

1 **Resource Article**

2  
3 **Stress Combinations and their Interactions in**  
4 **Plants Database (SCIPDb): A one-stop resource for understanding**  
5 **combined stress responses in plants**

6  
7 **Running title:** A database for combined stress responses in plants

8  
9 **Authors and institutional affiliation**

10 Piyush Priya<sup>#</sup>, Mahesh Patil<sup>#</sup>, Prachi Pandey, Anupriya Singh, Vishnu Sudha Babu &  
11 Muthappa Senthil-Kumar\*

12 National Institute of Plant Genome Research, Aruna Asaf Ali Marg, P.O. Box No.  
13 10531, New Delhi 110067, India

14  
15 **Full Address for Correspondence**

16 \*Muthappa Senthil-Kumar

17 National Institute of Plant Genome Research

18 New Delhi, India 110067

19 Tel: 91-11-26741612

20 Email: [skmuthappa@nipgr.ac.in](mailto:skmuthappa@nipgr.ac.in)

21  
22 \* to whom correspondence should be addressed

23 # equal contribution

24

25

26

27

28

29

30

31

32

33

34 **ABSTRACT**

35

36 We have developed **Stress Combinations and their Interactions in Plants Database**  
37 (SCIPDb; <http://www.nipgr.ac.in/scipdb.php>), a compendium and interactive platform  
38 offering information on both morpho-physio-biochemical (phenome) and molecular  
39 (transcriptome) responses of plants to different combinations of stresses. To  
40 delineate the effects of various stress combinations/categories on yield in major  
41 agricultural crops, global phenome data from 939 studies was analyzed and results  
42 showed that yield was affected to the greatest extent under the abiotic–abiotic stress  
43 category, followed by the biotic–biotic and abiotic–biotic stress categories. In the  
44 abiotic–abiotic stress category, drought–heat, heat–salinity, and ozone–UV are the  
45 major stress combinations causing high yield loss in barley, wheat, soybean, and  
46 quinoa crops. In the abiotic–biotic stress category, the salinity–weed stress  
47 combination causes highest yield loss in rice crop. In the biotic–biotic stress  
48 category, the nematode–fungus combination was most detrimental, causing  
49 considerable yield losses in potato, groundnut, and sugar beet crops. Transcriptome  
50 datasets from 36 studies hosted in SCIPDb identified novel genes. Thus far, these  
51 genes have not been known to play a role in combined stress. Integretome analysis  
52 under combined drought–heat stress pinpointed carbohydrate, amino acid, and  
53 energy metabolism pathways as the crucial metabolic, proteomic, and transcriptional  
54 components in plant tolerance to combined stress. These examples illustrate the  
55 application of SCIPDb in identifying novel genes and pathways involved in combined  
56 stress tolerance. Further, we showed the application of this database in identifying  
57 novel candidate genes and pathways for combined drought and pathogen stress  
58 tolerance in Arabidopsis and chickpea. To our knowledge, SCIPDb is the only  
59 publicly available platform that provides extensive information and paves the way for  
60 advancing mechanistic understanding of plant responses to combined stresses.

61

62 **Keywords:** biocuration, big data, climate resilience, data visualization, plant stress  
63 informatics hub, integretome, pathway enrichment, phenome, transcriptome, trait  
64 and gene ontology

65

66

67

68 **INTRODUCTION**

69 Abiotic and biotic stresses are the major deterrents to the achievement of global food  
70 security, necessitating the urgency to develop better-adapted crops (IPCC, 2022;  
71 Mittler and Blumwald, 2010). Plants are often exposed to combinations of stresses  
72 during their life cycle, and increasing evidence highlights that stress combinations  
73 are more potent and realistic threats to plant growth and productivity than individual  
74 stresses (Atkinson and Urwin, 2012; Ahuja et al., 2010; Desaint et al., 2021; Sinha et  
75 al., 2021, Zandalinas et al., 2021a, b). Considerable information on plant stress has  
76 accumulated over the years, but our understanding of the physiological and  
77 molecular responses of plants to combined stress remains poor (Pandey et al., 2017;  
78 Mahanligam et al., 2021; Zandalinas et al., 2020a; Zandalinas and Mittler, 2022).  
79 Combined stress studies, although under-represented compared to individual stress  
80 studies, entail voluminous and highly complex information on plant response to  
81 combined stresses (Cohen et al., 2021; Zandalinas et al., 2020b; Zandalinas et al.,  
82 2021a).

83

84 A plant perceives combined stress as a new state of stress, and adaptation  
85 strategies to stress combinations are based on the interaction between the  
86 physiological and molecular responses simultaneously triggered by each stress  
87 entity independently (Gupta et al., 2016; Lopez-Delacalle et al., 2021; Pandey et al.,  
88 2017). The outcome of such interactions may be “positive” or “negative,” wherein  
89 combined stress causes less or more damage, respectively, than the individual  
90 stresses. The outcome also depends on many factors like plant age, genotype,  
91 stress intensity, duration of the stresses, and order of stress perceived by the plant,  
92 which makes combined stress more complex to understand (Mittler, 2006; Pandey et  
93 al., 2015; Zandalinas et al., 2021b). In addition, the time of imitation of the second  
94 stress since the first stress also decides the outcome of the interaction between the  
95 stresses (Choudhary et al., 2022). These responses are mediated by switching on  
96 specific pathways and processes that are unique, specific, and sometimes even  
97 contrasting from the individual stress responses. Plants also exhibit shared  
98 responses common among individual and combined stresses (Suzuki et al., 2014;  
99 Zhang and Sonnewald, 2017).

100

101 Thus, to better comprehend the complexities of combined stress responses

102 and fill existing gaps, there is a pressing need for a pertinent database. There is no  
103 database or platform solely dedicated to combined stress. TOMRES  
104 (<https://www.tomres.eu/>) and Stress Combination: A New Field in Molecular Stress  
105 Research by the University of North Texas  
106 (<http://biology.unt.edu/stresscombination/>) are two combined stress web resources  
107 available for specific plants and for one type of stress combination, apart from  
108 individual stress databases such as STIFDB2, QlicRice, and the Arabidopsis stress-  
109 responsive gene database (Borkotoky et al., 2013; Naika et al., 2013; Smita et al.,  
110 2011). But these resources are not extensive and broad. Here, we developed the  
111 **Stress Combinations and their Interactions In Plants** database (SCIPDb;  
112 <http://www.nipgr.ac.in/SCIPdb.php>), a user-friendly platform providing options to  
113 browse, search, analyze, and download data for various stress combinations studied  
114 to date. SCIPDb provides researchers easy access to combined stress-related  
115 information and tools for extracting need-based, specific information.

116

## 117 **RESULTS AND DISCUSSION**

118

### 119 **SCIPDb and its key features**

120

121 SCIPDb is a comprehensive collection of morphological, physiological, biochemical,  
122 and transcriptomic data on combined stresses published to date, systematically  
123 analyzed and presented in an easy-to-use interactive database and web server  
124 (Figure 1A and 1B; Supplemental Figure 1). Currently, SCIPDb hosts phenome data  
125 curated from 939 studies, covering 123 stress combinations, 118 plant species, 283  
126 pathogenic agents (including bacteria, fungi, oomycetes, nematodes, viruses,  
127 mycoplasmas, viroids, and insects), and 7 weed species (Figure 1). From the  
128 analysis of the phenome data, 107 agronomic traits affected by various stress  
129 combinations were identified. Of these, 45 traits were mapped to the identified Trait  
130 Ontology (TO) terms. Twenty traits among the 45 were related to plant morphology  
131 and yield; 11 were related to plant physiology; and 15 were biochemical traits  
132 corresponding to changes in enzymes, metabolites, and hormone levels. These traits  
133 can be targeted for trait-based breeding programs to develop combined stress-  
134 tolerant crops. Further, gene-to-TO relationships (Pan et al., 2019) can be derived to  
135 decipher the genome-to-phenome relationships under combined stress. The



136 transcriptome data hosted in SCIPDb is from 36 studies available in the public  
137 domain thus far, representing 58 stress combinations and 16 plant species  
138 ([Supplemental Figure 2](#)).

139

#### 140 ***Phenomics***

141 Systematically analyzed phenomes are presented as data pages based on plant  
142 species ([Supplemental Figure 3](#)). For a holistic view of trends in the analyzed  
143 phenome data, interactive visualizations such as combined stress matrices, radial  
144 trees, and global combined stress distribution maps have been provided ([Figure 1](#)).  
145 The interactive stress matrices show the overall impact of different stress  
146 combinations on various plant species ([Figure 1C](#)). These visualizations will aid in  
147 deciphering and distilling comprehensive overviews of stress combinations across  
148 plant species, unlike from individual stresses alone. Among the 123 stress  
149 combinations, 69 combinations showed a negative impact on plant growth and  
150 productivity ([Supplemental Figure 4](#)). Twenty stress combinations showed a positive  
151 impact on plants, many of them belonging to the abiotic–biotic stress category. No  
152 combination in the abiotic–abiotic stress category showed a positive interaction,  
153 pegging abiotic stress combinations as the major threats to plant yield ([Supplemental](#)  
154 [Figure 4](#)). In 12 stress combinations, an equal number of studies reported both  
155 positive and negative impacts of combined stress on plants, with the majority  
156 belonging to the abiotic–biotic stress category (10 combinations) ([Supplemental](#)  
157 [Figure 4](#)). To decipher the impact of stress combinations on growth, yield, and  
158 physiological and pathogen-associated traits in various plant species, data were  
159 visualized in the form of a radial tree ([Figure 1D](#)). Our analysis of the different abiotic  
160 and biotic stress combinations reveals many pathogen infections that are aggravated  
161 under several concurrent abiotic stresses. It also reflects a number of pests–  
162 pathogen complexes that can pose a challenge to agricultural productivity. A global  
163 combined stress distribution map, another feature of SCIPDb, shows the prevalence  
164 of particular stress combinations in a locality with their impact on crop growth ([Figure](#)  
165 [1E](#)). Knowledge of the occurrence of important stress combinations based on this  
166 interactive geographical distribution map can assist researchers in identifying  
167 agronomically relevant stress combinations. Our analysis of studies published from  
168 1952 to 2021 showed a steep increase in publications about combined stress, most  
169 of which were from the Americas, Asia, and Europe, particularly from the last decade

170 (Supplemental Figure 5A and 5B). Thus, the increase in the occurrence of combined  
171 stresses in these areas is deepening crop losses.

172

### 173 ***Transcriptomics***

174

175 Transcriptome data were analyzed and presented as interactive bootstrap tables,  
176 which enlist differentially expressed genes (DEGs) and their associated metadata in  
177 the form of KEGG pathways and genes (Supplemental Figure 6). Cross-references  
178 to important resources are provided to enable users to acquire more information  
179 directly. To further visualize the high-dimensional transcriptome data, each DEG  
180 table has been linked to interactive heatmaps, Venn diagrams, co-functional  
181 networks, and Manhattan plots (Figure 1F–1H). SCIPDb hosts co-functional  
182 networks for the top differentially expressed unique genes under multiple combined  
183 stresses. It provides speculative evidence about the genes that are co-regulated and  
184 thus might share a similar biological function or act together to control a specific  
185 phenotype. The functional annotation of DEGs acts as a key resource to elucidate  
186 the biological processes, functions, and pathways controlling various combined  
187 stresses in plants. Gene Ontology annotations provided in the form of Manhattan  
188 plots can be used to visualize enriched biological processes, molecular functions,  
189 and cellular components and pathways.

190

### 191 ***Additional features of SCIPDb***

192

193 A large fraction of genes in non-model plant species remains uncharacterized, which  
194 means that they lack functional annotation. Prioritizing candidate genes without any  
195 functional evidence in such species is challenging. The standalone BLAST server  
196 integrated with SCIPDb provides an option to query the database with batch  
197 nucleotide or protein sequences and will help users identify genes related to  
198 combined stress in the genomes of the ever-increasing repertoire of newly  
199 sequenced crop species (Figure 1I). SCIPDb hosts several videos, slides, podcasts,  
200 and protocols related to combined stress, making it a potential outreach portal to  
201 promote scientific communication and education (Figure 1J). A unique keyword-  
202 based search option allows a user to mine desired information from both phenome  
203 and transcriptome datasets (Figure 1K). SCIPDb datasets are hosted on a local FTP

204 server, allowing users to download all curated phenomes, genotypes,  
205 transcriptomes, and references locally with just a few clicks. A user-defined  
206 download can also be done through specific sections of the database. These  
207 datasets can be further used for other downstream analyses to clearly grasp plant  
208 responses to combined stresses (Figure 1L). SCIPDb also encourages users to  
209 submit their data to the web portal to promote two-way communication and ultimately  
210 contribute to making the database a dynamic, robust, and single-stop platform for  
211 disseminating novel findings on combined stresses.

212

213 The interactive network developed by global combined stress transcriptome profiling  
214 and pathway enrichment analysis in Arabidopsis depicts the common and unique  
215 pathways between major combined stress categories hosted under the  
216 transcriptome visualization section. The “Applications” section hosts several case  
217 studies, which can help users understand how to use the diverse datasets hosted in  
218 SCIPDb to answer various biological questions about combined stress. The  
219 “References and links” section provides access to complete references of the  
220 research articles used in developing the data page, along with other related articles  
221 such as reviews, theses, and reports. A meta-phenome presents a combined trend  
222 of the net impact of stress combinations on plant performance after analyzing all the  
223 studies reported for a specific crop for a particular stress combination. Overall, these  
224 important features and tools in SCIPDb provide comprehensive information on each  
225 stress combination and can help identify the most prominent stress combination in a  
226 specific crop affecting polygenic traits like growth and yield.

227

## 228 **Effects of combined stress on yield and yield-attributing traits in major crops**

229

230 Among the 123 reported stress combinations, 58, 41, and 24 were from the abiotic–  
231 biotic, abiotic–abiotic, and biotic–biotic stress categories, respectively (Figure 2A;  
232 Supplemental Figures 7–9). Out of the 58 stress combinations reported in the  
233 abiotic–biotic stress category, 87 studies, covering 26 plant species, were on the  
234 nematode–fungus stress combination, indicating it as one of the most evident stress  
235 combinations (Supplemental Figure 9). Global analysis of yield and yield-attributing  
236 traits belonging to plant performance, plant physiological response, and plant  
237 pathogenesis response showed greater reductions in yield under the abiotic–abiotic

238 stress category, followed by the biotic–biotic stress category (Figure 2B). Evidently,  
239 combined drought and heat stress have caused enormous economic loss (four times  
240 greater than losses incurred by drought stress alone) amounting to ~\$200 billion in  
241 US between the year 1980-2012 (Mittler, 2006;  
242 <http://www.ncdc.noaa.gov/billions/events>). Several upcoming studies have indicated  
243 the role of combined drought, heat and high light in affecting plant development and  
244 metabolism (Zandalinas et al., 2020a, 2020b, 2021a). Apart from drought-heat stress  
245 combination, fungus–waterlogging, and salinity–weeds stress combinations  
246 substantially affected the yields of important monocots like wheat and barley,  
247 respectively (Supplemental Figure 10). Wheat yield in particular was greatly affected  
248 under drought–heat, drought–cold, boron deficiency–cold, and *Fusarium poae*–  
249 waterlogging stress combinations (Figure 2C). However, in the case of nematode–  
250 fungus and fungus–fungus stress combinations, the wheat yield response varied with  
251 the type of pathogen species involved in the interaction and the order of stress  
252 perceived by the plant, as shown in Figure 2C. The database also highlights several  
253 other important but lesser-known stress combinations significantly affecting plant  
254 yields. For example, in pulses and oilseeds such as peanut, cowpea, soybean, and  
255 common bean, yields were more affected under nematode–fungus, ozone–UV,  
256 fungus–insects, and drought–weeds stress combinations (Supplemental Figure 10).  
257 Among solanaceous crops, fungus (*Verticillium dahlia*) in association with  
258 nematodes (*Heterodera rostochiensis*, *Globodera rostochiensis*, and *Pratylenchus*  
259 *neglectus*) showed markedly reduction in potato yield (Supplemental Figure 10).  
260 Further, in view of understanding the aggravation of plant diseases and emergence  
261 of new disease complex, we found that biotic factors were critical in exacerbating  
262 several pathogen infections. (Supplemental Figures 11–12). In the biotic–biotic  
263 stress category, nematode (*Meloidogyne incognita* and *Heterodera indicus*) and  
264 fungus (*Fusarium udum*, *F. oxysporum*, *F. moniliforme*, and *Macrophomina*  
265 *phaseolina*) stress combinations were highly detrimental to maize, pigeon pea,  
266 cotton, and chickpea crops, causing more disease incidence and damage compared  
267 to individual stresses (Supplemental Figure 12). These results indicate that  
268 combined biotic stresses are more detrimental to crops than the stressors  
269 individually. In contrast, abiotic stresses have shown a positive effect in terms of  
270 reducing pathogen infection and its progression, e.g., ozone–*Phytophthora sojae* in  
271 soybean, ozone–*Bean common mosaic virus* in pinto bean, salinity–weeds in

272 sorghum, shade–*Colletotrichum kahawae* in coffee, Mn toxicity– *Uncinula necator* in  
273 grapevine, and *Pythium myriotylum*–*R. solani* in peanut showed significant  
274 reductions in disease incidence under combined stress ([Supplemental Figure 11](#)).  
275 However, recent reviews on combined stress have also indicated that elevated  
276 drought, high temperature, and nutrient conditions make plants more vulnerable to  
277 pest or pathogen infection (Cohen and Leach, 2020; Desaint et al., 2021; Hamann et  
278 al., 2020; Savary and Willocquet, 2020).

