Title:

Leaf metabolic traits reveal hidden dimensions of plant form and function

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One sentence summary:

Leaf metabolic traits describe novel dimensions of plant life-history variation that expand the functional trait concept.

Abstract:

The metabolome is the biochemical basis of plant form and function, but we know little about its macroecological variation across the plant kingdom. Here, we used the plant functional trait concept to interpret leaf metabolome variation among 457 tropical and 339 temperate plant species. Distilling metabolite chemistry into five metabolic functional traits reveals that plants vary on two major axes of leaf metabolic specialization – a leaf chemical defense spectrum and an expression of leaf longevity. Axes are similar for tropical and temperate species, with many trait combinations being viable. However, metabolic traits vary orthogonally to life-history strategies described by widely used functional traits. The metabolome thus expands the functional trait concept by providing novel axes of metabolic specialization for examining plant form and function.

Main Text:

Plants produce a staggering diversity of metabolites – upwards of one million throughout the plant kingdom and many thousands within an individual (*1*) (the metabolome). The plant metabolome is well known to human society, being the source of most cosmetics (*2*), flavors (*3*), and medicines (*4*). Yet, little is known about how the metabolome varies across the plant kingdom. The metabolome is the biochemical basis of physiology, comprising primary metabolites involved in cellular function (e.g., carbohydrates, amino acids) and specialized metabolites produced to confront stress (e.g., flavonoids, terpenoids) (*1*, *5*, *6*). The metabolome thus encompasses the biochemical mechanisms through which evolutionary and ecological processes shape plant form and function (i.e., morphology and physiology (*7*)) (*8*, *9*). Plant form and function vary predictably among species because evolutionary and ecological processes generally act to maximize fitness (*10*–*14*), thus limiting the number of morphological or physiological strategies that are viable (*7*, *15*, *16*). It follows that the metabolome should also be constrained to a limited number of strategies that maximize fitness (*17*). However, although cross-species studies are now emerging (*18*–*21*), no attempt has been made to characterize how the metabolome varies systematically throughout the plant kingdom. We thus remain unable to place the vast diversity of the plant metabolome into a coherent ecological context.

The plant functional trait concept offers a powerful framework to contextualize the plant metabolome. Plant functional traits are a standardized set of morphological and physiological characteristics that provide universal metrics of plant form and function (*22*). Plant functional traits have been pivotal in identifying the life-history strategies that govern plant fitness (*7*, *15*, *16*), understanding plant impacts on population (*23*), community (*24*), and ecosystem (*25*) processes, and predicting global change effects on ecosystems (*26*). Plant functional traits thus provide a strong reference point from which to interpret variation in the plant metabolome. However, measurements of the metabolome remain absent from the functional trait concept, in part because they yield complex data describing thousands of metabolites from hundreds of biochemical pathways (*17*). Advances in chemoinformatics make it now possible to translate metabolite identities into a targeted set of chemical properties (*27*, *28*). Doing so resonates with the functional trait concept – i.e., that quantitative characteristics provide a bridge between identity and function (*22*) – and is an intuitive way to contextualize the metabolome against plant functional traits. Yet, while chemoinformatics is commonplace in natural products chemistry (*29*–*31*), it remains entirely absent from ecology.

Contextualizing the plant metabolome against existing plant functional traits raises two alternative hypotheses. If the metabolome varies colinearly with functional traits, then it offers a biochemical validation of the functional trait concept. Such validation is necessary because functional traits are emergent properties of multiple biochemical processes (*22*, *32*), making them proxies for physiology that can be poor predictors of ecological processes (*33*–*35*). Alternatively, if the metabolome varies orthogonally to functional traits, then it describes dimensions of plant life-history variation missed by existing functional traits. Such orthogonal variation would enhance the explanatory power of the functional trait concept by providing additional axes of trait specialization to examine plant form and function. Either way, integrating measurements of the plant metabolome into the plant functional trait concept will yield insight into how the metabolome varies across the plant kingdom, while also offering a high-resolution mechanistic lens with which to advance the functional trait concept itself.

