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KNApSAcK Metabolite Activity Database for Retrieving the Relationships Between Metabolites and Biological Activities

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Databases (DBs) are required by various omics fields because the volume of molecular biology data is increasing rapidly. In this study, we provide instructions for users and describe the current status of our metabolite activity DB. To facilitate a comprehensive understanding of the interactions between the metabolites of organisms and the chemical-level contribution of metabolites to human health, we constructed a metabolite activity DB known as the KNApSAcK Metabolite Activity DB. It comprises 9,584 triplet relationships (metabolite–biological activity–target species), including 2,356 metabolites, 140 activity categories, 2,963 specific descriptions of biological activities and 778 target species. Approximately 46% of the activities described in the DB are related to chemical ecology, most of which are attributed to antimicrobial agents and plant growth regulators. The majority of the metabolites with antimicrobial activities are flavonoids and phenylpropanoids. The metabolites with plant growth regulatory effects include plant hormones. Over half of the DB contents are related to human health care and medicine. The five largest groups are toxins, anticancer agents, nervous system agents, cardiovascular agents and non-therapeutic agents, such as flavors and fragrances. The KNApSAcK Metabolite Activity DB is integrated within the KNApSAcK Family DBs to facilitate further systematized research in various omics fields, especially metabolomics, nutrigenomics and foodomics. The KNApSAcK Metabolite Activity DB could also be utilized for developing novel drugs and materials, as well as for identifying viable drug resources and other useful compounds.

Keywords: Database • KNApSAcK family • Metabolite–activity relationship.

Abbreviation: DB, database.

Introduction

Plant metabolomics has been highlighted in studies conducted to detect complete sets of metabolites in tissues and cells (Bino et al. 2004, Tohge and Fernie 2009, Macel et al. 2010, Saito and Matsuda 2010), as well as in more complex fields, such as understanding species–species relationships based on secondary metabolites. This has led to further studies of the biological interactions between organisms in ecosystems (Ikeda et al. 2013) because secondary metabolites are used during plant interactions in the environment, such as pest and pathogen defense compounds, and in UV-B sunscreens (Dixon 2001, Halkier and Gershenzon 2006, Bednarek and Osboum 2009). Metabolome studies have also been extended from model species such as crops and medicinal plants to health care and medicinal systems based on the interactions between organisms and humans (Ikeda et al. 2013, Kell and Goodacre 2013). Secondary metabolites continue to play highly significant roles in the drug discovery process because the available biodiversity is an almost unlimited source of novel chemicals that are potential drug leads. The secondary metabolites synthesized by plants, fungi and microorganisms are diverse, e.g. there are at least 30,000 terpenoids (Connolly and Hill 1991), 9,000 flavonoids, 1,600 isoflavonoids and 12,000 alkaloids (Ziegler and Facchini 2008). These metabolites have been deposited in the species–metabolite relational database (DB) known as the KNApSAcK Core DB, which contains 109,976 species–metabolite relationships that encompass 22,399 species and 50,897 metabolites (Afendi et al. 2012). These secondary metabolites have a wide variety of activities such as UV protection, flower coloration, interspecies interaction and plant defense, which are involved in the interactions between plants and their environmental partners (Martens and Mithofer 2005, Lapcik 2007). Furthermore, a wide variety of secondary