279

## 280 **Global combined stress transcriptome analysis in plants**

281

282 Transcriptome analysis from 58 combined stress transcriptomes resulted in 45, 169  
283 unique DEGs from 16 plant species. Functional profiling of significantly enriched  
284 DEGs revealed the involvement of genes encoding key proteins like heat-shock  
285 proteins (HSPs), Ca<sup>2+</sup> signal transduction proteins, phytohormone-related genes,  
286 defense-related genes, reactive oxygen species (ROS), peroxidases, cell wall-  
287 modifying genes, and cytochrome P450 superfamily proteins. Transcription factor  
288 (TF) enrichment analysis revealed significant enrichment of dehydration response  
289 element-binding protein (DREB), ABA-responsive element-binding protein (ARF),  
290 ethylene-responsive element-binding factor (ERF), heat-shock transcription factor  
291 (HSF), NAC domain-containing protein, MYB, LOB domain-containing protein, GATA  
292 TFs, and WRKY DNA-binding protein families in the DEGs. MYBs and NAC TFs  
293 have been reported to regulate pathogen and phytohormone responses like  
294 ethylene, jasmonate, and/or salicylate (Bian et al., 2021, Vemanna et al., 2019). MYB  
295 TFs have also been reported to regulate the production of secondary metabolites  
296 during the induction of stress responses via the phenylpropanoid pathway and cell  
297 wall biosynthesis (Cao et al., 2020). They are also considered excellent candidates  
298 for broad-spectrum stress tolerance improvement in plants (Atkinson et al., 2013;  
299 Rasmussen et al., 2013, Zandalinas et al 2020a, b).

300

301 Twenty different combined stress transcriptomes were analyzed in *Arabidopsis*  
302 ([Figure 3A](#)), which resulted in 10,804 DEGs uniquely expressed under combined  
303 stress. Further categorization into major combined stress categories, followed by an  
304 intersection analysis revealed 3,587, 3,182, and 866 DEGs unique to abiotic–biotic,  
305 abiotic–abiotic, and biotic–biotic categories, respectively. ([Figure 3B](#)). Pathway

306 enrichment analysis of these DEGs specific to major combined stress categories  
307 suggested several key pathway clusters consistently altered under the three major  
308 combined stress categories. This includes pathways related to the metabolism of  
309 amino acids, carbohydrates, energy, carbon, lipids, secondary metabolites, and  
310 cofactors and vitamins (Figure 3C). Pathways related to glycan biosynthesis and  
311 metabolic pathways like glycosphingolipid biosynthesis, glycosaminoglycan  
312 degradation, and N-glycan biosynthesis were unique and majorly enriched in biotic–  
313 biotic combined stress categories. Ethylene and phytochrome signaling pathways  
314 were also found to be unique to biotic–biotic combined stress categories. Genetic  
315 interactions between sugar and hormone signaling, inositol phosphate metabolism,  
316 photosynthesis, and ABC transporter pathways were found to be unique under the  
317 abiotic–biotic stress category. For the abiotic–abiotic combined stress category,  
318 glycosylphosphatidylinositol (GPI)-anchor biosynthesis, mRNA surveillance pathway,  
319 ketone body synthesis and degradation, and glucose sensing and signaling in  
320 Arabidopsis were found to be unique.

321

### 322 ***Deciphering key genes and pathways under combined drought and heat stress*** 323 ***by integrative multi-omics***

324

325 While multi-omics approaches like joint pathway analysis have been limited, they are  
326 now being increasingly used in plants (Bjornson et al., 2017; Crandall et al., 2020;  
327 López-Hidalgo et al., 2018), with the underlying hypothesis that by combining  
328 evidence from multi-omics, it will be possible to concretely pinpoint the pathways  
329 involved in the underlying biological processes. Carbohydrate metabolism and  
330 related gene expression have been identified to contribute to the superior heat and  
331 drought tolerance of anthers in the rice cultivar N22 compared to the cultivar  
332 Moroberekan (Li et al., 2015). The joint pathway analysis approach, integrating  
333 changes in gene expression, proteome, and metabolite concentrations in drought  
334 and heat combined stress treatments, suggested significant enrichment of four major  
335 classes of pathways enriched based on the KEGG BRITE hierarchy. Amino acid  
336 metabolism, energy metabolism, carbohydrate metabolism, and signal transduction  
337 pathways were supported by all three omics (Figure 4A) (Zandalinas et al., 2022).  
338 Within the amino acid metabolism class, significantly enriched pathways were those  
339 related to glutathione metabolism; alanine, aspartate, and glutamate metabolism;



340 glycine, serine, and threonine metabolism; and cysteine and methionine metabolism.  
341 Pentose phosphate pathway; glycolysis or gluconeogenesis; and pyruvate, fructose,  
342 mannose, ascorbate, aldarate, amino sugar, and nucleotide sugar metabolism  
343 pathways were found to be enriched within the energy metabolism class, while  
344 carbon fixation in photosynthetic organisms, nitrogen metabolism, and sulfur  
345 metabolism pathways were enriched under the carbohydrate metabolism class.  
346 Among the signal transduction pathways, phosphatidylinositol signaling system  
347 pathways mapped to all the three omics data analyzed. Thus, genes commonly  
348 associated between these pathway classes may play a significant role in combined  
349 stress tolerance in plants ([Figure 4B](#)).

350

### 351 **Future perspectives**

352 Global phenome data analysis shows that abiotic–abiotic stress combinations are  
353 major threats to crop productivity. In the face of global climate change, the  
354 occurrence of these stress combinations is projected to increase in coming years.  
355 Therefore, dedicated studies on this aspect are essential to sustain crop yields in the  
356 future. Key takeaways from yield analyses are that monocots will be more affected  
357 under the abiotic–abiotic and abiotic–biotic stress category, whereas pulses,  
358 oilseeds, and vegetable crops will be more affected under the biotic–biotic stress  
359 category.

360

361 Our unique combined stress integretome developed using multi-omics data  
362 integration highlights sugar metabolism, energy metabolism, and amino acid  
363 metabolism as the key pathways operating under combined stress conditions. The  
364 addition of proteomics and metabolomics data to the database with multi-omics  
365 analysis will further demystify combined stress responses of plants. Unraveling the  
366 mechanisms by which the molecular signatures associated with these pathways  
367 impact plant response to combined stress can open new vistas for developing  
368 resilient crop varieties with better adaption to changing climate and global warming.

369

370 SCIPDb is a comprehensive database amenable to data mining and data-driven  
371 research on combined stresses in plants. With the continual accumulation of  
372 available data in the field of combined stress, we will update the database annually  
373 by incorporating newer studies. We intend to add other omics datasets related to

374 combined stress research in the future version of SCIPDb, together with novel  
375 features like prediction modeling based on machine learning and meteorological data  
376 integration with geographical distribution information. Overall, SCIPDb is an  
377 informative and valuable resource for combined stress research in plants.

378

## 379 **METHODS**

380

### 381 **Data acquisition**

382 SCIPDb hosts two major omics datasets: phenomics and transcriptomics. For the  
383 acquisition of both the datasets, widely used search engines and public databases  
384 were extensively mined.

385

#### 386 ***Data mining for phenomics***

387 To retrieve all available articles and to have greater than 90% literature coverage,  
388 several search engines were queried using suitable and carefully designed keywords  
389 (including several variants). Bibliography from each article was also searched to  
390 achieve better coverage.

391

#### 392 ***Data mining for transcriptomics***

393 The relevant transcriptome datasets for combined stress in plants were compiled  
394 and curated using two major public databanks for microarray data, including Gene  
395 Expression Omnibus (GEO) (<https://www.ncbi.nlm.nih.gov/geo/>) and Array Express  
396 (<http://www.ebi.ac.uk/arrayexpress/>). The NCBI GEO and ArrayExpress functional  
397 genomics repository were queried using a large number of keywords as listed in the  
398 database. For the compilation of RNA-seq transcriptomics data, the NCBI Sequence  
399 Read Archive (SRA) (<https://www.ncbi.nlm.nih.gov/sra>) database was used.

400

### 401 **Database implementation**

402 The frontend user interface was implemented using HTML5, CSS, and PHP (version:  
403 7.0.12). The back-end schema was designed using MySQL, an open-source  
404 relational database management system, and data were stored in MySQL tables  
405 (Version: 5.7.17). To provide an interactive interface and enhanced user experience,  
406 we used Bootstrap 4, JavaScript, and jQuery. SCIPDb has been deployed in an  
407 Apache web server that runs on the CentOS Linux 7 ([Supplemental Figure 1](#)).



408

409

### 410 **Arabidopsis combined stress transcriptome**

411 The upset plot was generated using the UpSetR package, while the circos plot was  
412 generated using Metascape, a gene annotation and analysis resource.  
413 (<https://metascape.org/gp/index.html#/main/step1>). Pathway enrichment analysis  
414 was done using major pathway databases like KEGG  
415 (<https://www.kegg.jp/kegg/rest/keggapi.html>), Aracyc  
416 (<https://plantcyc.org/typeofpublication/aracyc>), and Wikipathways  
417 (<https://www.wikipathways.org/index.php/WikiPathways>). Final visualization and  
418 network analysis were done using Cytoscape, v3.8.2 (<https://cytoscape.org/>).

419

### 420 **Integretome analysis**

421 MetaboAnalystR package was used to perform joint pathway analysis of the  
422 transcriptome, proteome, and metabolome profiles. For enrichment analysis (ORA)  
423 hypergeometric analysis was used, while for topology measure, degree centrality  
424 was used. Combining p-values at the pathway level was used for the integration of  
425 the three omics datasets.

426

427

## 428 **SUPPLEMENTAL FIGURES**

429 **Supplemental Figure 1.** Content and construction of SCIPDb.

430 **Supplemental Figure 2.** Combined stress transcriptome articles were analyzed and  
431 integrated into SCIPDb.

432 **Supplemental Figure 3.** A typical data page entry for phenome in SCIPDb.

433 **Supplemental Figure 4:** The heat map depicting the various stress combinations of  
434 potential environmental stresses that affect crops in the field.

435 **Supplemental Figure 5.** Literature analysis of combined stress articles published  
436 from 1950 to 2021.

437 **Supplemental Figure 6.** A typical data page entry for transcriptome in SCIPDb and  
438 its associated visualizations.

439 **Supplemental Figure 7.** Literature analysis of combined stress articles published  
440 from 1950 to 2021 under the abiotic–abiotic stress category.

441 **Supplemental Figure 8.** Literature analysis of combined stress articles published

442 from 1950 to 2021 under the abiotic–biotic stress category.

443 **Supplemental Figure 9.** Literature analysis of combined stress articles published  
444 from 1950 to 2021 under the biotic–biotic stress category.

445 **Supplemental Figure 10.** Literature analysis of combined stress growth and yield  
446 data on various plant species.

447 **Supplemental Figure 11.** Literature analysis of combined stress physiological data  
448 on various plant species.

449 **Supplemental Figure 12.** Literature analysis of disease incidence data under  
450 combined stress on various plant species.

451

## 452 **FUNDING**

453 This work was supported by funding to M.S-K. from the National Institute of Plant  
454 Genome Research core funding and a project from Science and Engineering  
455 Research Board (SERB; CRG/2019/005659). Pi.P. and M.P were supported by  
456 fellowships from CSIR (No.13 (9106-A)/2020-Pool) and No.13 (9064-A)/2019-Pool)),  
457 respectively.

458

## 459 **AUTHOR CONTRIBUTIONS**

460 M.S-K. conceived the idea, designed the database, outlined the manuscript, and  
461 provided all resources. Pi.P. developed the webtool and performed data integration  
462 and data visualization. M.P. and Pr.P. contributed to the phenomics part. Pi.P., M.P.,  
463 and Pr.P. performed overall data analysis. A.S. contributed to the data collection for  
464 the phenomics part of the manuscript. Pi.P. and V.S.B. contributed to the data  
465 collection and analysis part of transcriptomics. M.S-K., Pi.P., M.P., and Pr.P. drafted  
466 the manuscript. M.S-K. edited and finalized the manuscript and SCIP database. All  
467 authors agreed to the submitted version of the manuscript.

468

## 469 **ACKNOWLEDGMENTS**

470 The authors are thankful to the Department of Biotechnology (DBT)-eLibrary  
471 Consortium, India, and the NIPGR library for providing access to e-resources.  
472 Computational facilities provided by Genome Analysis Facility and the DBT-DISC  
473 facility at NIPGR are also duly acknowledged for sharing resources. We  
474 acknowledge Dr. Jyoti Singh for her contribution in collecting data for the phenome  
475 part.

476

477 **CONFLICT OF INTEREST**

478 The authors declare no conflicts of interest.

479

480 **REFERENCES**

481 **Ahuja, I, de Vos, R.C., Bones, A.M., and Hall, R.D.** (2010). Plant molecular stress  
482 responses face climate change. *Trends in Plant Sci.* **15**:664–674.

483

484 **Atkinson, N.J., and Urwin, P.E.** (2012). The interaction of plant biotic and abiotic  
485 stresses: from genes to the field. *J. Exp. Bot.* **63**:3523–3543.

486

487 **Atkinson, N.J., Lilley, C.J., and Urwin, P.E.** (2013). Identification of genes involved  
488 in the response of Arabidopsis to simultaneous biotic and abiotic stresses. *Plant*  
489 *Physiol.* **162**(4):2028–2041.

490

491 **Bjornson, M., Balcke, G.U., Xiao, Y., de Souza, A., Wang, J.Z., Zhabinskaya, D.,**  
492 **Tagkopoulos, I., Tissier, A. and Dehesh, K.** (2017). Integrated omics analyses of  
493 retrograde signaling mutant delineate interrelated stress-response strata. *Plant J.*  
494 **91**(1):70–84.

495

496 **Bian, Z., Gao, H. and Wang, C.** (2020). NAC transcription factors as positive or  
497 negative regulators during ongoing battle between pathogens and our food crops.  
498 *Int. J. Mol. Sci.* **22**(1):81.

499

500 **Borkotoky, S., Saravanan, V., Jaiswal, A., Das, B., Selvaraj, S., Murali, A., and**  
501 **Lakshmi, P.T.V.** (2013). The Arabidopsis stress responsive gene database. *Int. J.*  
502 *Plant Genome* **2013**.

503

504 **Cao, Y., Li, K., Li, Y., Zhao, X. and Wang, L.** (2020). MYB transcription factors as  
505 regulators of secondary metabolism in plants. *Biology* **9**(3):61.

506

507 **Choudhary, A. and Senthil-Kumar, M.** (2022). Drought attenuates plant defence  
508 against bacterial pathogens by suppressing the expression of CBP60g/SARD1  
509 during combined stress. *Plant Cell Environ.* **45**(4):1127–1145.

510

511 **Cohen, S.P., and Leach, J.E.** (2020). High temperature-induced plant disease  
512 susceptibility: more than the sum of its parts. *Cur. Opin. Plant Biol.* **56**:235–241.