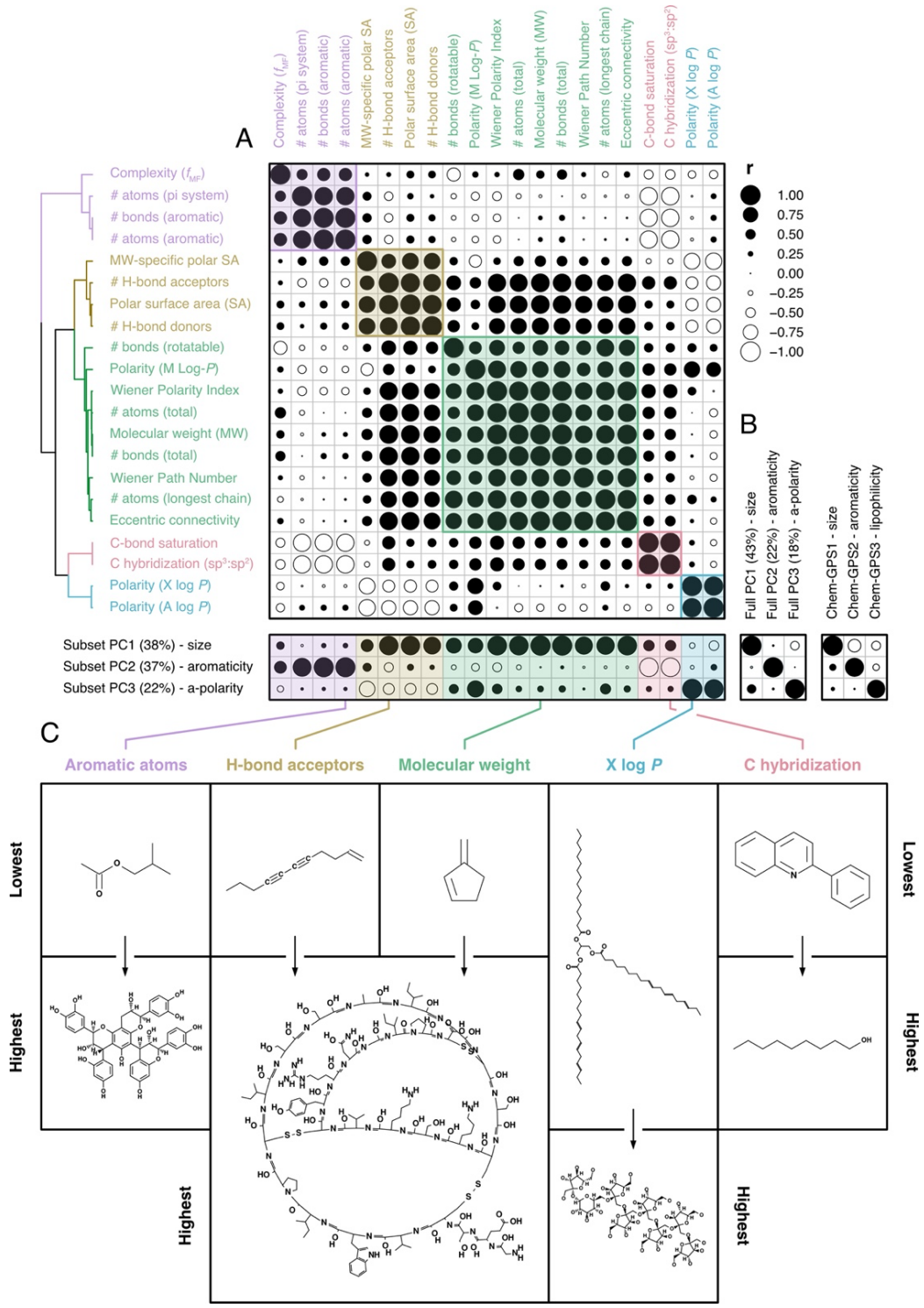

Figure 1 | Variation in leaf metabolite chemistry can be captured by five chemical properties. (A) Coefficients for Pearson correlations among 21 chemical properties (Table S1) of annotated metabolites detected in tropical and temperate datasets (N = 4292). Properties are ordered based on correlation similarity (hierarchical clustering; Ward), with colors separating distinct clusters of properties (maximal silhouette width: K = 5). The lower panel shows correlations between chemical properties and scores from the first three axes of a PCA performed on a subset of five properties, as well as (B) between subset PC scores and either scores from a PCA performed on all 21 properties (left panel) or metabolite positions on the first three axes of ChemGPS-NP (*31*) space (right panel). Circle sizes indicate coefficient strengths, while fills discriminate between positive (black) and negative (white) correlations. (C) The chemical properties selected to represent each cluster, alongside chemical graphs of metabolites with the lowest and highest values for each trait.

