine,[96] boost plant growth and stimulate the production of substances that combat various environmental conditions. These exogenous molecules are categorized in the plant growth regulator, with 1968 records in NPcVar (Figure 5). As shown in Figure 5, NPcVar also provides records of common abiotic stressors, such as salt, drought (H_2O), CO_2, and heavy metals, which are major causes of agricultural production and plant growth worldwide.[46]

Species Factor. In NPcVar, the mechanisms of species factors mainly comprised population comparisons and species interactions (Figure 5). For population comparisons, the primary records are between different populations of the same species, consequently facilitating the comparison of NP content in different varieties, cultivars, and accessions in the same species. NPcVar provides 1852 records of species interactions, including plant−microorganism, microorganism−microorganism, and plant−plant interactions (Figure 5). Many mutually beneficial symbiotic relationships exist between species in nature, for example, arbuscular mycorrhizal fungi (AMF), which enhances the tolerance of host plant response to stresses by improving nutrient uptake and affecting the secondary metabolism of the host plants;[97] coculture among the microorganisms may affect the synthesis of novel NPs.[98]

Environmental Condition. Among environmental condition mechanisms, harvest time was the most abundant, with 9380 records (Figure 5). Reports from this section primarily focus on the NP content and composition in plants harvested in different months, seasons, and growth stages. Factors described as NP content variation in plants from different origins or various altitudes in the same area are classified into geographical distribution, a concept similar to that of daodi medicinal materials. In the Chinese medicinal industry, traditional Chinese medicine with superior quality and clinical therapeutic effects due to their specific geographical location is called daodi medicinal materials.[99] Microorganisms alter cultivation parameters, including pH, incubation time, and temperature; trigger the expression of "cryptic" biosynthetic gene clusters (BGCs); and elicit the production of novel NPs.[47] NPcVar includes 1311 records providing the fermentation conditions of microorganisms under different cultivation processes, consequently saving scientists from performing large-scale laboratory experiments. Considerable common abiotic stress was also considered and categorized as environmental conditions, such as extreme temperatures and various radiation types (photosynthetic active and ultraviolet [UV] radiation) (Figure 5).

Combined Factor. Based on recent climate prediction models, the natural environment differs from the controlled conditions in laboratory studies.[46,100] Under field conditions, plants often exist under several different factors simultaneously, such as salinity and extreme temperatures, drought, and nutrient stress. Therefore, many studies have been conducted on combining the three mechanisms (molecular regulation, species factor, and environmental condition). As shown in Figure 5, of the 42 factor classes, 30 are combined factors such as "Heavy Metal Treatment (molecular regulation) + Species Interaction (species factor)". NPcVar contains 7502 records of combined factors, which will help elucidate how NP production in species responds to combined factors.

Data Retrieval, Access, and Application of NPcVar. NPcVar was designed with a user-friendly online interface and offers three distinct pages for searching and browsing information: species, NP, and factor pages. The species page enables users to search for a species by typing its name or by