513

514 **Cohen, I., Zandalinas, S.I., Huck, C., Fritschi, F.B., and Mittler, R.** (2021).  
515 Meta-analysis of drought and heat stress combination impact on crop yield and yield  
516 components. *Physiol. Plantarum* **171(1)**:66–76.

517

518 **Crandall, S.G., Gold, K.M., Jiménez-Gasco, M.D.M., Filgueiras, C.C. and Willett,**  
519 **D.S.** (2020). A multi-omics approach to solving problems in plant disease ecology.  
520 *Plos One* **15(9)**:e0237975.

521

522 **Desaint, H., Aoun, N., Deslandes, L., Vailleau, F., Roux, F., and Berthomé, R.**  
523 (2021). Fight hard or die trying: when plants face pathogens under heat stress. *New*  
524 *Phytol.* **229(2)**:712–734.

525

526 **Gupta, A., Sarkar, A.K., and Senthil-Kumar, M.** (2016). Global transcriptional  
527 analysis reveals unique and shared responses in *Arabidopsis thaliana* exposed to  
528 combined drought and pathogen stress. *Front. Plant Sci.* **7**:686.

529

530 **Hamann, E., Blevins, C., Franks, S.J., Jameel, M.I., and Anderson, J.T.** (2020).  
531 Climate change alters plant–herbivore interactions. *New Phytol.* **229**:1894–1910.

532

533 **IPCC Sixth Assessment Report: Climate Change 2022.**  
534 [https://www.unep.org/resources/report/ipcc-sixth-assessment-report-climate-](https://www.unep.org/resources/report/ipcc-sixth-assessment-report-climate-change-2022)  
535 [change-2022](https://www.unep.org/resources/report/ipcc-sixth-assessment-report-climate-change-2022)

536

537 **Li, X., Lawas, L.M., Malo, R., Glaubitz, U., Erban, A., Mauleon, R., Heuer, S.,**  
538 **Zuther, E., Kopka, J., Hinch, D.K. and Jagadish, K.S.** (2015). Metabolic and  
539 transcriptomic signatures of rice floral organs reveal sugar starvation as a factor in  
540 reproductive failure under heat and drought stress. *Plant Cell Environ.* **38(10)**:2171–  
541 2192.

542

543 **Lopez-Delacalle, M., Silva, C.J., Mestre, T.C., Martinez, V., Blanco-Ulate, B., and**

- 544 **Rivero, R.M.** (2021). Synchronization of proline, ascorbate and oxidative stress  
545 pathways under the combination of salinity and heat in tomato plants. *Env. Exp. Bot.*  
546 **183**:104351.
- 547
- 548 **Lopez-Hidalgo, C., Guerrero-Sánchez, V.M., Gómez-Gálvez, I., Sánchez-Lucas,**  
549 **R., Castillejo-Sánchez, M.A., Maldonado-Alconada, A.M., Valledor, L. and**  
550 **Jorrín-Novo, J.V.** (2018). A multi-omics analysis pipeline for the metabolic pathway  
551 reconstruction in the orphan species *Quercus ilex*. *Front. Plant Sci.* **9**:935.
- 552
- 553 **Mahalingam, R., Pandey, P., and Senthil-Kumar, M.** (2018). Progress and  
554 prospects of concurrent or combined stress studies in plants. *Ann. Plant Rev.*  
555 **15**:813–868.
- 556
- 557 **Mittler, R.** (2006). Abiotic stress, the field environment and stress combination.  
558 *Trends Plant Sci.* **11**:15–19.
- 559
- 560 **Mittler, R., and Blumwald, E.** (2010). Genetic engineering for modern agriculture:  
561 challenges and perspectives. *Annu. Rev. Plant Biol.* **61**:443–462.
- 562
- 563 **Naika, M., Shameer, K., Mathew, O.K., Gowda, R., and Sowdhamini, R.** (2013).  
564 STIFDB2: an updated version of plant stress-responsive transcription factor  
565 database with additional stress signals, stress-responsive transcription factor binding  
566 sites and stress-responsive genes in *Arabidopsis* and rice. *Plant Cell Physiol.*  
567 **54(2)**:e8-e8.
- 568
- 569 **Pandey, P., Ramegowda, V., and Senthil-Kumar, M.** (2015). Shared and unique  
570 responses of plants to multiple individual stresses and stress combinations:  
571 physiological and molecular mechanisms. *Front Plant Sci.* **6**:723.
- 572
- 573 **Pandey, P., Irulappan, V., Bagavathiannan, M.V., and Senthil-Kumar, M.** (2017).  
574 Impact of combined abiotic and biotic stresses on plant growth and avenues for crop  
575 improvement by exploiting physio-morphological traits. *Front Plant Sci.* **8**:537.
- 576
- 577 **Pan, Q., Wei, J., Guo, F., Huang, S., Gong, Y., Liu, H., Liu, J. and Li, L.** (2019).

578 Trait ontology analysis based on association mapping studies bridges the gap  
579 between crop genomics and Phenomics. *BMC Genomics* **20(1)**:1–13.

580

581 **Rasmussen, S., Barah, P., Suarez-Rodriguez, M.C., Bressendorff, S., Friis, P.,**  
582 **Costantino, P., Bones, A.M., Nielsen, H.B. and Mundy, J.** (2013). Transcriptome  
583 responses to combinations of stresses in Arabidopsis. *Plant Physiol.* **161(4)**:1783–  
584 1794.

585

586 **Savary, S., and Willocquet, L.** (2020). Modeling the impact of crop diseases on  
587 global food security. *Ann. Rev. Phytopathol.* **58**:313–341.

588

589 **Sinha, R., Irulappan, V., Patil, B.S., Reddy, P.C.O., Ramegowda, V., Mohan-**  
590 **Raju, B., Rangappa, K., Singh, H.K., Bhartiya, S. and Senthil-Kumar, M.** (2021).  
591 Low soil moisture predisposes field-grown chickpea plants to dry root rot disease:  
592 evidence from simulation modeling and correlation analysis. *Sci. Rep.* **11(1)**:1–12.

593

594 **Smita, S., Lenka, S.K., Katiyar, A., Jaiswal, P., Preece, J., and Bansal, K.C.**  
595 (2011). QlicRice: a web interface for abiotic stress responsive QTL and loci  
596 interaction channels in rice. *Database* **2011**.

597

598 **Suzuki, N., Rivero, R.M., Shulaev, V., Blumwald, E., and Mittler, R.** (2014).  
599 Abiotic and biotic stress combinations. *New Phytol.* **203**:32–43.

600

601 **Vemanna, R.S., Bakade, R., Bharti, P., Kumar, M.K., Sreeman, S.M., Senthil-**  
602 **Kumar, M. and Makarla, U.** (2019). Cross-talk signaling in rice during combined  
603 drought and bacterial blight stress. *Front. Plant Sci.* **10**:193.

604

605 Zandalinas, S.I., Balfagón, D., Gómez-Cadenas, A., and Mittler, R. (2022).  
606 Responses of plants to climate change: Metabolic changes during abiotic stress  
607 combination in plants. *J. Exp. Bot.* erac073, <https://doi.org/10.1093/jxb/erac073>.

608

609 **Zandalinas, S.I., Fritschi, F.B., and Mittler, R.** (2020a). Signal transduction  
610 networks during stress combination. *J. Exp. Bot.* **71(5)**:1734–1741.

611

612 **Zandalinas, S.I., Fichman, Y., Devireddy, A.R., Sengupta, S., Azad, R.K., and**  
613 **Mittler, R.** (2020b). Systemic signaling during abiotic stress combination in plants.  
614 *Proc. Natl. Acad. Sci. USA* **117(24)**:13810–13820.

615

616 **Zandalinas, S.I., Fritschi, F.B., and Mittler, R.** (2021a). Global warming, climate  
617 change, and environmental pollution: Recipe for a multifactorial stress combination  
618 disaster. *Trends Plant Sci.* **26(6)**: 588–599.

619

620 Zandalinas, S.I., and Mittler, R. (2022). Plant responses to multifactorial stress  
621 combination. *New Phytologist*. DOI: 10.1111/nph.18087.

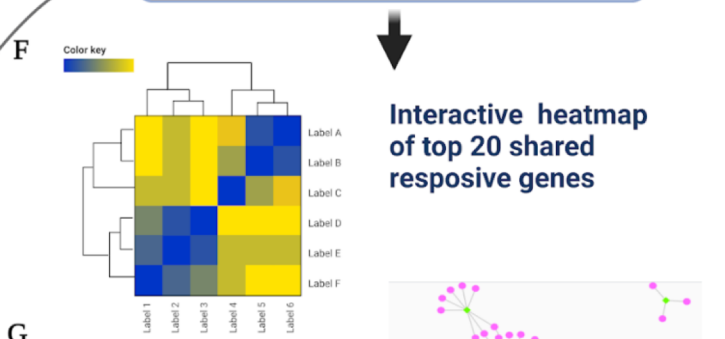
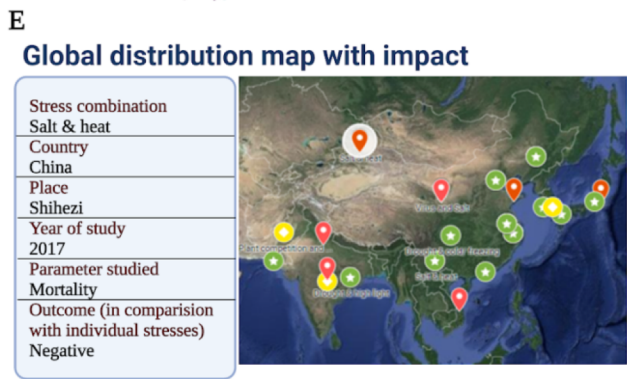
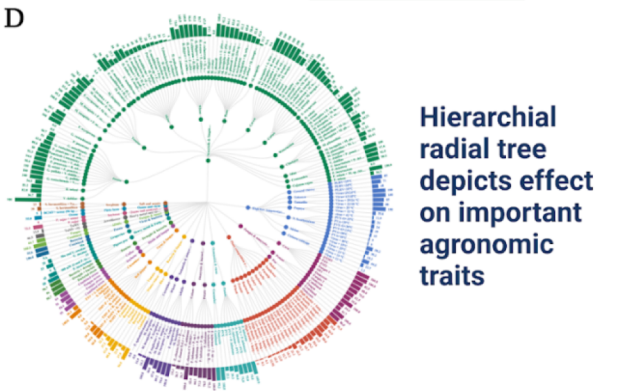
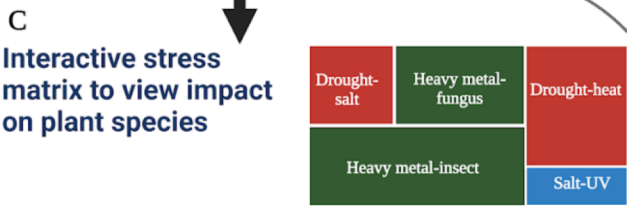
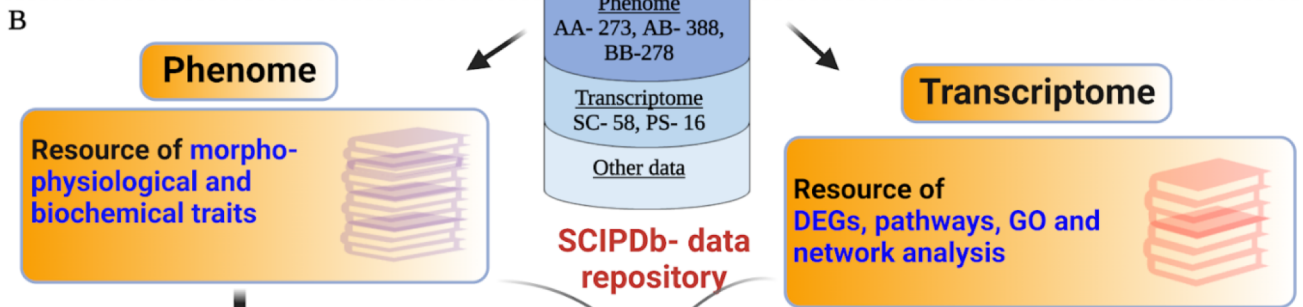
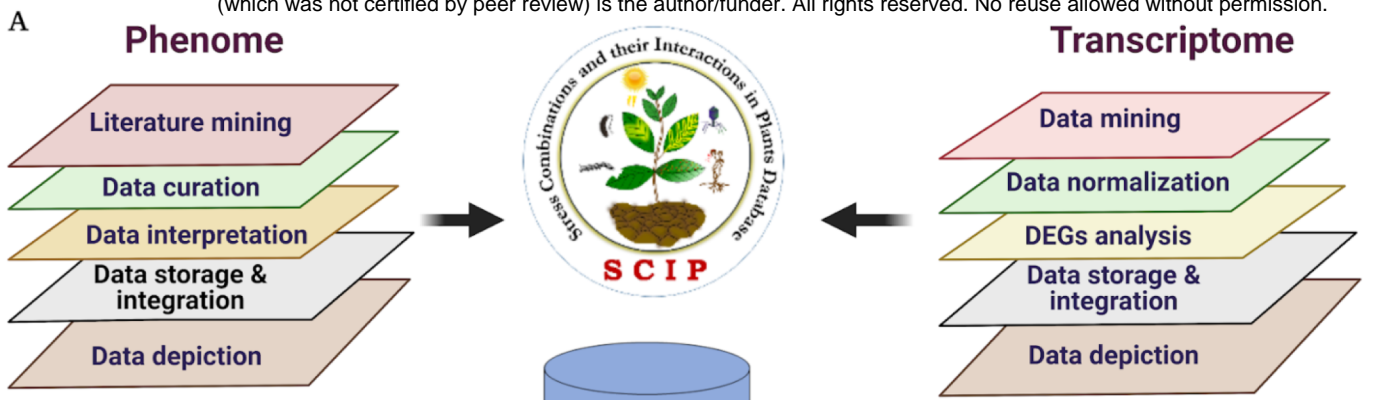
622

623 **Zandalinas, S.I., Sengupta, S., Fritschi, F.B., Azad, R.K., Nechushtai, R., and**  
624 **Mittler, R.** (2021b). The impact of multifactorial stress combination on plant growth  
625 and survival. *New Phytol.* **230(3)**:1034–1048.

626

627 **Zhang, H., and Sonnewald, U.** (2017). Differences and commonalities of plant  
628 responses to single and combined stresses. *Plant J.* **90**:839–855.