113 Here, we performed an assessment of the leaf metabolomes of 457 tropical and 339 temperate plant
114 species to characterize variation in the metabolome and test whether it validates, or expands upon,
115 existing plant functional traits. First, we examined the chemical properties of all identified metabolites
116 (N = 4292) to derive a minimum set of "metabolic functional traits" that capture chemical variation in
117 the leaf metabolome. We then characterized how metabolic traits vary among species to identify major
118 axes of leaf metabolic specialization in the plant kingdom. Finally, we combined metabolic traits with
119 eight widely used functional traits (plant height, seed mass, stem specific density, leaf area, specific
120 leaf area and leaf carbon, nitrogen and phosphorus concentrations; hereafter "classical traits") (*7*) to
121 determine whether axes of metabolic specialization are colinear with, or orthogonal to, plant life-history
122 strategies described by classical functional traits.
123
124 Five chemical properties capture chemical variation in the leaf metabolome
125 We expressed the leaf metabolomes of tropical (*36*) and temperate (*37*) plant species as the presence
126 or absence of annotated metabolic features (i.e., metabolites) detected through liquid chromatography
127 mass spectrometry (tropical N = 3356; temperate N = 2227). We then characterized the chemistry of
128 the leaf metabolome by examining variation in the chemical properties of all unique metabolites from
129 both datasets (N = 4292) (*31*). We focused on 21 properties describing metabolite constitution,
130 geometry, or topology that have relationships with (bio)chemical activity (Table S1). Pairwise
131 correlations among chemical properties (Fig. 1A, upper panel) reveal that properties separate into five
132 clusters, each representing a distinct facet of leaf metabolite chemistry. The largest cluster (Fig. 1A,
133 green) describes overall size and structural complexity, comprising total numbers of atoms and bonds,
134 molecular weight, a predictor of polarity based on the proportion of non-carbon atoms (M log *P*; (*38*)),
135 and related topological parameters (i.e., Wiener numbers (*39*), Eccentric Connectivity (*40*)). A second
136 cluster (Fig. 1A, purple) describes bond conjugation and reactivity, comprising numbers of aromatic
137 atoms and bonds, numbers of atoms in the largest conjugated (pi-) system, and a derived complexity
138 index indicative of promiscuous activity in drugs (f_{MF}; (*41*)). A third cluster (Fig. 1A, yellow) describes
139 polar intermolecular (non-covalent) forces, comprising total and mass-specific polar surface area and
140 numbers of hydrogen (H) bond donors or acceptors (*42*, *43*). Such forces are important for the
141 selective binding of small molecules to DNA (*44*), RNA (*45*), and proteins (*46*). A fourth cluster (Fig.
142 1A, blue) comprises two predictors of metabolite polarity based on summed properties of atoms and
143 bonds (X log *P* (*47*), A log *P* (*48*)), where lower values indicate higher polarity. A final cluster (Fig. 1A,
144 red) describes carbon bond saturation *via* the relative occurrence of sp^3 (unsaturated, three-
145 dimensional) and sp^2 (saturated, planar) hybridization (*49*). Overall, these clusters indicate that leaf
146 metabolite chemistry is highly structured and can be described by five distinct facets: size/complexity,
147 bond conjugation/reactivity, contributions to polar intermolecular forces, general polarity, and carbon
148 bond saturation.
149
150 The strong collinearity among chemical properties (Fig. 1A, upper panel) suggests that the five facets
151 of leaf chemistry can be represented by a small number of discriminant variables. Indeed, a PCA
152 performed on a subset of five chemical properties, one from each cluster (Fig. 1C), is equivalent to a
153 PCA performed on all 21 properties (Fig. 1B, left panel; PC1: $r_{4290} = 0.97$; PC2: $r_{4290} = 0.99$; PC3: r_{4290}
154 $= 0.93$; $P < 0.001$ in all cases). We selected molecular weight, H-bond acceptor count, aromatic atom
155 count, polarity (X log *P*), and carbon hybridization (sp^3:sp^2) as five properties that are intuitive for non-
156 specialists to interpret (Fig. 1C; Table S1). However, most combinations of properties covering all
157 facets of leaf chemistry also yield equivalent PCAs (Fig. S5). Pairwise correlations between all
158 properties and subset PC scores further confirm that selected properties capture observed leaf