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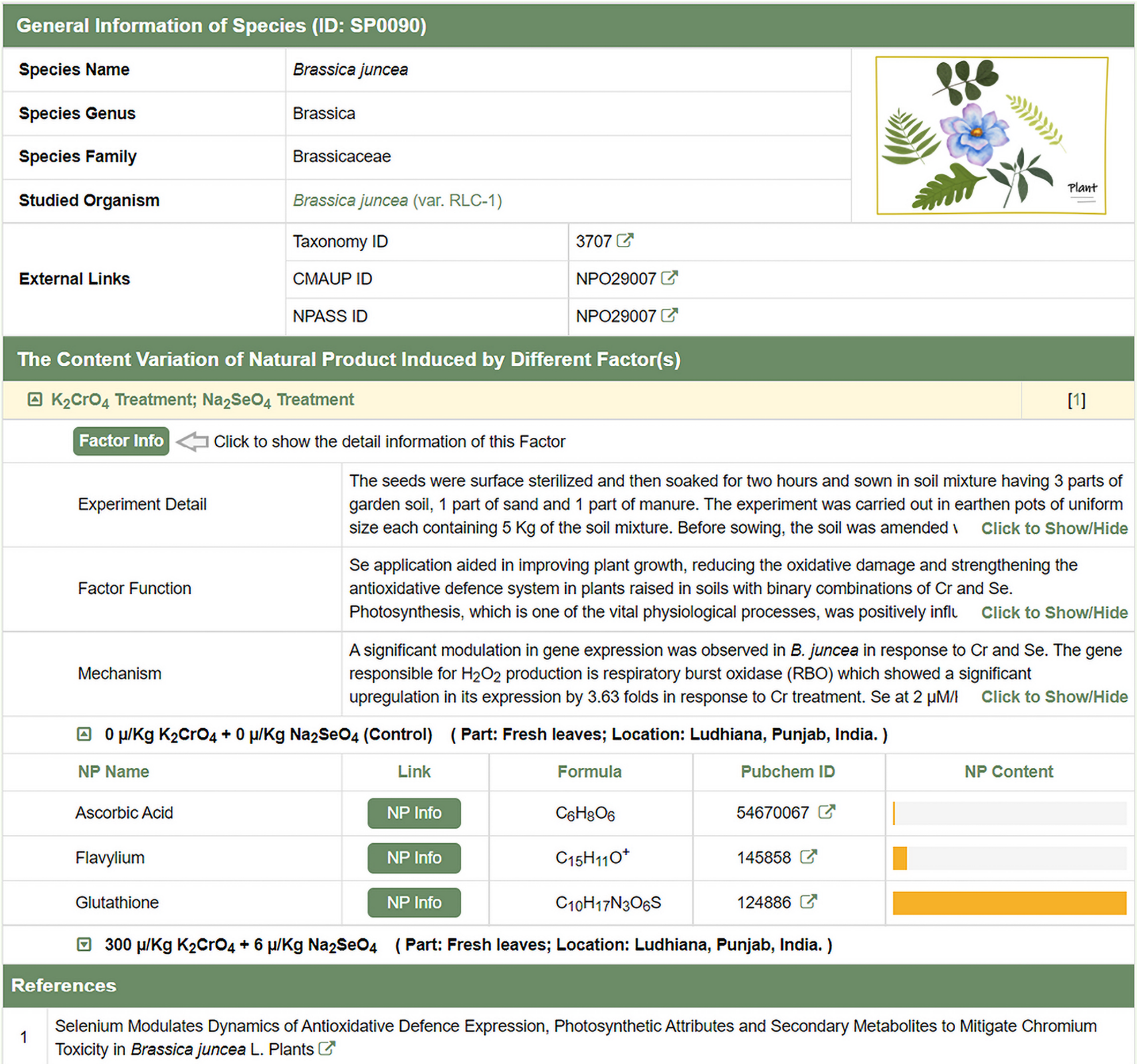

Figure 6. General information on the species together with the induced factor and corresponding NP content data. In the first section, the general data of species was provided, which included scientific name, species family and genus, the full name of the studied organism, symbiotic relationships of plants and microorganisms, and external links to well-established databases. In the second section, all NPs produced by the species under various factors were explicitly described, which included details of the experiment, factor function, mechanism of factor, the diverse specific conditions, NP basic information, and their corresponding content. NP content is shown as a histogram, and the data were provided by hovering the mouse over it.

selecting a species family and choosing a species. The first section of the species page provides general information about the species, as shown in Figure 6, including the scientific name, species family and genus, the full name of the studied organism, and symbiotic relationships with host plants and colonized microorganisms. It also includes external links to other databases: Taxonomy,[72] NPASS,[57] CMAUP,[58] HIT 2.0,[60] and GenBank.[68] The second section of the page lists the factors that have been studied in relation to the species, along with their corresponding literature references, and also explicitly describes the species studied under each factor, including details of the experiment, factor function, mechanism of the factor, and specific conditions. Additionally, the page lists all NPs produced by the species under various factors, with detailed information such as the NP name, formula, PubChem ID, parts of the plant that produce NPs, location of the experiment, and NP content. This information can be displayed or hidden by clicking on the row of the specific condition name, as shown in Figure 6. The NP content is presented as a histogram, and data can be accessed by hovering the mouse over it. Users can also click on the "Factor Info" or "NP Info" buttons to go to a new page with more detailed information about the specific factor or NP. Finally, the species page provides the titles of the source references as well as links to them.

On the NP page, users can search for NPs by typing the NP name and formula, or by selecting an NP class or species. As illustrated in Figure 7, the NP page provides detailed

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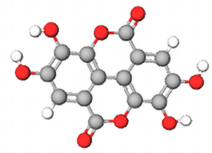
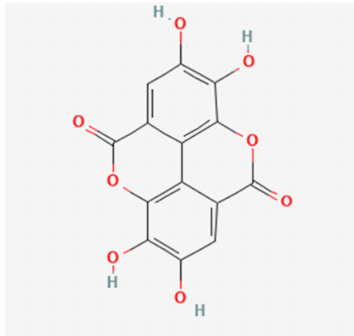
General Information of Natural Product (ID: NP0825)