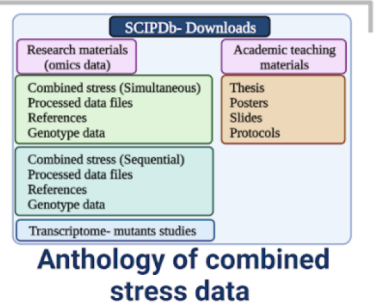
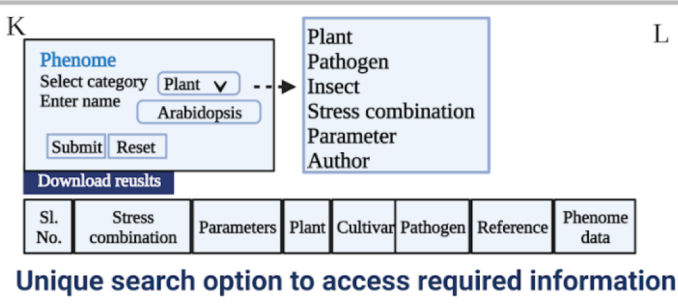
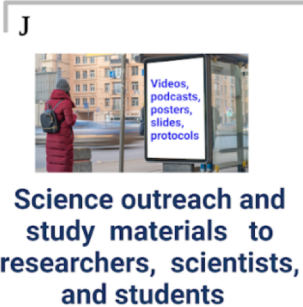




**I**

Blast server to find out homologs & orthologs

Query	Subject	Identity (%)	Plant sps	Stress combination	Gene name	Log FC
AT1G69490	AT1G69490.1	100	Arabidopsis	Drought & nonhost pathogen	NAC-like	2.9
AT1G69490	AT1G69490.1	88	Arabidopsis	Drought & heat	bZIP12	3.2





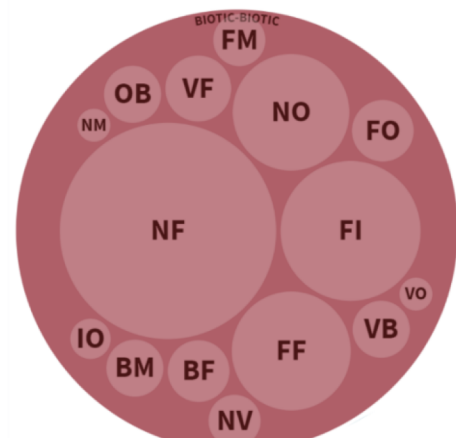
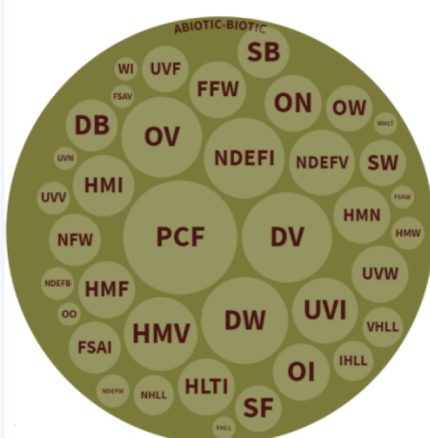
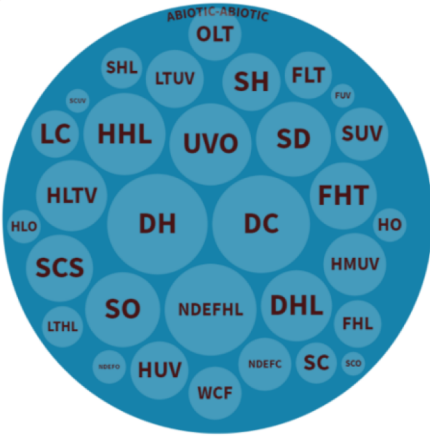
**Figure 1. Outline of the Stress Combinations and their Interactions in Plants Database (SCIPDb), indicating its key features and applications. (A)** The upper panel shows the steps involved in data mining, curation, analysis, and integration of phenome and transcriptome data into SCIPDb. **(B)** The lower panel shows the key features and applications offered to the users in the phenome and transcriptome sections. Orange boxes indicate the two major data sets hosted in SCIPDb. **(C)** The interactive stress matrix shows the net impact of the interaction between the stresses. The net impact of combined stress was determined by analyzing the percent reduction in plant growth, yield, and physiological traits. Three possible interactions, namely, positive (less damage under combined stress), negative (greater damage under combined stress), and others (equal damage under combined and individual stress), are depicted in green, red, and blue boxes, respectively. A stress combination is classified as positive, negative, or others based on the maximum number of studies in a particular interaction. The size of the box indicates the number of studies showing a particular interaction, i.e., a bigger size represents a greater number of studies. **(D)** The radial tree depicts the effect of individual and combined stresses on various traits in different plant species arranged in hierarchical order (starting from most to least damage). The parameters considered for developing radial trees were growth, yield, physiological, and pathogen-associated parameters. To normalize the data, percent change over control or percent change over individual stresses (in the case of pathogen-associated traits) was calculated for each trait and presented. **(E)** The interactive global map provides information on the global distribution of combined stresses and their effect on morpho-physiological, biochemical, and pathogen-associated traits. The map was generated using the geographic coordinates of the locations where the studies were conducted. **(F)** An interactive heatmap enables users to visualize the gene expression profile of the top 20 differentially expressed genes (DEGs) for a particular transcriptome. **(G)** A co-functional network depicts the correlation of the top 20 DEGs in the form of an interactive network. The co-functional network allows the user to interact with the graph, and it includes all the required gestures, including pinch-to-zoom, box selection, panning, etc., to access other metadata for each node and edge. **(H)** An interactive Manhattan plot depicts functional profiling of DEGs using various kinds of biological evidence, including Gene Ontology terms, biological pathways, and regulatory DNA elements. The X-axis represents functional terms grouped and color-coded by data sources, while the Y-axis shows the adjusted enrichment p-values in negative log<sub>10</sub> scales. **(I)** BLAST server to find potential homologs and orthologs in SCIPDb. **(J)** SCIPDb hosts science outreach materials like posters, slides, videos, and podcasts related to combined stress, which will be useful for students, researchers, and scientists working in the area of combined stress. **(K)** The unique keyword-based search option helps to access all combined stress-related data with a single click. Searches can be performed using keywords like plant name, pathogen, insect, name of combined stress, gene ID, and gene name. **(L)** The download section provides processed phenome and transcriptome data and a reference list of combined stress articles hosted in SCIPDb. It also provides a link to mutant transcriptome studies and diverse resources related to combined stress. Numbers within the cylinder indicate the total number of articles curated and presented in the phenome and the total number of stress combinations covered under transcriptome. AA: abiotic–abiotic stress, AB: abiotic–biotic stress, BB: biotic–biotic stress, SC: stress combinations, PS: plant species. The figure was created with BioRender.com.

A

Abiotic-abiotic

Abiotic-biotic

Biotic-biotic



B

Applications

Phenome

Provides information on effect of stress combinations on growth, yield, physiological, and pathogenesis associated traits

Phenome

A) Plant performance

Provide information on growth and yield attributing traits in various plant species

What is the effect of stress combinations on plant performance?

B) Plant physiological response

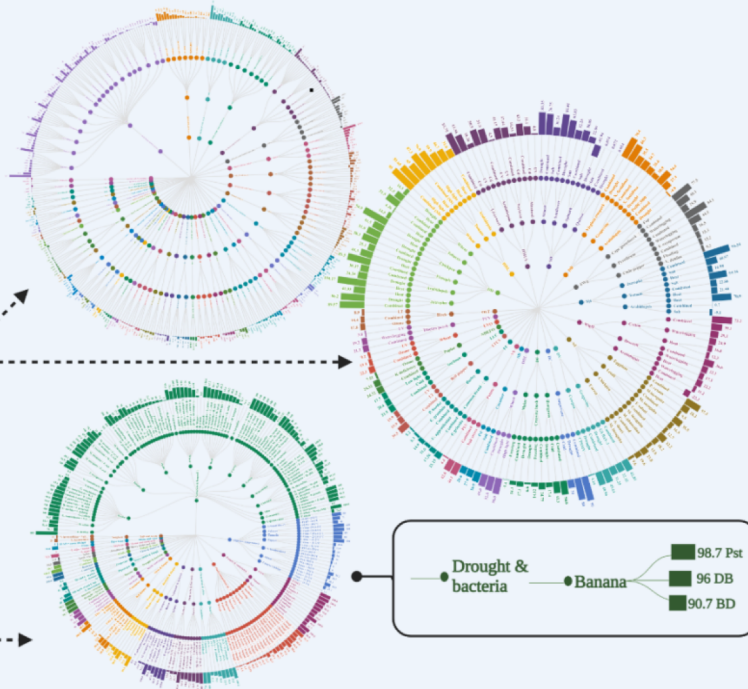
Provide information on physiological traits in various plant species

What is the effect of stress combinations on plant physiological traits?

C) Pathogenesis response

Provide information on disease incidence in various plant species

What is the effect of stress combinations on pathogenesis traits?



C

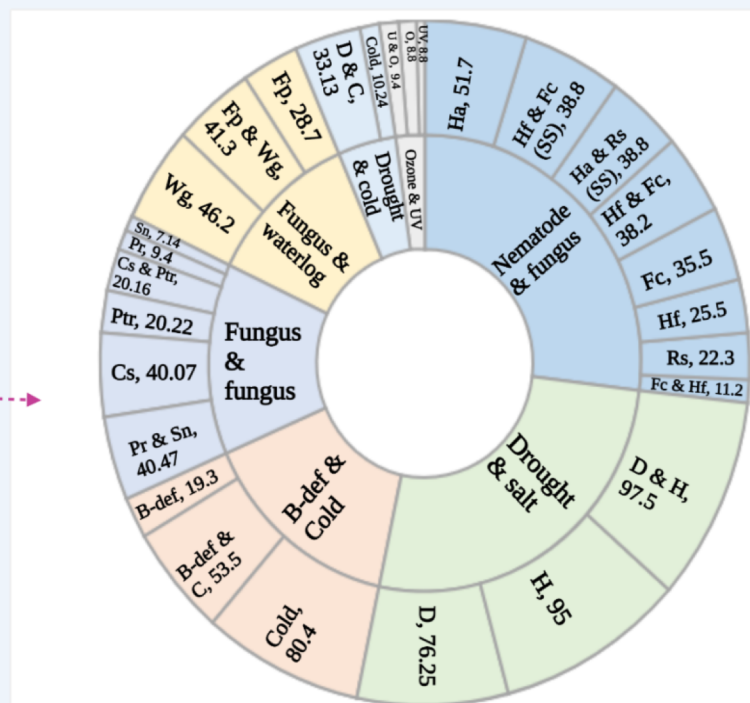
Phenome

A) Plant performance

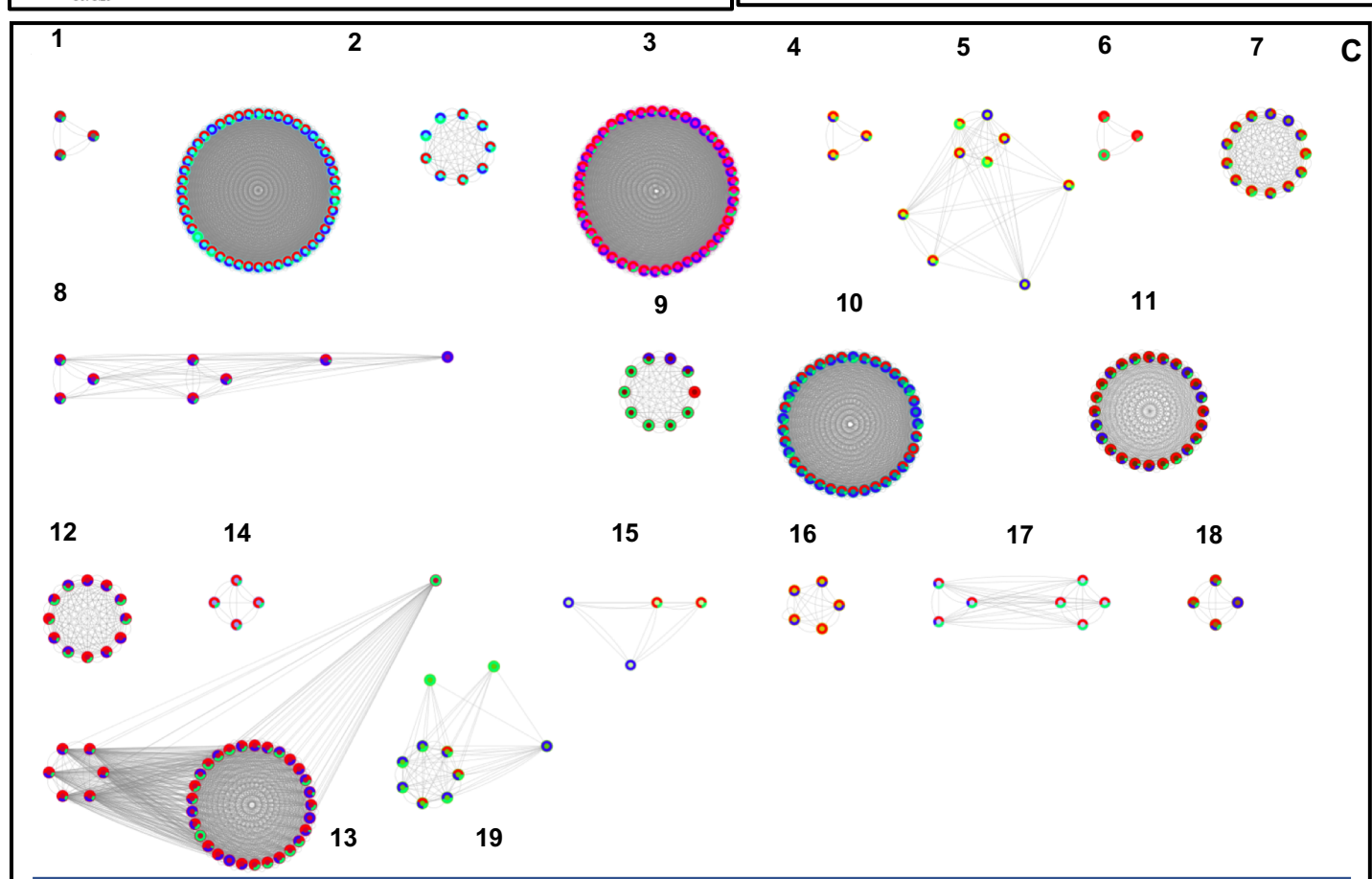
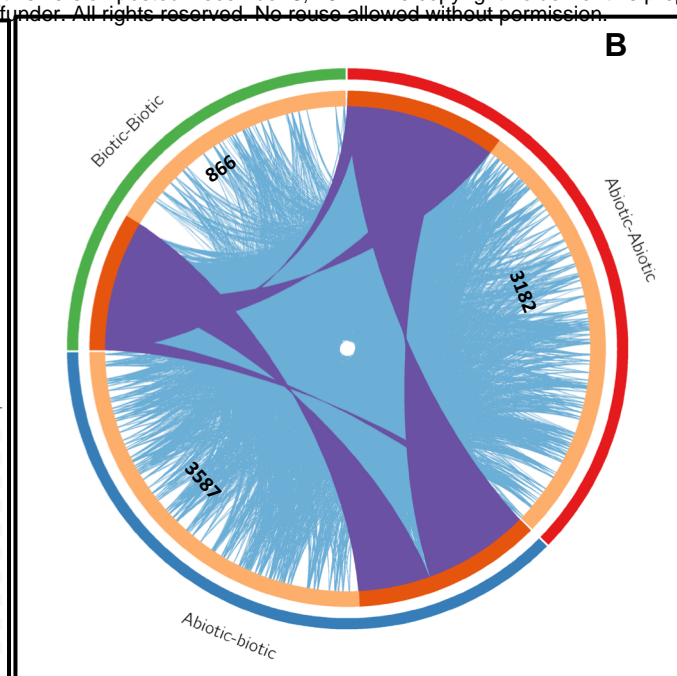
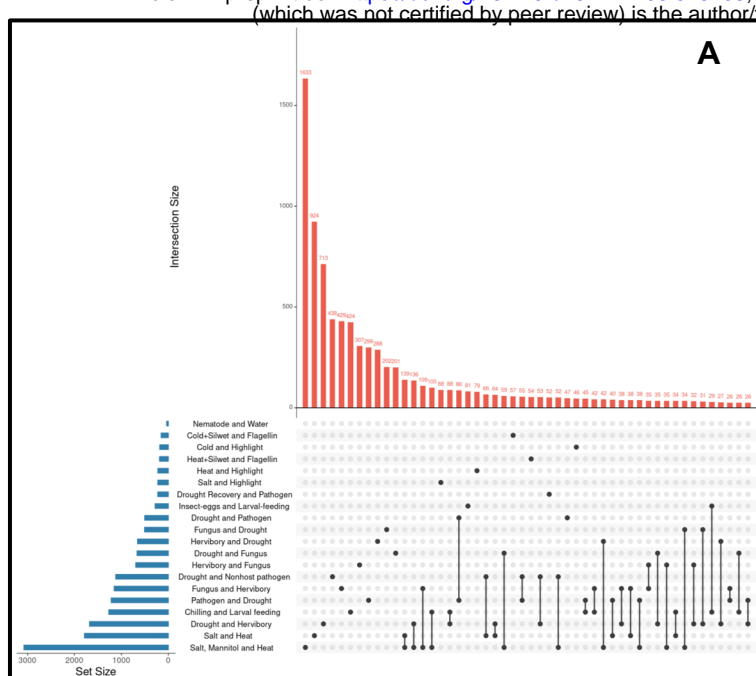
Provide information on growth and yield attributing traits in various plant species

What is the effect of stress combinations on plant performance?