159 chemical variation, in that correlations are consistent within each cluster (Fig. 1A, lower panel).
160 Selected properties also describe biologically relevant chemical space according to an existing
161 framework that classifies natural products based on size, then aromaticity, then lipophilicity (Fig. 1B,
162 right panel; PC1: $r_{4290} = 0.99$; PC2: $r_{4290} = 0.87$; $r_{4290} = 0.81$; $P < 0.001$ in all cases) (*31*). The first axis
163 of the subset PCA (38% variance) separates heavy metabolites with many H-bond acceptors from
164 light metabolites with fewer H-bond acceptors. Alignment between metabolite size and numbers of H-
165 bond acceptors is expected because larger molecules usually engage in stronger intermolecular
166 interactions (*50*). The second axis (37% variance) separates reactive metabolites with more aromatic
167 carbon bonds from unreactive metabolites with more saturated carbon bonds. This axis is also intuitive
168 because conjugated bond systems are unsaturated, reactive, and planar, whereas saturated bonds,
169 such as those abundant in fatty acids, are unreactive and three-dimensional (*51*). The third axis (18%
170 variance) separates nonpolar metabolites from polar metabolites (*29*). Our findings thus show that leaf
171 chemical variation can be represented by five chemical properties, one from each facet of leaf
172 chemistry.
173
174 <u>Five chemical properties provide more information than metabolite family</u>
175 The five selected chemical properties not only represent leaf metabolite chemistry (Fig. 1), but also
176 reflect known differences among metabolite families. Using the subset PCA to interpret variation
177 among metabolite families (Fig. 2), we observe that peptides are large, display average bond
178 saturation, and are moderately polar; carbohydrates are of average size, display high bond saturation,
179 and are highly polar; and fatty acids are smaller, display high bond saturation, and are of average
180 polarity. Lignans, alkaloids, coumarins and flavonoids, families of specialized metabolites, display low
181 bond saturation due to the presence of many aromatic bonds, with alkaloids and coumarins also being
182 relatively small. Terpenoids, a family of abundant specialized metabolites (N = 2306), vary in size,
183 bond saturation, and polarity, echoing their diversity across the plant kingdom (*52*). Although chemical
184 properties generally differentiate among metabolite families, all families possess variable and
185 overlapping chemistries (Fig. 2, marginal boxplots). We thus suggest that chemical properties,
186 quantitative metrics of the chemistry that underpins metabolite composition and activity, provide more
187 precise information about metabolite function than metabolite family identity. Indeed, drug discovery
188 and medicinal chemistry rely on many of the same chemical properties to screen for bioactive
189 molecules (*29–31*). Such a perspective resonates with the functional trait concept by reaching beyond
190 taxonomy to describe function (*22*) and provides a strong foundation for a novel set of metabolic
191 functional traits.
192
193