Natural Product Name	Ellagic Acid	
Synonyms	ellagic acid; 476-66-4; Benzoaric acid; Elagostasine; Lagistase; 2,3,7,8-Tetrahydroxychromeno[5,4,3-cde]chromene-5,10-dione; Eleagic acid; Alizarine Yellow; Gallogen; Llagic acid; Acide ellagique; Acido elagico; Acidum ellagicum; C.I. 55005; C.I. 75270; Ellagicacid; Ellagate; UNII-19YRN3ZS9P; Gallogen, Click to Show/Hide	
Formula	$C_{14}H_6O_8$	
Weight	302.19	
Structure	3D Structure Download	2D Structure Download
InChI	InChI=1S/C14H6O8/c15-5-1-3-7-8-4(14(20)22-11(7)9(5)17)2-6(16)10(18)12(8)21-13(3)19/h1-2,15-18H	
InChI Key	AFSDNFLWKVMVRB-UHFFFAOYSA-N	
Isomeric SMILES	C1=C2C3=C(C(=C1O)O)OC(=O)C4=CC(=C(C(=C43)OC2=O)O)O	
Canonical SMILES	C1=C2C3=C(C(=C1O)O)OC(=O)C4=CC(=C(C(=C43)OC2=O)O)O	
External Links	PubChem ID	5281855
	CAS ID	476-66-4
	NPASS ID	NPC178134
	HIT ID	C0039
	CHEMBL ID	CHEMBL6246
NP Activity Charts	Click to show/hide	





The Content Variation of Natural Product Induced by Different Factor(s)

Species Name: *Amaranthus tricolor* genotype VA13

Factor Name: NaCl Treatment [1]

Species Info Factor Info

Experiment Detail	On the basis of previous studies, an antioxidant enriched high yield potential genotype (Accession VA13) was selected for this investigation. This genotype was grown in pots of a rain shelter open field of Bangabandhu Sheikh Mujibur Rahman Agricultural University, Bangladesh (AEZ-28, 24° 23′ north latitude, 90° 08′ eas Click to Show/Hide
Factor Function	At Moderate salinity stress (MSS) and Severe salinity stress (SSS) conditions, leaf color parameters and pigments, vitamins, phenolic acids, flavonoids and antioxidant capacity of *A. tricolor* leaves were very high compared to control condition. Hence, salt-stressed *A. tricolor* leaves had a good source of natural antioxidai Click to Show/Hide

Factor	Part	Location	NP Content
No saline water (Control)	Leaves	Bangabandhu	
25 mM NaCl (Low salinity stress)	Leaves	Bangabandhu	
50 mM NaCl (Moderate salinity stress)	Leaves	Bangabandhu	

Figure 7. The upper section provided the general information on NPs such as name, synonyms, formula, weight, structures, and external links. The bottom section described all species that can produce this NP under various factors. Each term is similar to the species page.

information for each NP in the "NP General Information" section, including the NP name, synonyms, formula, weight, 3D and 2D molecular structures, International Chemical Identifier (InChI), InChIKey, Isomeric SMILES, and Canonical SMILES, as well as links to external databases such as PubChem,[66] CAS,[69] NPASS,[57] HIT 2.0,[60] and ChEMBL.[71] Moreover, a set of activity charts derived from ChEMBL that include a summary pie chart of the compound's bioactivity are embedded. The content variation section of the NP page, which is similar to the species page (shown in Figure 7), presents information on all species that produce the NP under various factors. This information can be displayed or hidden by clicking on the species name and row of factors.

The factor page presents general information on a selected factor, including its name, type of mechanism, and a description, as shown in Figure 8. The NP content variation