1. What is the effect of stress combinations on rice crop yield?
2. What are the most deleterious stress combinations affecting yield of pulse crops?
3. What are the major stress combinations affecting growth and yield of oilseed crops?
4. What are the major stress combinations affecting monocots yield?
5. How is wheat yield affected under combined stress?
6. What is the effect of stress combinations on growth and yield of tomato crop?
7. What are the major stress combinations affecting wheat growth?
9. How cotton growth and yield are regulated under combined stress?
10. What are the major stress combinations affecting growth and yield of solanaceous crops?
11. What are the stress combinations favours growth and yield of crops in comparison to the individual stresses?



**Figure 2. Phenome data analysis to assess the effect of stress combinations on agronomic traits.** (A) The bubble diagrams depict the total stress combinations covered in SCIPDb under abiotic–abiotic, abiotic–biotic, and biotic–biotic stress categories. The size of the bubble is directly proportional to the number of studies under the respective stress combinations. For crop-wise stress combinations, bubble diagrams are presented in [Supplemental Figures 7–9](#). (B) Schematic representation of the phenome application page and key features offered on various plant traits. Traits are classified into three major groups: plant performance (including growth and yield traits), plant physiological response (including physiological traits), and plant pathogenic response (including pathogen-associated traits). Complete information on a particular class of traits can be accessed by clicking on a particular text. The radial tree shows the overall impact of combined stress on various classes of plant traits. The tree comprises four layers: stress combination, plant species, stress treatments, and the calculated value of the trait in the form of stack bars as shown in the inset (drought and bacteria). For growth and physiological traits, values were calculated as “percent change under stress over the control,” and for pathogenesis traits, “percent change under combined stress over individual pathogen stress.” The tree should be read clockwise, where stress combinations are listed in hierarchical order based on their extent of impact on a trait, i.e., from most deleterious to least deleterious stress combination. Within a combination, stress treatments are also mentioned following similar criteria. Enlarged versions of radial trees are given in [Supplementary Figures 10–12](#). and interactive versions are presented in database. (C) Representation indicating the effect of different stress combinations on wheat yield. Sunburst diagrams comprise two layers; the inner layer represents the name of the stress combination, and the outer layer represents the stress treatments with the calculated percent value. Percent change in parameter value was calculated as percent change under stress over the control. In the outer layer, the size of the box is directly proportional to the percent value, i.e., higher the percent value, bigger the box. Similarly, data for other plant species can be accessed using multiple questions listed under each group. Traits included in the plant performance group are plant height, root length, biomass, leaf number, leaf area, and yield. The figure was created with BioRender.com.



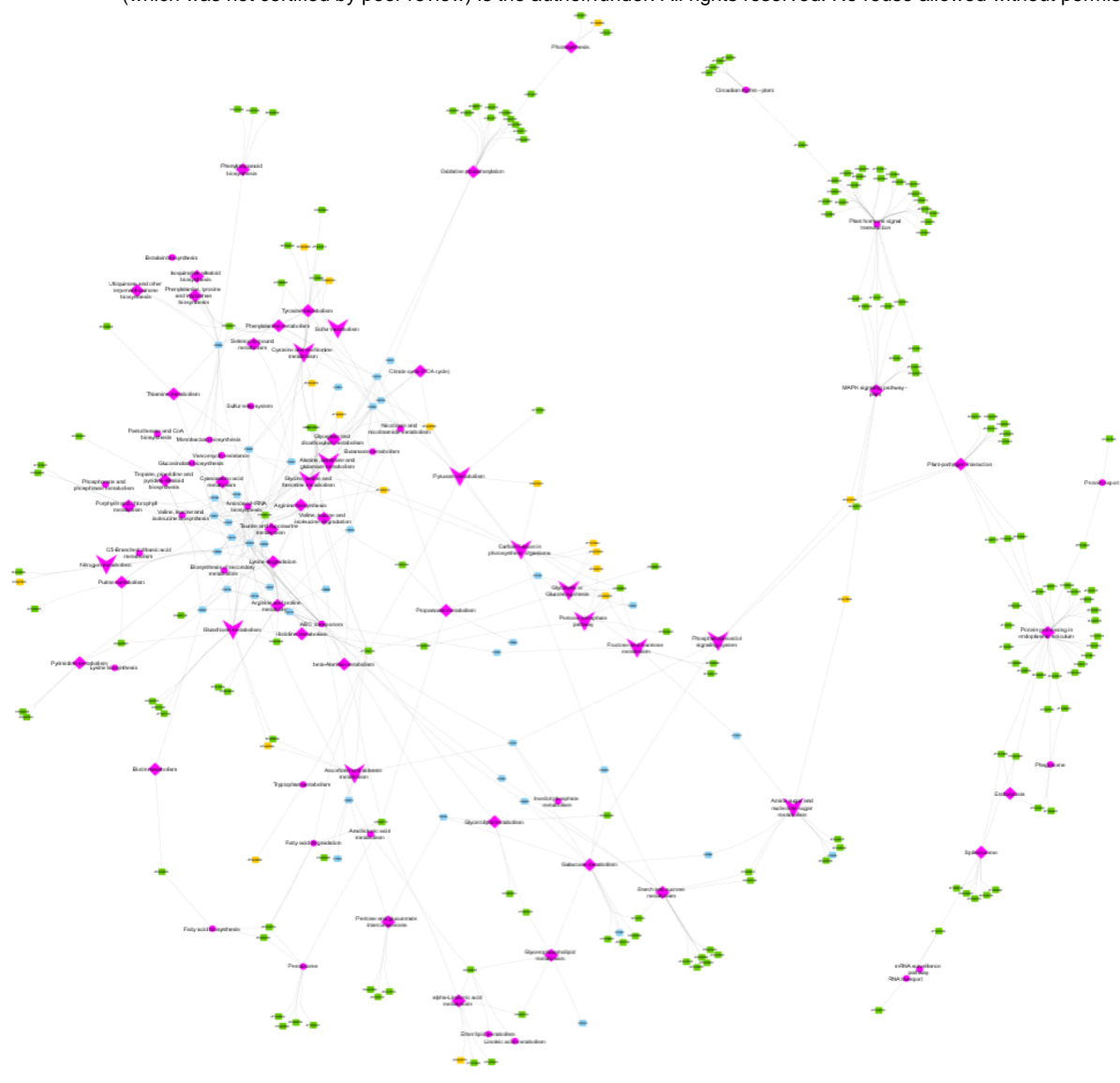
**Node colour code**

1. Oxocarboxylic acid metabolism	8 Environmental Adaptation	17. Replication & repair
2. Amino acid metabolism	9. Glycan biosynthesis & metabolism	18. Reproductive development
3. Carbohydrate metabolism	10. Lipid metabolism	19. Signal transduction
4. Carbon metabolism	11. Metabolism of cofactors & vitamins	Abiotic - Abiotic
5. Cellular transport & catabolism	12 & 13. Secondary metabolism	Abiotic - Biotic
6. Replication & repair	14. Nucleotide metabolism	Biotic - Biotic
7. Energy metabolism	15 & 16. Protein synthesis	

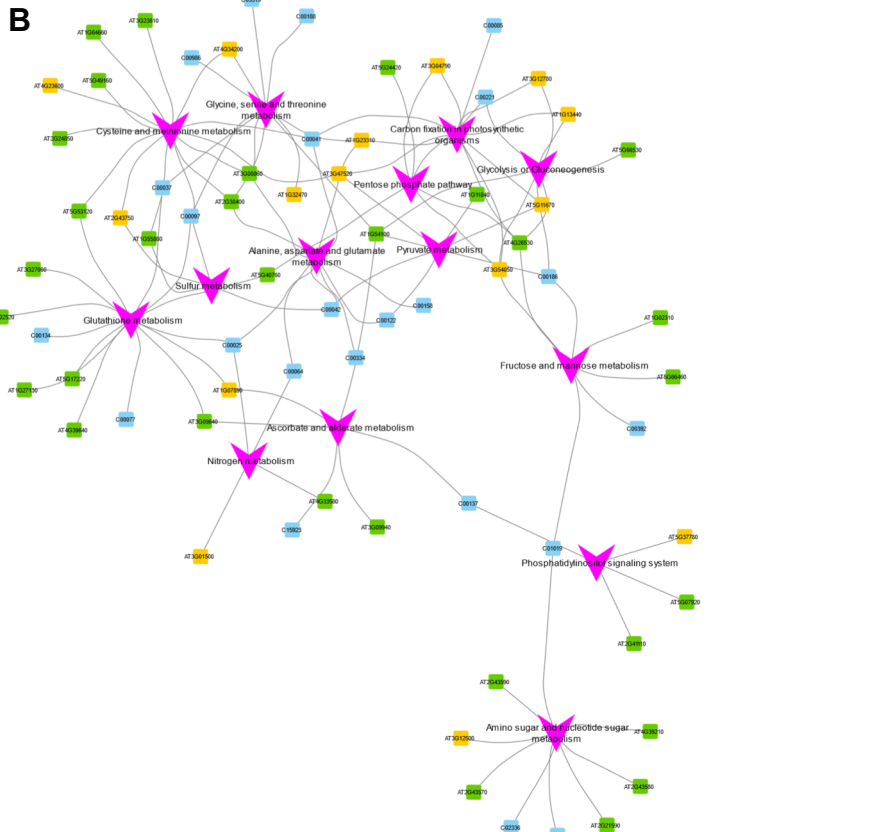


**Figure 3. Global pathway and process enrichment analysis of differentially expressed combined stress genes in *Arabidopsis thaliana*.** **(A)** Intersections among combined stress DEGs in *Arabidopsis* across different stress combinations. The numbers above bars indicate the number of genes within each intersection. Horizontal bars depict set size and set names. Connected dots represent common genes between the transcriptomes, while unconnected dots represent unique genes. **(B)** Circos plot representing the overlap between category-wise DEGs lists in abiotic–abiotic, abiotic–biotic, and biotic–biotic categories. The inner circle represents gene lists, where hits are arranged in the form of an arc. Genes that hit multiple lists are colored in dark orange, and genes unique to a list are shown in light orange. Purple curves link shared genes between the three categories, and blue curves link genes that belong to the same enriched ontology term. **(C)** Network representation of unique and common pathway clusters among the major combined stress categories. Analysis showed the enrichment of seven main pathway clusters, namely, lipid metabolism, carbohydrate metabolism, amino acid metabolism, biosynthesis of plant hormones, sugar and hormone signaling, secondary metabolite biosynthesis, and glycan metabolism. Ellipse-shaped nodes depicted as donuts are key pathway clusters (names indicated). The pathway clusters were grouped into broader categories based on KEGG pathway classification (for details on each node, refer to the “Transcriptome – Visualize Transcriptomics data” link in the database). Nodes in the circle represent the genes mapped to those pathways. The color of the nodes indicates the different enriched pathways and their corresponding genes in green. The network is visualized with Cytoscape (v3.8.2) with a “Group by attribute circle” layout. The network of enriched terms is represented as donut charts, where donuts are color-coded based on the identities of gene lists. The size of a donut is proportional to the total number of hits that fall into that specific term.

A



B



Node shape & color code

-  **Transcripts; T**
-  **Proteins; P**
-  **Metabolites; M**
-  **Pathways supported by all three omics i.e., T, P & M**
-  **Pathways supported by two omics i.e., T\_P; P\_M; T\_M**
-  **Pathway supported by single omics**

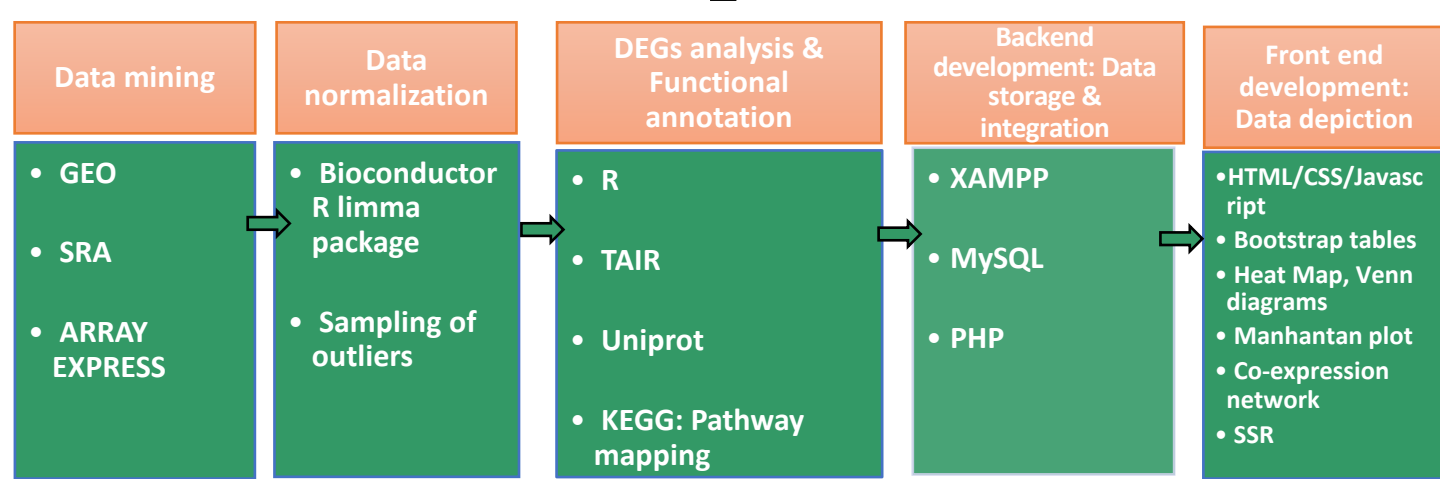
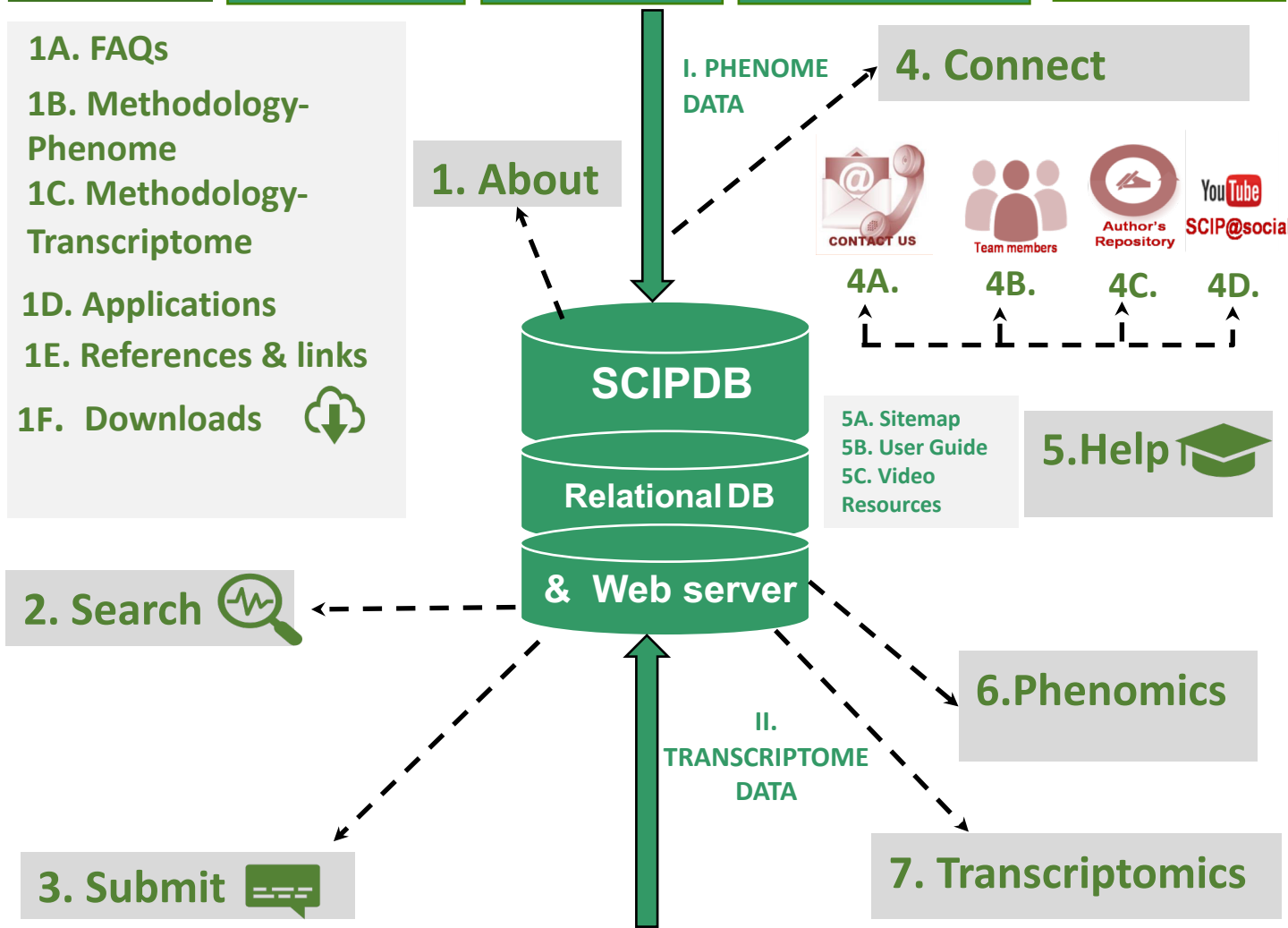
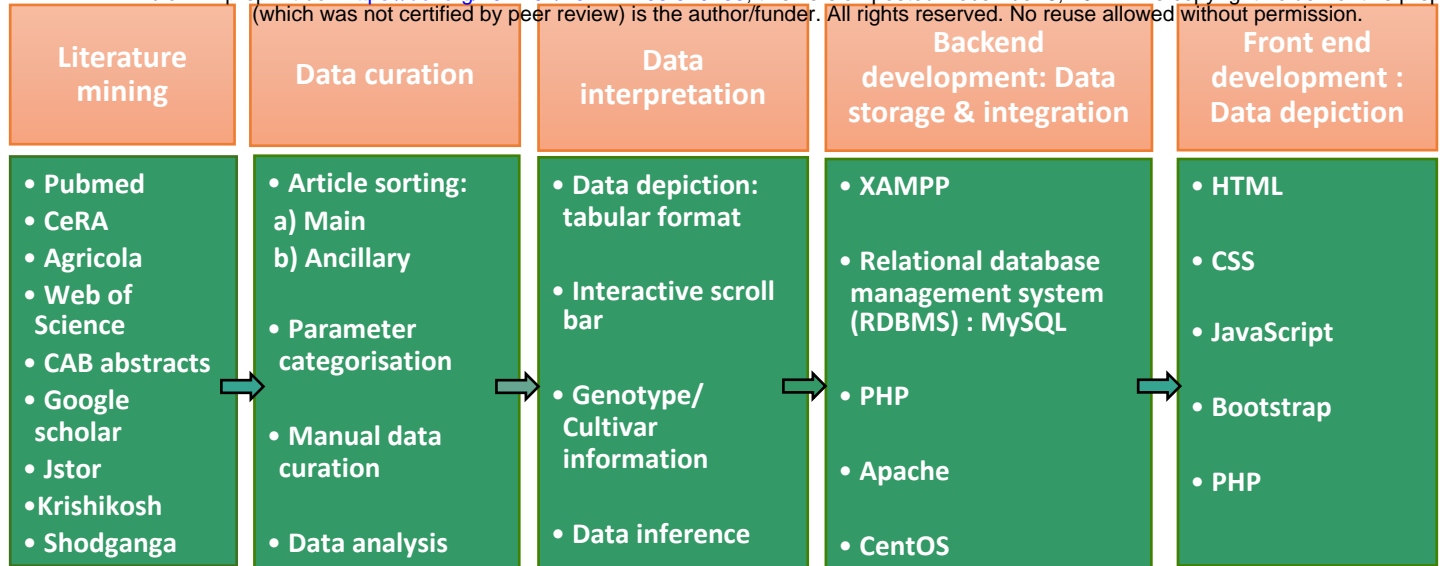
**Figure 4. Integrative multi-omics analysis to decipher key omics features and pathways differentially altered during the drought and heat stress combination in Arabidopsis. (A)** The network representation of differentially regulated genes, proteins, and metabolites under the drought and heat stress combination in Arabidopsis was done via joint pathway analysis and visualized in the “Edge weighted spring embedded” layout in Cytoscape (v3.8.2). The network is presented as nodes indicating various pathways and their associated omics features connected by edges. Edges have been bundled for clarity. The size of a pathway node represents the pathway impact in terms of evidence from omics features, wherein arrow-headed nodes signify pathways having evidence from all the three omics features (transcriptome (T), proteome (P), and metabolome (M)), while diamond-shaped nodes have evidence from either of the two omics features (T-P, P-M, or T-M). Nodes shown in the ellipse represent pathways that show evidence from single omics (T, P, or M). Node color corresponds to the class of the pathway or features as mentioned in the node shape and color code box. **(B)** An enlarged and detailed version of the network highlighting pathways supported by all the three omics features (T, P, and M). T: transcriptomics, P: proteomics, and M: metabolomics.