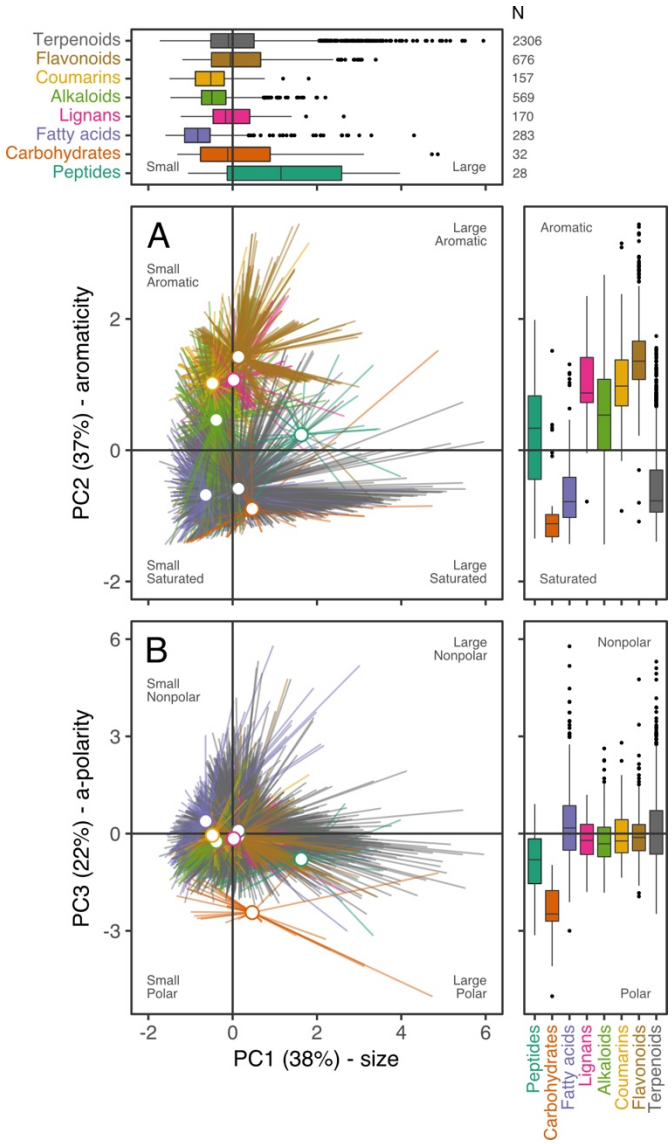

Figure 2 | Five chemical properties describe variation among and within metabolite families. Biplots of PC1 scores and (A) PC2 scores or (B) PC3 scores from a PCA describing variation in selected chemical properties (C hybridization, H-bond acceptors, molecular weight, polarity, aromatic atoms) among all annotated leaf metabolites (N = 4221) detected in 862 plant species. The PCA is functionally equivalent to a PCA containing all 21 chemical properties (see Main Text), with axes separating leaf metabolites based on size (PC1), aromaticity (PC2), and a-polarity (PC3; see Fig. 1A, lower panel). Colors separate metabolite families as defined by marginal boxplot fills/labels (center: median; box: 25% to 75% quantiles; whiskers: 1.5 × IQR; points: outliers beyond whiskers).

<u>Five metabolic functional traits describe two axes of leaf metabolic specialisation</u>

We converted selected properties into plant-level metabolic functional traits to examine how the leaf metabolome varies among tropical and temperate plant species. We first compared the volume and "lumpiness" (i.e., aggregation around values) of multidimensional space occupied by metabolic traits to four null models to test whether species converge on a restricted set of interrelated trait combinations (*7*). Observed hypervolumes of metabolic traits are 98.1% to 99.8% smaller and 71.0% to 94.7% lumpier than those of three null models assuming no trait covariance (Table S2; Table S3; always $P < 0.001$ in all cases). However, observed hypervolumes are larger (tropical: $P = 0.002$;

temperate: $P = 0.047$) than that of the null model assuming trait covariance and selection against extreme values, while also being similarly lumpy (tropical: $P = 0.662$; temperate: $P = 0.858$). By comparison, observed hypervolumes of eight classical traits are smaller than null models assuming no trait covariance (Table S2; $P < 0.001$ in all cases), either the same size as (tropical species; $P = 0.154$) or smaller than (temperate species; $P = 0.018$) that of the null model assuming selection against extreme values, and lumpier than all null models (Table S3; $P < 0.001$ in all cases). Collectively, these findings yield three insights. First, metabolic functional traits are interrelated, so plants are constrained to a limited number of viable metabolic trait combinations. Second, while extreme metabolic trait values may be selected against in temperate species, this is not so for tropical species. Expressing extreme leaf metabolome chemistry is thus a viable life-history strategy in tropical environments, potentially due to more intense biotic interactions selecting for a diversity of defensive leaf metabolites and thus divergence of chemical strategies (*53*). Third, metabolic traits are less aggregated around non-extreme values than classical traits. As such, although plants converge towards one of several viable classical trait strategies (e.g., woody, non-woody; (*7*)), they can possess a wider array of leaf metabolome strategies.