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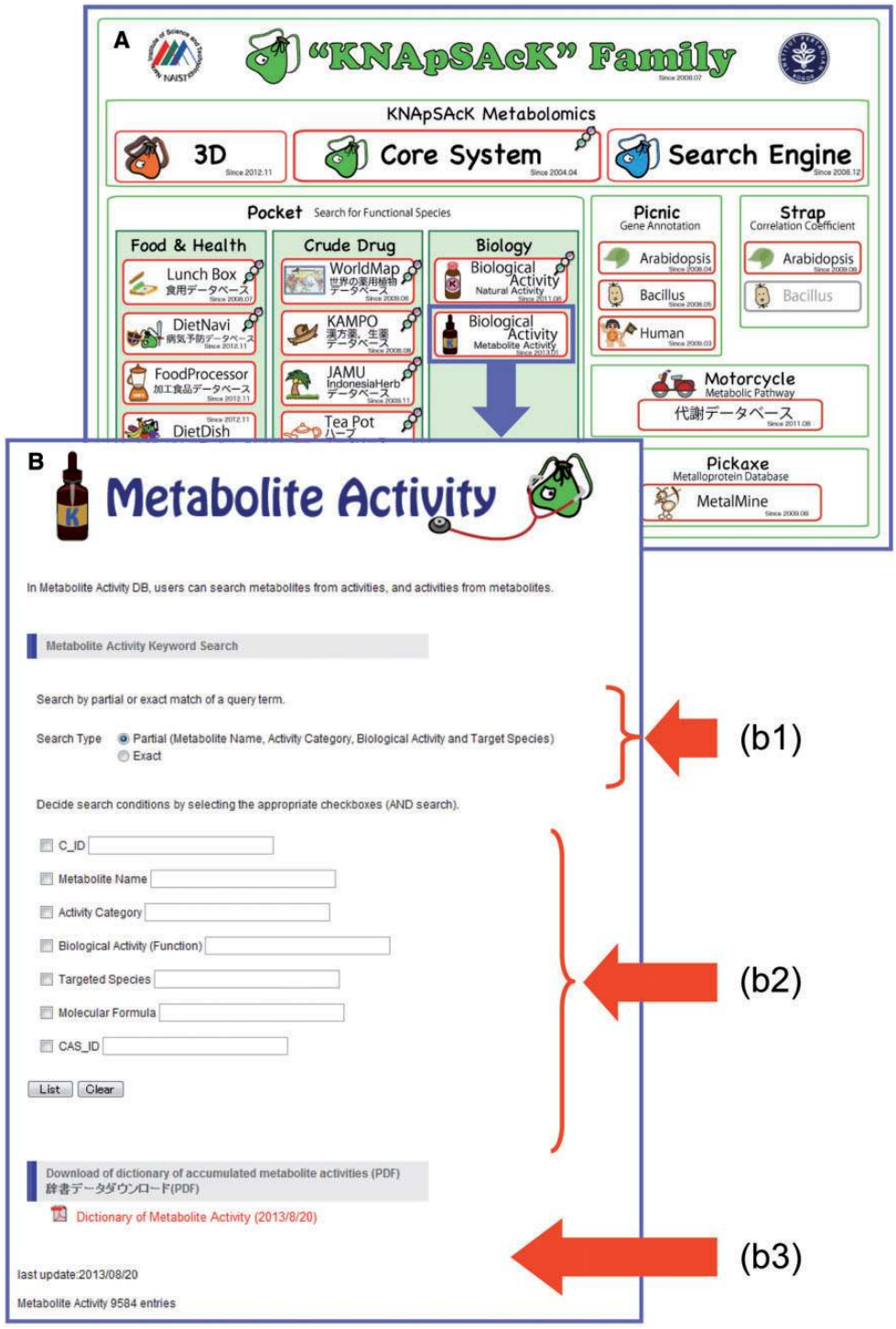

Fig. 1 Accessing the KNApSAcK Metabolite Activity DB. (A) The main window of the KNApSAcK Family DB. Users can access the Metabolite Activity DB by clicking the Biological Activity–Metabolite Activity button. (B) The main window of the Metabolite Activity DB. (b1) Section used to select the search type. (b2) Section used to select the search conditions and to input keywords. (b3) Section used to access the 'Download of the dictionary of accumulated metabolite activities (PDF)'.

metabolites are exploited in human health care (Diplock 1999, Krzyzanowska et al. 2010, Wahle et al. 2010).

To facilitate a comprehensive understanding of the interactions between the metabolites of organisms and their chemical-level contribution to human health, we constructed a metabolite–activity DB called the KNApSAcK Metabolite Activity DB, which comprises triplets, i.e. metabolites, target species and activities. In the present study, we introduce the KNApSAcK

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Table 1 Statistics for the 140 activity categories