**Stress Combinations and their Interactions in  
Plants Database (SCIPDb): A one-stop resource for understanding  
combined stress responses in plants**

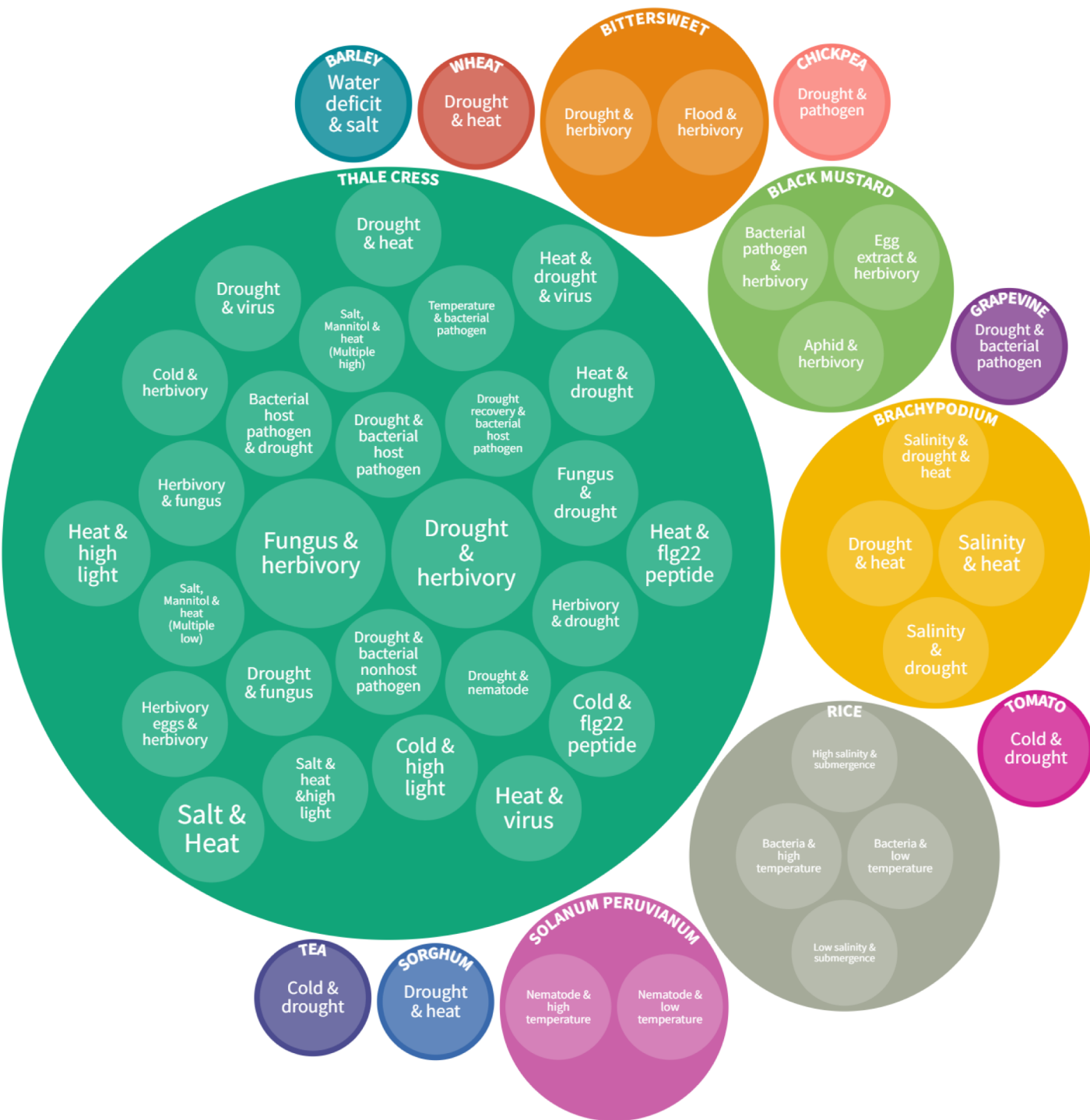
Piyush Priya<sup>#</sup>, Mahesh Patil<sup>#</sup>, Prachi Pandey, Anupriya Singh, Vishnu Sudha  
Babu & Muthappa Senthil-Kumar\*

National Institute of Plant Genome Research, Aruna Asaf Ali Marg, P.O. Box  
No. 10531, New Delhi 110067, India





**Supplemental Figure 1. Content and construction of SCIPDb.** SCIPDb provides a user-friendly interface to browse, search, download and visualize stress combination data of plants. The figure outlines the schematic representation of SCIPDb main menus and submenus. About, Search, Submit, Connect, Help, Phenomics, and Transcriptomics, are the main menus. **(1) About** menu further is subdivided into **1A. FAQs:** address common concerns, and questions, that users have. **1B. Methodology Phenome & 1C. Transcriptome:** outlines and details the steps followed to collect, curate and interpret the phenomics and transcriptomics dataset integrated into SCIPDb, **1D. Applications:** depicts the multifarious uses of SCIPDb, **1E. References & Links:** provides easy access to the entire list of research articles used in developing data pages along with other related articles such as reviews, thesis, and reports. Weblinks of labs and scientists, important books, and articles on combined stress are also provided. **1F. Downloads:** section catalogs the entire list of raw data files, references, genotypes covered in SCIPDb, along with several academic teaching materials, which can be downloaded by the user locally using the FTP server hosted hereby. **(2) The Search** menu provides the user an option to query the SCIPDb dataset based on keywords and sequence to fetch relevant information. **(3) Submit** menu provides the users with an option to submit combined stress data on phenome and transcriptome to SCIPDb. **(4) Connect** section provides the user information about **4A. Contact details**, **4B. Team members**, **4C. Author repository**, that provides details of authors working in the area of combined stress and **4D. SCIP@Social**, which hosts several videos and podcasts related to the area of combined stress. **(5) Help**, hosts **5A.** that further details each section and tabs of SCIPDb, **5B.** User guide: Detailed tutorial explaining steps needed to easily navigate and use SCIPDb **5C.** Video resources: Videos related to combined stress in plants. **(6) Phenomics:** Hosts morphological, physiological, and biochemical data associated with various stress combinations. **(7) Transcriptomics:** hosts a comprehensive collection of combined stress-responsive differentially expressed genes (DEGs) identified in publicly available transcriptomic data from various plant species.



**Supplemental Figure 2. Combined stress transcriptome articles were analyzed and integrated into SCIPDb.** The bubble diagram has been color-coded based on plant species and has been organized hierarchically into two layers where the first layer represents the plant species and the second layer represents the stress combinations. The size of the bubble is directly proportional to the number of articles i.e., the bigger the size more the number of studies in that stress combination for that plant species.

**A. Brief introduction of stress combination, with links to important publications and representative figure**

Plant response to individual drought and bacterial pathogen stress has been well documented in different crop species, but only 10 studies showing the effect of combined drought and bacterial pathogen stress have been reported in chickpea, Arabidopsis, grapevine, tobacco, rice, Virginia creeper, and banana. Results from these studies indicated both positive and negative impact on plant growth and development. The extent of the impact is mainly dependent on plant species, age, the order of occurrence, stress severity, stress duration, and environmental factors like temperature and humidity. For more clarity on terminology, like combined stress, sequential stress, and multiple individual stress please refer to [Pawsey et al., 2017](#).



Figure: Grapevine plants subjected to combined drought and bacterial pathogen *Xylella fastidiosus* infection (Choi et al., 2018)

Pictures show the effect of combined drought and bacterial pathogen stress on disease development in grapevine. Grapevines exposed to combined drought and *X. fastidiosus* infection showed more scoring symptoms compared to plants which are only exposed to *X. fastidiosus* infection alone. (pictures reproduced with permission)

**Effect on thale cress (*Arabidopsis thaliana* ecotype Col 0)**

**1. Net impact of individual and combined stress on plant growth**

Crop: Thale cress (*Arabidopsis*)  
Stress 1: Drought  
Stress 2: *Pseudomonas syringae* pv. tomatos DC3000

Table showing net impact of individual and combined stress on chlorophyll content and cell death

Parameters studied	Drought levels (field capacity %)	Bacterial Concentration (CFU mL <sup>-1</sup> )	Plant response to stress over control			Parameter type*
			Combined	Drought stress	Bacterial pathogen stress at 100% FC	
Reduction in total chlorophyll content over control (%) at 24 hpt	60	2x10 <sup>3</sup>	4.02	2.46		Type B
	60	2x10 <sup>3</sup>	5.35	-4.92	16.43	
	40	2x10 <sup>3</sup>	-4.65	0.00		
	20	2x10 <sup>3</sup>	4.68	-1.64		
	60	5x10 <sup>3</sup>	24.68	NA	21.07	
	60	5x10 <sup>3</sup>	21.01	NA		
	40	5x10 <sup>3</sup>	26.01	NA		
	20	5x10 <sup>3</sup>	4.02	NA		
	60	1x10 <sup>4</sup>	41.58	NA	51.70	
	40	1x10 <sup>4</sup>	24.68	NA		
	20	1x10 <sup>4</sup>	6.68	NA		
	60	1x10 <sup>5</sup>	44.68	NA	54.30	
40	1x10 <sup>5</sup>	27.35	NA			
20	1x10 <sup>5</sup>	22.01	NA			
60	2x10 <sup>3</sup>	5.08	1.75	11.2		
20	2x10 <sup>3</sup>	31.71	11.57	NA		
60	1x10 <sup>3</sup>	15.4	NA	NA		
20	1x10 <sup>3</sup>	7.03	NA	17.27		

CFU: Colony forming units; hpt: Hours post-stress treatment; FC: Field capacity; NA: Data not available. For raw data - Click here (xlsx file) Reference- Gupta et al., 2016

Relative over control (%) -> Over Under

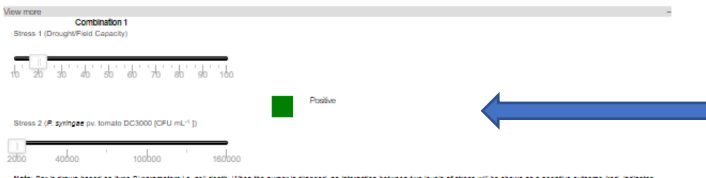
1) - Indicates no change in parameter under stress

2) + Indicates parameter is more affected by stress that leads to high susceptibility (higher the value more the damage)

3) - Indicates parameter is less affected by stress that leads to improved resistance (higher the value lesser the damage)

\*\*\* For more information on parameters classification please refer to methodology file.

Bar showing net impact of combined stress over control



Note: Bar is drawn based on type B parameters i.e. cell death. When the cursor is dropped, an interaction between two levels of stress will be shown as a negative outcome (red) - indicates combined stress caused more deleterious effects on plants or positive outcome (green) - indicates combined stress caused less deleterious effects on plants.