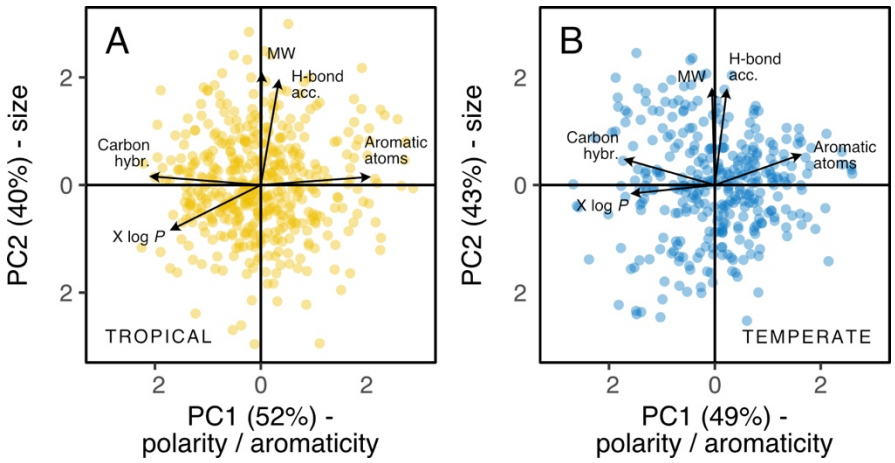

Figure 3 | Metabolic traits describe two axes of leaf metabolic specialization among plant species. Biplots of PC1 and PC2 scores for PCAs describing variation in five metabolic functional traits (arrows) between (A) tropical (yellow; N = 457) and (B) temperate (blue; N = 339) plant species. Axes separate species based on the mean aromaticity *versus* polarity (inverse X log *P*) and carbon bond saturation (PC1) and mean size/complexity (PC2) of all annotated leaf metabolites present (Methods).

We performed PCAs on metabolic traits to characterize major axes of leaf metabolic specialization among species. Metabolic trait variation is consistent among tropical and temperate species, with 92% variation being explained by the first two PCs (Fig. 3). The first axis (tropical: 52%; temperate 49%) separates species that produce more unsaturated, aromatic, nonpolar leaf metabolites from those that produce more saturated, polar, leaf metabolites. This axis likely describes a spectrum of leaf chemical defense strategies (*12*). Unsaturated aromatic metabolites, such as alkaloids, coumarins, and flavonoids (Fig. 2), are reactive and serve as toxins or antioxidants in response to stress. For instance, conjugated bond structures can interfere with protein function by binding covalently to sidechains (*54*), generate or quench oxidative stress (*55*), or absorb damaging wavelengths of light (*56*). By contrast, saturated non-aromatic metabolites can play different roles in leaf defense, both directly as toxins (*57*)