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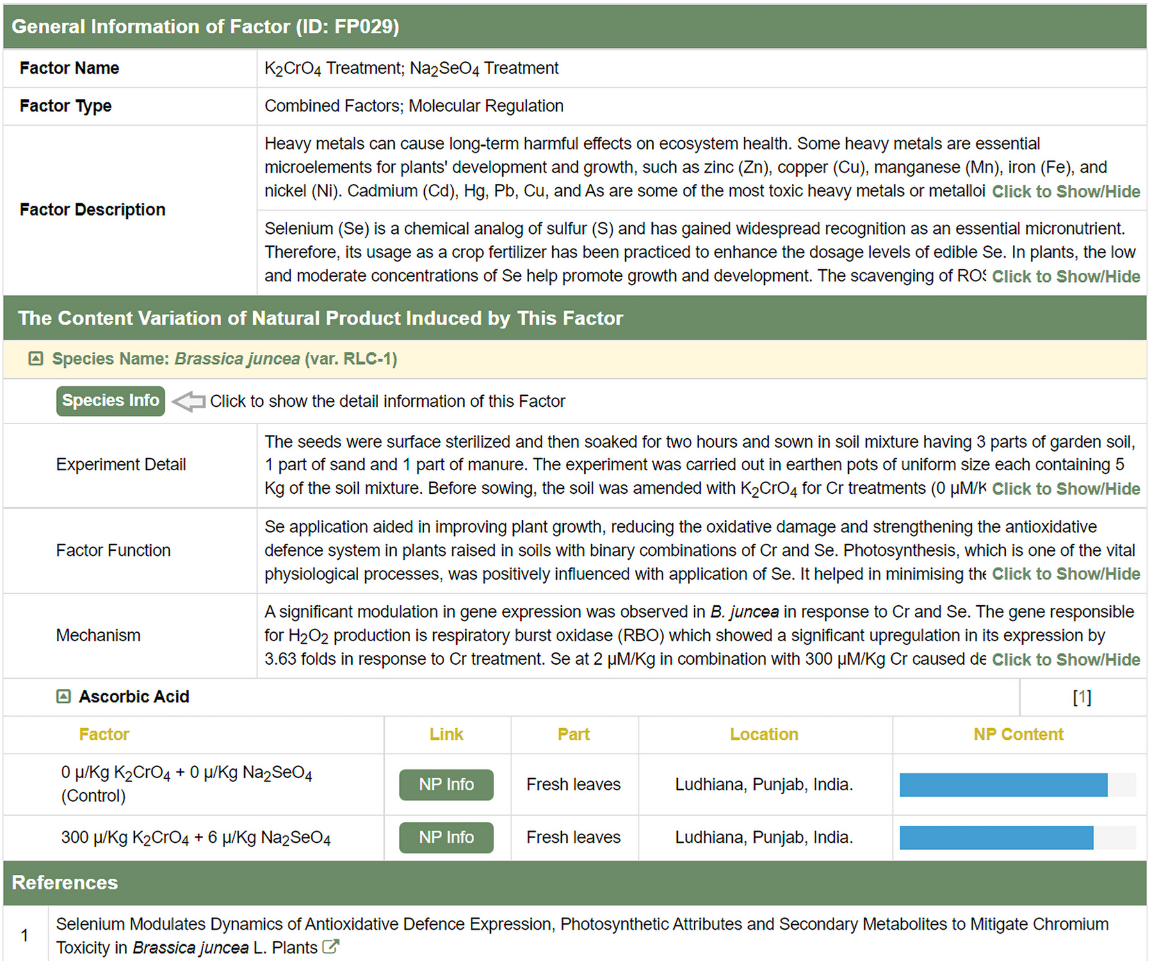

Figure 8. In the section "General Information of Factor", the factor, mechanism type, and description of the factor were provided. The terms in the second part are the same as on the species and NP pages but illustrate all species induced by the factor and their NPs.

section illustrates all species induced by the factor and the NPs they produce. Detailed information on the species and NPs can be accessed by clicking on the rows of the species and NP names, respectively. The "Species Info" and "NP Info" buttons provide users with further information on the species and NPs, respectively.

■ CONCLUSIONS

NPs are widely used in human production and are increasingly sought. To increase NP yield from natural resources, data on NP content under specific conditions were obtained, and a comprehensive platform was developed. The NPcVar contains 2201 NPs and 694 biological resources, including plants, bacteria, and fungi, which have been curated using 126 diverse factors. In summary, NPcVar has several unique properties. First, it is the first platform to systematically provide information on the content variations of thousands of NPs. Second, it provides a comprehensive list of mechanisms for each content variation. Finally, it differentiates NPs from traditional NP databases by presenting NPs in a dynamic and variable state rather than a static one. Given the recently increased interest in the study of NP content variations, efforts toward constructing this platform are anticipated to facilitate and prompt pioneering NP-related research.

■ ASSOCIATED CONTENT

Data Availability Statement

NPcVar is freely accessible by all users without any login requirement at http://npcvar.idrblab.net, and all data in NPcVar can be downloaded online.

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Author Contributions

⊥H. Xu, W. Zhang, and Y. Zhou contributed equally to this work as cofirst authors. H. Xu collected the data, analyzed the results, and wrote the manuscript. W. Zhang developed the server. Y. Zhou wrote the manuscript. Z. Yue, T. Yan, Y. Zhang, Y. Liu, and Y. Hong collected the data. S. Liu, L. Tao, and F. Zhu conceived this study, supervised the project, and wrote the manuscript. All authors read and approved the final manuscript.

Notes

The authors declare no competing financial interest.

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