**2. Interaction between drought and bacterial pathogen stress at plant interphase**

Table showing effect of drought on bacterial pathogen multiplication and disease progression under combined stress

Drought levels (field capacity %)	Bacterial pathogen concentration (CFU mL <sup>-1</sup> ) and duration	Response under combined stress			Parameter type*
		Change in in-plant bacterial number under combined stress over individual bacterial pathogen stress (%) at 72 hpt	Disease score (%)**	Score 3	
60	2x10 <sup>3</sup>	32.65	0	0	Type B
60	5x10 <sup>3</sup>	-2.19	30.71	6.36	
60	1x10 <sup>4</sup>	-28.70	7.64	2.82	
60	1x10 <sup>5</sup>	-10.32	16.7	26.1	
60	2x10 <sup>3</sup>	29.09	17.25	0	
60	5x10 <sup>3</sup>	-20.47	0	5.36	
60	1x10 <sup>4</sup>	-16.04	36.9	0	
60	1x10 <sup>5</sup>	-20.11	21.83	22.53	
40	2x10 <sup>3</sup>	-3.42	0	0	
40	5x10 <sup>3</sup>	-16.43	25.9	0	
40	1x10 <sup>4</sup>	-16.59	13.2	0	
40	1x10 <sup>5</sup>	-24.31	11.8	11.96	
20	2x10 <sup>3</sup>	-8.55	14.1	0	
20	5x10 <sup>3</sup>	-43.77	0	0	
20	1x10 <sup>4</sup>	-44.59	0	0	
20	1x10 <sup>5</sup>	-39.07	10.47	33.8	
100	2x10 <sup>3</sup>	-	6.1	0	
100	5x10 <sup>3</sup>	-	42.9	6.36	
100	1x10 <sup>4</sup>	-	15.28	16.9	
100	1x10 <sup>5</sup>	-	6.84	23.2	

CFU: Colony forming units; FC: Field capacity; hpt: Hours post combined stress treatment. For raw data - Click here (xlsx file) Reference- Gupta et al., 2016

Note: Reduction in in-plant bacterial number under combined stress over individual bacterial pathogen stress was calculated using the formula described below:

View more  
1) + Indicates parameter is less/not affected by combined stress leading to improved resistance (i.e., higher the negative value, lesser the damage).  
2) - Indicates parameter is affected under combined stress leading to high susceptibility (i.e., higher the positive value, more the damage).  
\*\*\* For more information on parameters classification please refer to methodology file.  
\*\*\* Disease score was calculated based on percent leaf area showing chlorotic symptoms and scored as 0 to 5 where '0' indicates healthy leaf and '5' indicates 100% leaf chlorosis. For more information on calculation please refer source article.

Inference from the study: Gupta et al., 2018 study aimed to understand the physiological response of *Arabidopsis* plant to combined drought and *P. syringae* pv. tomatos DC3000 (Pst DC3000) infection. Plants infected with Pst DC3000 only showed more reduction in chlorophyll content and higher cell death compared to plants exposed to combined stress as well as drought stress alone. The trend was same across different combined drought and Pst DC3000 treatments and intensity of infection was reduced as drought severity increased. A similar trend was also observed with pathogen multiplication and disease symptoms i.e. with increasing drought severity pathogen multiplication and disease symptoms were reduced under combined stress as compared to pathogen stress alone. Reduction in bacterial pathogen number increased with drought intensity may be because of activated plant basal defense mechanism and also reduced water availability for invading bacterial pathogens.

Intensity drought stress is crucial for the bacterial pathogen *P. syringae* pv. tomatos DC3000 multiplication in *Arabidopsis*.

**B. Tabular depiction of Phenome data showing net impact of individual and combined stress**

**C. Links to raw data and corresponding reference. For studies having cultivar or genotype data, link for the same is also provided.**

**D. Formula used for calculation for percent reduction over control for particular parameter**

**E. Interactive scroll bar depicting net impact of combined stress**

**F. Additional table depicting interaction of two stresses at plant interface**

**G. Inference of the study**

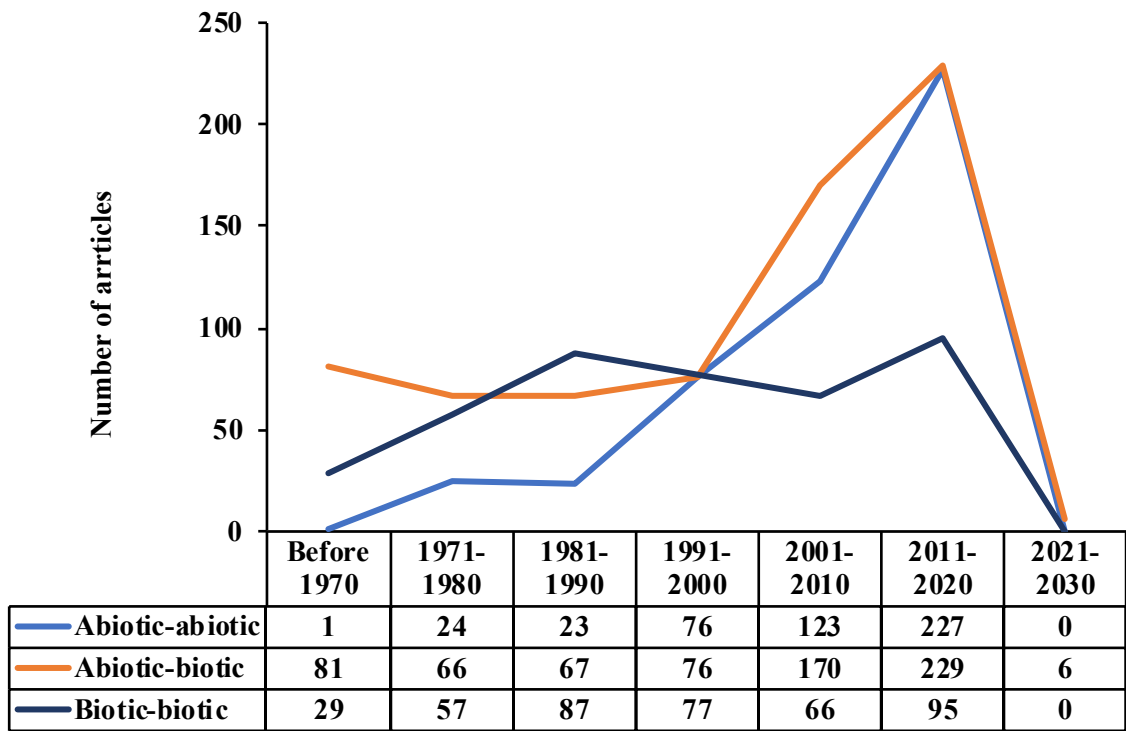
**Supplemental Figure 3. A typical data page entry for phenome in SCIPDb.** The figure shows the analyzed phenome data integrated into SCIPDb. The phenome data page is organized and presented based on major stress categories, stress combinations, and plant species selection by the user. A-G details various components of the phenome data page integrated into the SCIPDb.

Outcome -1  1

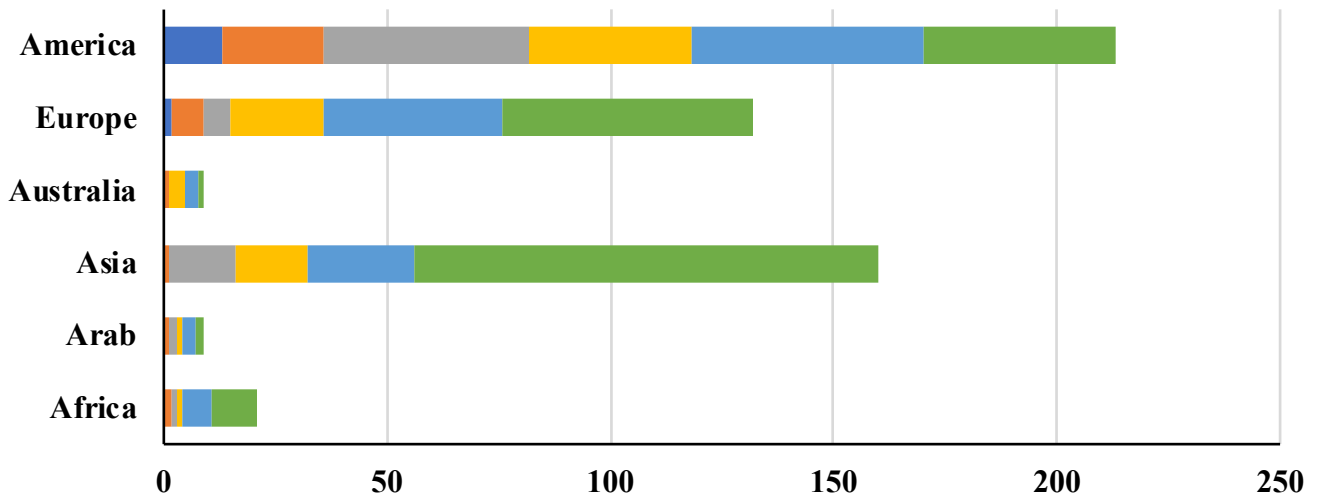


**Supplemental Figure 4: The Heat map depicting the various stress combinations of potential environmental stresses that affect crops in the field.** The gradation in the color depicts potential outcomes based on findings of many studies analyzed in SCIPDb for each stress combination. Red color (-1) shows potential negative outcome, i.e, plants under these combined stresses are affected to a greater extent compared to individual stresses while green color (+1) shows potential positive outcome implying plants under these combined stresses are less/equally affected as compared to one or both the individual stresses.

A



B



	Africa	Arab	Asia	Australia	Europe	America
Before 1970	0	0	0	0	2	13
1971-1980	2	1	1	1	7	23
1981-1990	1	2	15	0	6	46
1991-2000	1	1	16	4	21	36
2001-2010	7	3	24	3	40	52
2011-2021	10	2	104	1	56	43

### Supplemental Figure 5. Literature analysis of combined stress articles published from 1950 to 2021.

A. Graphs show the year-wise total number of articles published until the year 2021 under the abiotic-abiotic, abiotic-biotic, and biotic-biotic stress categories. B. Graph shows the year-wise distribution of combined stress articles published in eight major regions of the world. Only research articles were considered in generating these figures other types of articles like reviews, reports, mutant/transgenic studies, and articles on tree species were excluded.

**Drought and nonhost pathogen stress in Thale cress**

**Unique genes**

Search results matching your query

Show 10 entries Search:

Sl.no.	Gene ID	Gene name	Transcript Fold change (FC)	Nature of change in expression	Pathway & metadata
1	AT3G21580	UDP-Glycosyltransferase superfamily protein	8.30	Uniquely expressed under nonhost pathogen	ath00940-Phenylpropanoid_biosynthesis
2	AT5G18440	isopentenyl diphosphate isomerase 1	7.90	Uniquely expressed under drought	ath00900-Terpenoid_backbone_biosynthesis; ath01100-Metabolic_pathways; ath01110-Biosynthesis_of_secondary_metabolites
3	AT1G57630	Toll-Interleukin-Resistance (TIR) domain family protein	7.80	Uniquely expressed under drought and nonhost pathogen stress	KEGG Genes Link
4	AT5G10730	Plant protein of unknown function (DUF827)	7.20	Uniquely expressed under drought	KEGG Genes Link
5	AT1G69490	NAC-like, activated by AP3/PI	7.30	Uniquely expressed under drought and nonhost pathogen stress	KEGG Genes Link
6	AT5G16780	Inositol 1,3,4-trisphosphate 5/6-kinase family protein	8.80	Uniquely expressed under drought	ath00552-Inositol phosphate metabolism; ath01100-Metabolic pathways; ath04070-Phosphatidylinositol signaling system

**A. Bootstrap table for unique category of DEGS**

**B. DEGs mapped to KEGG pathway wherever possible**

**C. Platform, plant, stress treatments, GEO/SRA Ids and publication information**

Platform	Plant	Stress	GEO/SRA IDs	Publication
Gene Chip Gene 1.0ST, Cat#901915, Affymetrix, California, USA	Arabidopsis thaliana ecotype Col-0 (accession number#CS70000)	Drought - 40% FC & pathogen- Pseudomonas syringae pv. tabaci (Pta)- 3x10000000 CFU/mL, 5x10000000 CFU/mL and 2x100000000 CFU/mL	GSE79681	Choudhary et al., 2017

[View GO Enrichment](#) [View Co-functional network](#) [Download complete results](#)

**D. Manhattan Plot**   **E. Co-functional network**   **F. Download link**

**Drought and nonhost pathogen stress in Arabidopsis**

**Genes common to all stresses (D, NH and DNH)**

Search results matching your query

Show 10 entries Search:

Sl.no.	Gene ID	Gene name	Transcript Fold change (FC)	Nature of change in expression	Pathway & metadata
1	AT1G62300	WRKY family transcription factor	NH:8.7; D:1.8 ; DNH: -2.1	Tailored response	KEGG Genes Link
2	AT5G39520	Protein of unknown function (DUF1997)	DNH: 3.1; NH: 1.50; D: 8.11	Similar expression/response under all stress	KEGG Genes Link
3	AT5G38210	Protein kinase family protein	DNH: 2.40; NH: 2.30; D: 6.68	Similar expression/response under all stress	KEGG Genes Link
4	AT1G51860	Leucine-rich repeat protein kinase family protein	DNH: 6.70; NH: 2.90; D: -1.90	Tailored response	KEGG Genes Link
5	AT1G47890	Receptor like protein 7	DNH: 6.60; NH: 1.80; D: -1.50	Tailored response	KEGG Genes Link
6	AT1G58225	NA	DNH: 6.50; NH: 1.50; D: -1.50	Tailored response	KEGG Genes Link
7	AT5G26340	Major facilitator superfamily protein	DNH: 2.70; NH: 1.50; D: 6.40	Similar expression/response under all stress	KEGG Genes Link
8	AT1G76970	Target of Myb protein 1	DNH: 6.10; NH: 2.40; D: -2.30	Tailored response	KEGG Genes Link
9	AT1G66880	Protein kinase superfamily protein	DNH: 6.00; NH: 2.50; D: -1.60	Tailored response	KEGG Genes Link
10	AT4G33150	Lysine-ketoglutarate reductase/saccharopine dehydrogenase bifunctional enzyme	DNH: 5.60; NH: 3.00; D: -1.40	Tailored response	ath00310-Lysine degradation; ath01100-Metabolic pathways; ath01110-Biosynthesis of secondary metabolites

**G. Bootstrap table for common categories of DEGS**

Showing 1 to 10 of 20 entries

Previous **1** 2 Next

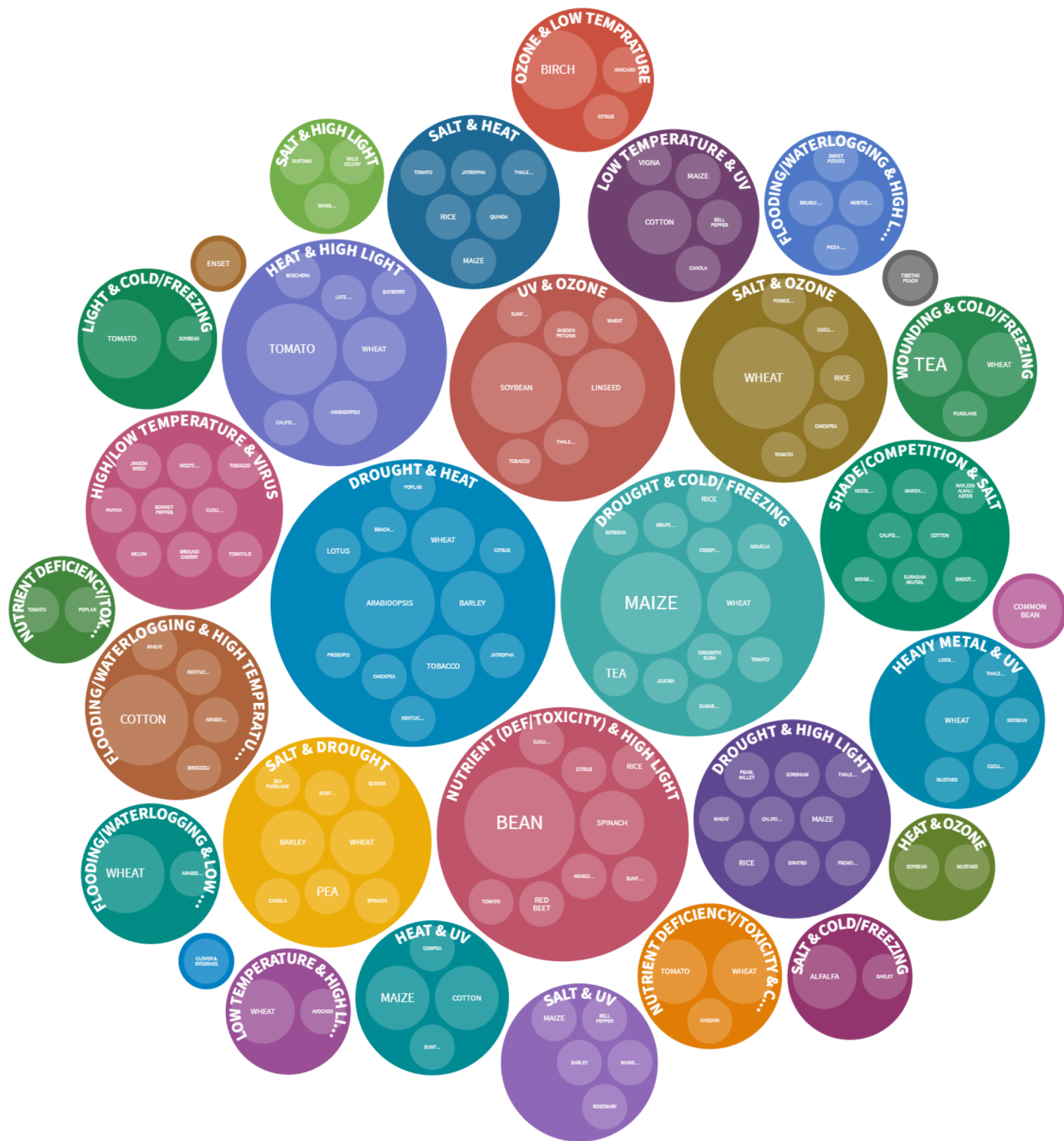
Platform	Plant	Stress	GEO/SRA IDs	Publication
Illumina-RNA Seq	Chickpea	Stress 1: Drought; Stress 2: Pathogen (Rhizoctonia bataticola); Combined: Drought and Pathogen	SRP133479	Ostthoff, A., Donà dalle Rose, P., Baldauf, J.A. et al. 2019