249 and indirectly as signaling molecules (*58*). An alternative explanation is that the first axis reflects an
250 investment (or not) into defense metabolites (*12*), which could arise due to the high cost of
251 synthesizing aromatic metabolites (*13*). However, all plants must defend their leaves against stress,
252 and we find that plants can maximize fitness at either end of this axis (Fig. 3). It is thus more plausible
253 that the first axis represents a leaf chemical defense spectrum.
254
255 The second PCA axis (tropical: 40%; temperate: 43%) discriminates species that produce larger
256 metabolites with many H-bond acceptors from those that produce smaller metabolites with fewer H-
257 bond acceptors. This axis likely relates to leaf longevity, since large metabolites, such as lignans,
258 peptides, and waxes, form the basis of long-lived physical (*59*, *60*) and storage (*61*) structures. Many
259 of these structures also depend on strong intermolecular forces to form stable macromolecules or
260 complexes (*62*, *63*), which are enhanced by H-bond donors and acceptors (*43*). As for the first axis,
261 plants can maximize fitness at either end of the second axis, with species at the positive end of the
262 axis investing in metabolites indicative of a longer leaf lifespan. As such, the second axis is probably a
263 manifestation of the fast-slow continuum (*64*) at the leaf level. Alternatively, the second axis may
264 reflect an investment (or not) into structurally complex metabolites for physical defense, such as
265 lignans or waxes (*59*, *60*). However, such metabolites act by creating rigid structures that lengthen leaf
266 lifespan anyway (*65*), so physical protection is one component of leaf longevity. Taken together,
267 metabolic trait PCAs reveal two major axes of leaf metabolic specialization. These axes relate to
268 metabolite bond saturation and polarity (i.e., a leaf chemical defense spectrum) and metabolite size
269 and propensity for intermolecular interactions (i.e., leaf longevity), with many combinations yielding
270 successful life-history strategies.
271
272 <u>Axes of leaf metabolic specialisation reveal hidden dimensions of plant form and function</u>
273 The apparent consistency of metabolic trait variation with classical life-history theory (*7*, *12*, *13*, *15*, *16*,
274 *64*, *65*) raises the possibility that metabolic traits describe aspects of plant form and function already
275 captured by classical traits. We thus performed a PCA on metabolic traits plus the same widely used
276 functional traits used above to test whether axes of leaf metabolic specialization are colinear with, or
277 orthogonal to, trait-based life-history strategies. Considered alone, classical trait variation supports life-
278 history theory (*7*), with the first two PCs (tropical: 49%; temperate: 51%) describing the leaf economics
279 spectrum (SLA, leaf nitrogen, leaf phosphorus; (*16*)) and variation indicative of plant longevity (plant
280 height, seed mass; (*64*)) and hardiness (stem density, leaf carbon; (*15*)) (Fig. S1). However, when
281 combining classical and metabolic traits in the same PCA, the first four PCs (tropical: 66%; temperate:
282 67%) are equivalent to axes described by individual PCAs (Fig. 4A, lower marginal matrices). The first
283 and third axes describe the first two axes of leaf metabolic specialization (Fig. 3), whereas the second
284 and fourth axes describe the first two axes of classical trait specialization (Fig. S1). Pairwise
285 correlations among all traits further show that metabolic and classical traits do not covary (Fig. 4A,B),
286 but separate into six clusters describing unique aspects of either metabolic or classical trait variation.
287 As such, major axes of leaf metabolic specialization vary orthogonally to major axes of classical trait
288 variation (Fig. S4) and are at least equally relevant for describing variation in plant form and function
289 among tropical and temperate plant species.
290
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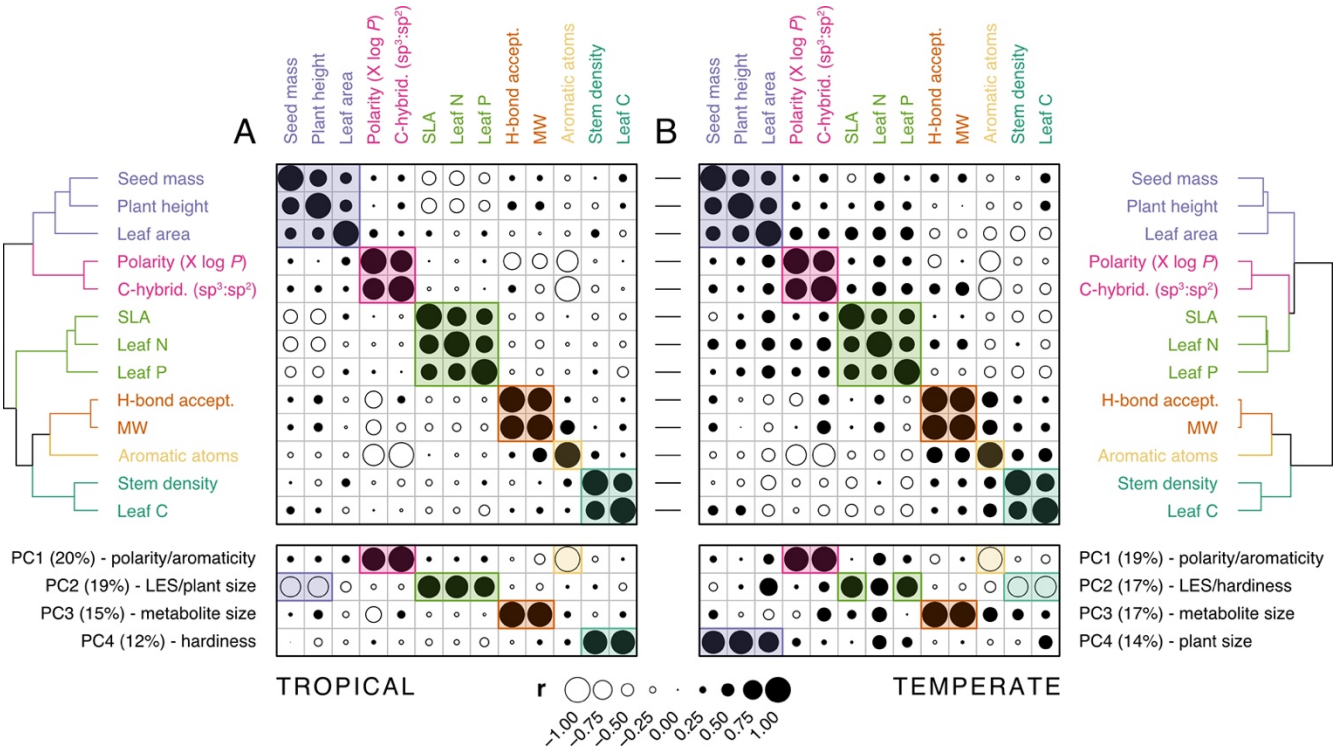

Figure 4 | Metabolic and classical traits describe unique dimensions of plant form and function. Correlation coefficients for pairwise Pearson correlations among metabolic (Fig. 3) and classical functional traits (Fig. S1) in (A) tropical (N = 457) and (B) temperate (N = 339) species. Traits are ordered based on correlation similarity (hierarchical clustering; Ward), with colors separating distinct clusters (maximal silhouette width: K = 6) and horizontal lines between matrices showing correspondence between tropical and temperate traits. Lower panel shows correlations between traits and scores from the first four axes of a PCA of the same traits (tropical: 66%; temperate: 67%; LES = leaf economics spectrum). Circle sizes indicate coefficient strengths, while fills discriminate between positive (black) and negative (white) correlations.

Leaf metabolism underpins energy production *via* photosynthesis (*66*), but in doing so yields tissue that is sensitive to light (*67*) and temperature (*68*) and is of high nutritional value to herbivores (*65*). Plants are thus under selective pressure to maximize photosynthetic rates while also protecting leaf tissue against damage. While this trade-off is consistent with life-history trade-offs derived from classical traits (*7*, *15*, *16*), it does not necessarily follow that individuals apply the same strategy in every organ to maintain fitness. Indeed, we observe that species with “productive” trait values (e.g., high SLA, high leaf nitrogen) can produce leaves containing many complex aromatic metabolites, species possessing “hardy” trait values (e.g., high stem density, high leaf carbon) can produce leaves containing many simple polar metabolites, and species possessing trait values typical of a fast pace of life (e.g., low stature, small seeds) can produce leaves with many large stable or structural metabolites. Our findings thus question classical trait (*16*) and plant defense (*12*) theory that predicts relationships between the leaf chemical phenotype, plant productivity, and pace of life. In short, metabolic functional traits describe unique dimensions of plant life-history variation that are complementary to, and independent from, those captured by classical functional traits.

Concluding remarks

In summary, we show that leaf metabolite chemistry is highly structured and can be described by five chemical properties. Using chemical properties as metabolic functional traits reveals that plants vary

321 on two axes of leaf metabolic specialization – a leaf chemical defense spectrum (i.e., bond saturation,
322 polarity) and leaf longevity (i.e., size, propensity for intermolecular interactions). Axes of metabolic
323 specialization are similar in tropical and temperate species, with many combinations of trait values
324 yielding successful life-history strategies. Axes are also consistent with expectations from life-history
325 theory that plants invest strategically in tissue defense (*12*, *13*, *16*) and between a fast *versus* slow
326 pace of life (*7*, *64*). Nevertheless, we find that metabolic trait variation is orthogonal to, not colinear
327 with, classical trait variation. Metabolic functional traits thus reveal dimensions of plant life-history
328 variation missed by existing functional traits. It is important to note that metabolomics data were
329 acquired differently for tropical and temperate species and were matched to open functional trait
330 databases. Nevertheless, we find consistent variation in the leaf metabolomes of 457 tropical and 339
331 temperate species that possess distinct geographic distributions and evolutionary histories (Fig.
332 S1A,B), as well as that encompass most documented functional trait variation (Fig. S1G, red ribbons).
333 We thus propose that distilling the leaf metabolome into metabolic functional traits captures
334 macroecological patterns of metabolic variation widely across the plant kingdom, enhances the
335 explanatory power of the functional trait concept, and offers a new set of tools for the discovery of
336 species or genotypes with trait combinations adapted to societal needs.

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Supplementary Materials
Materials and Methods
Figs. S1 to S5
Tables S1 to S3