[View Heat Map](#) [View Venn diagram](#) [Download complete results](#)

**H. Interactive Heat Map**   **I. Venn diagram**   **J. Download link**

**Supplemental Figure 6. A typical data page entry for transcriptome in SCIPDb and its associated visualizations.** The figure shows the analyzed transcriptome data represented in the form of an interactive bootstrap table, showing a list of DEGs, gene name, log FC, and associated metadata in the form of KEGG pathways and genes. The transcriptome data page is organized and presented based on plant, stress combination, and DEGs category selection by the user. A-J details various components of the transcriptome data page integrated into SCIPDb.

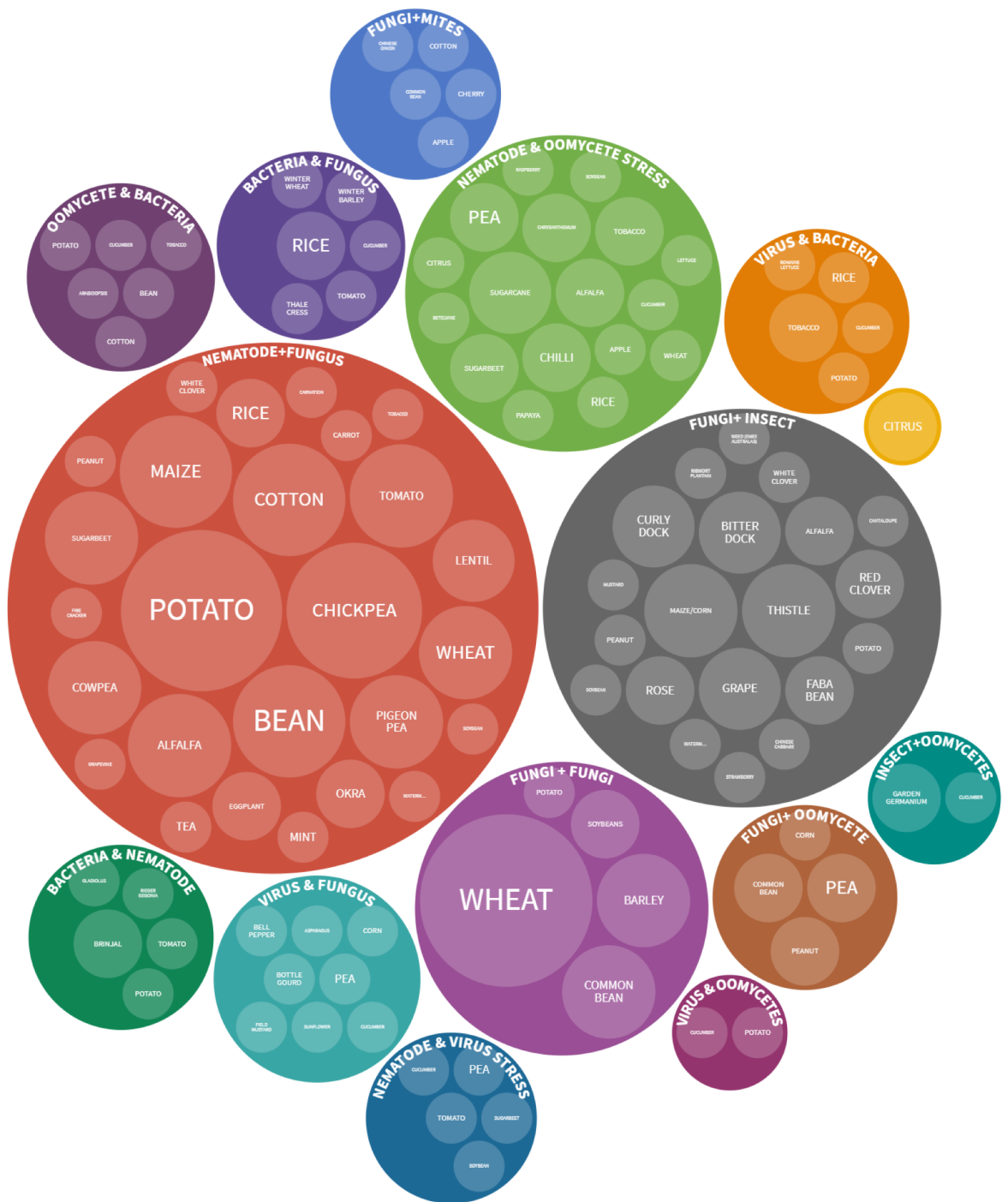




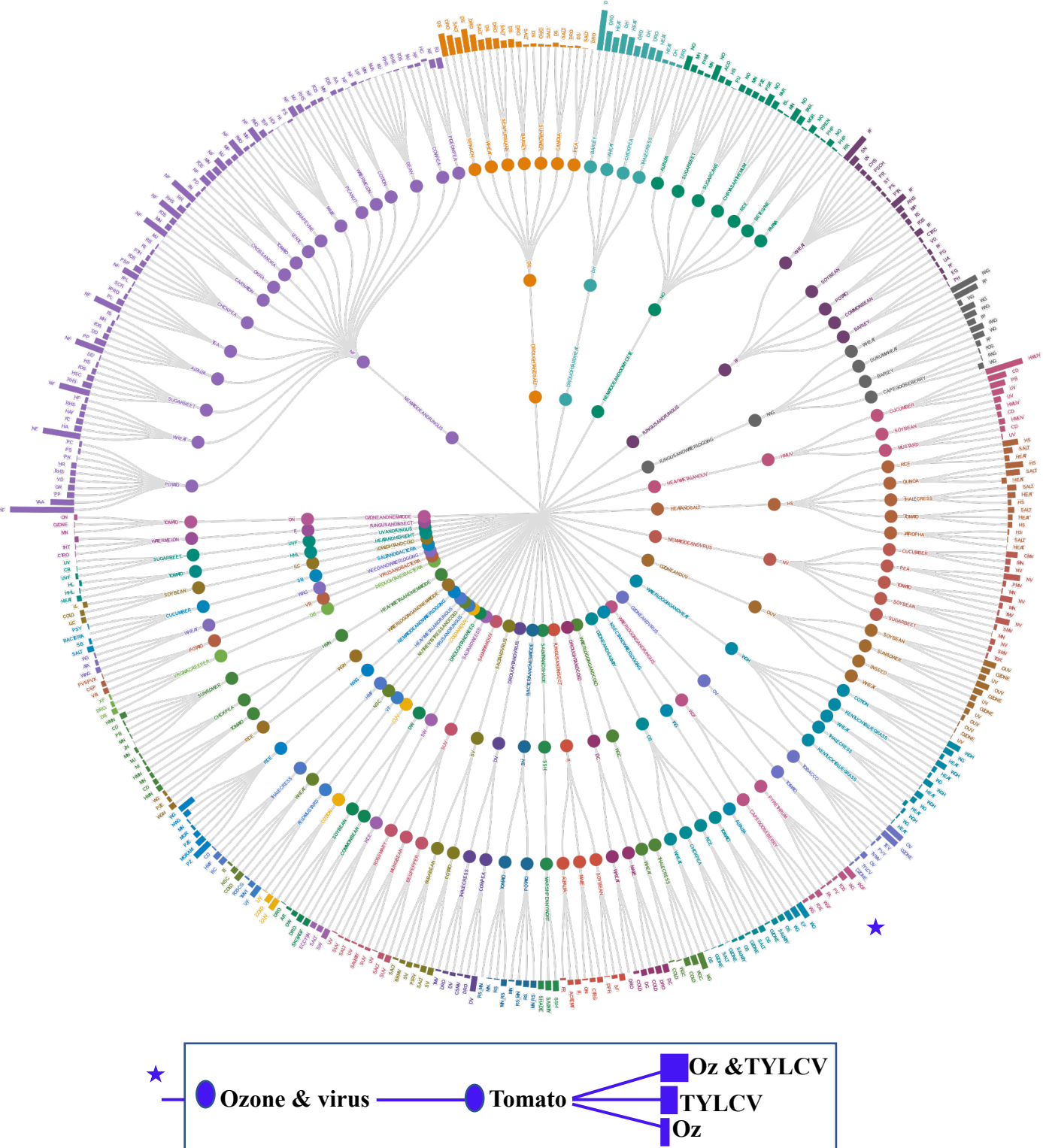
**Supplemental Figure 7. Literature analysis of combined stress articles published from 1950 to 2021 under the abiotic-abiotic stress category.** The bubble diagram shows the list of stress combinations with plant species studied under the abiotic-abiotic stress category. Each bubble represents stress combinations and the size of the bubble is directly proportional to the number of articles i.e. bigger the size more the number of studies in that stress combination or plant species.



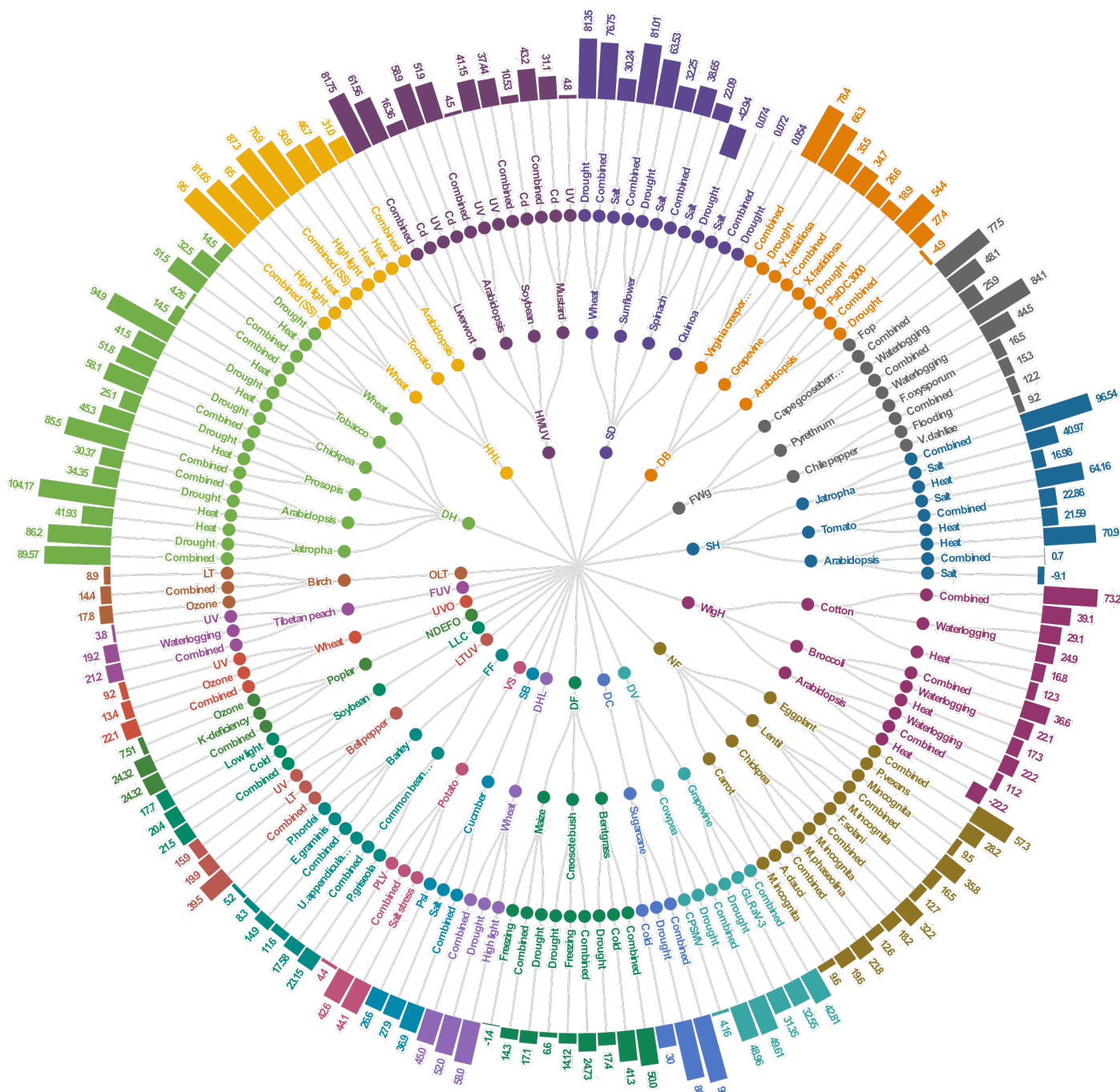




**Supplemental Figure 9. Literature analysis of combined stress articles published from 1950 to 2021 under the biotic-biotic stress category.** The bubble diagram shows the list of stress combinations with plant species studied under the biotic-biotic stress category. Each bubble represents stress combinations and the size of the bubble is directly proportional to the number of articles i.e., the bigger the size more the number of studies in that stress combination or plant species.



**Supplemental Figure 10. Literature analysis of combined stress growth and yield data on various plant species.** The radial tree shows the effect of stress combination on growth and yield attributing traits on various plant species. The tree was developed using Flourish studio (<https://flourish.studio>) and Tidyverse package in R(<https://www.tidyverse.org/packages/>). Traits included are plant height, leaf area, leaf number, shoot weight, biomass, root weight, root length, seed weight, seed number, and yield. Percent under stress over control was calculated and using those values tree was developed. An interactive view of this tree is given on the SCIPDb website.



**Supplemental Figure 11. Literature analysis of combined stress physiological data on various plant species.** The radial tree shows the effect of stress combination on physiological traits on various plant species. The tree was developed using Flourish studio (<https://flourish.studio>) and Tidyverse package in R (<https://www.tidyverse.org/packages/>). Traits included are photosynthesis, stomatal conductance, photochemical efficiency, Fv/Fm, and chlorophyll content. Percent under stress over control was calculated and using those values tree was developed. An interactive view of this tree is given on the SCIPDb website.





**Supplemental Figure 12. Literature analysis of disease incidence data under combined stress on various plant species.** The radial tree shows the percent disease incidence in individual and combined stress conditions on various plant species. The tree was developed using Flourish studio (<https://flourish.studio>) and Tidyverse package in R(<https://www.tidyverse.org/packages/>). Organisms like bacteria, viruses, nematodes, fungus, mites, oomycetes, and insects were included in this analysis. Percent change in disease incidence under combined stress over individual stress was calculated and using those values tree was developed. An interactive view of this tree is given on the SCIPDb website.