General description	Activity category	No. of records
Plant growth regulator (946)	Enhance germination (E01)	26
	Enhance stem growth (E02)	138
	Enhance root growth (E03)	46
	Enhance leaf growth (E04)	48
	Enhance flowering (E05)	42
	Enhance fruiting (E06)	44
	Enhance plant growth (E07)	124
	Inhibit seed germination (E08)	27
	Inhibit stem growth (E09)	51
	Inhibit root growth (E10)	32
	Inhibit leaf growth (E11)	29
	Inhibit flowering (E12)	12
	Inhibit fruiting (E13)	3
	Inhibit plant growth (E14)	91
	Allelopathic (E15)	70
	Phytoalexin (E16)	163
Attractant/ repellent (236)	Feeding attractant (E17)	33
	Feeding deterrent (E18)	81
	Pollinator attractant (E19)	44
	Oviposition attractant (E20)	26
	Oviposition deterrent (E21)	3
	Sex attractant (E22)	22
	Attractant (E23)	13
	Repellent (E24)	14
Selective toxicity (163)	Phytotoxic (E25)	45
	Herbicidal (E26)	6
	Insecticidal (E27)	78
	Acaricidal (E28)	2
	Molluscicidal (E29)	12
	Piscicidal (E30)	15
	Nematocidal (E31)	5
Antimicrobial agent (1238)	Antibacterial (E32)	692
	Antituberculosis (E33)	42
	Antileprotic (E34)	7
	Antifungal (E35)	407
	Inhibit spore germination (E36)	15
	Antimicrobial (E37)	75
Antiviral agent (106)	Antiviral (E38)	83
	Antihepatitic (E39)	4
	Anti-HIV (E40)	7
	Anti-HSV (E41)	12
Antiparasitic agent (217)	Anthelmintic (E42)	46
	Antiprotozoal (E43)	7
	Antiamebic (E44)	12
	Antimalarial (E45)	64
	Antileishmanial (E46)	32
	Antitrypanosomal (E47)	54
	Pediculicide (E48)	2
Nervous system agent (443)	Antipyretic (M01)	31
	Analgesic (M02)	66
	Antiarthritic (M03)	4
	Anesthetics (M04)	21
	Sedative (M05)	75
	Antispasmodic (M06)	60
	Anticonvulsant (M07)	12
	Antidementic (M08)	15
	Antidepressant (M09)	10
	CNS stimulant (M10)	30
	Diaphoretic (M11)	6
	Emetic (M12)	5
	Antiemetic (M13)	7
	Antigout (M14)	5
	Antimigraine (M15)	4
	Antimyasthenic (M16)	8
	Antiparkinson (M17)	26
	Antipsychotic (M18)	25
	Muscle relaxant (M19)	33
Cardiovascular agent (398)	Antidiabetic (M20)	58
	Hemostatic (M21)	8
	Antithrombotic (M22)	2
	Cardiotonic (M23)	38
	Antiarrhythmic (M24)	18
	Diuretic (M25)	16
	Antihypertensive (M26)	165
	Antihyperlipidemic (M27)	29
	Antianemic (M28)	4
	Other cardiovascular agent (M29)	60
Respiratory tract agent (108)	Antitussive (M30)	29
	Expectorant (M31)	13
	Antiasthmatic (M32)	57
	Other respiratory tract agent (M33)	9
Digestive organ agent (168)	Antidiarrheic (M34)	12
	Carminative (M35)	5
	Stomachic (M36)	3
	Laxative (M37)	38
	Choleretic (M38)	17
	Antihepatotoxic (M39)	49
	Other digestive organ agent (M40)	44
Genitourinary agent (54)	Oxytocic (M41)	21
	Antifertility (M42)	22
	Abortifacient (M43)	5
	Other genitourinary agent (M44)	6
Anticancer agent (495)	Antioxidant (M45)	94
	Anticancer (M46)	267
	Antitumor (M47)	83
	Antineoplastic (M48)	38
	Antimutagenic (M49)	13
Anti-inflammatory agent (257)	Anti-inflammatory (M50)	149
	Antiallergic (M51)	57
	UV shield (M52)	7
	Antidermatitic (M53)	19
	Antiedemic (M54)	25
Immunological agent (31)	Immunosuppressant (M55)	11
	Immunostimulant (M56)	11
	Immunomodulator (M57)	9
Nutrient (76)	Nucleic acid (M58)	4
	Essential amino acid (M59)	15
	Nonessential amino acid (M60)	8
	Vitamin (M61)	14
	Nutrient (M62)	25
	Tonic (M63)	10

(continued)

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Table 1 Continued

General description	Activity category	No. of records
Nontherapeutic agent (332)	Solvent (M64)	4
	Flavor (M65)	127
	Odor (M66)	67
	Pigment (M67)	98
	Emulsifying agent (M68)	2
	Antiseptic (M69)	34
Other health agent (195)	Antiulcerogenic (M70)	25
	Depilatory (M71)	6
	Antidote (M72)	17
	Hormonal (M73)	13
	Dental (M74)	5
	Other health agent (M75)	129
Narcotic (14) Toxic (640)	Narcotic (M76)	14
	Phototoxic (M77)	33
	Neurotoxic (M78)	47
	Pneumotoxic (M79)	27
	Hepatotoxic (M80)	41
	Cytotoxic (M81)	57
	Toxic (M82)	435
Tumorigenic (79)	Tumorigenic (M83)	24
	Mutagenic (M84)	32
	Genotoxic (M85)	4
	Teratogenic (M86)	19
Other disease-causing agent (159)	Psychotomimetic (M87)	23
	Hemolytic (M88)	52
	Allergenic (M89)	23
	Irritant (M90)	37
	Dermatitic (M91)	21
	Edematous (M92)	3

The 140 categories are tentatively classified into 21 general descriptions, and 6,355 records in the Metabolite Activity DB are assigned to 140 activity categories.
The numbers in parentheses are the total number of activities in each general description.

Metabolite Activity DB and describe the current status of the KNApSAcK Family DBs. The basis of our Metabolite Activity DB was a search of scientific publications up to September 2012 using Pubmed (http://www.ncbi.nlm.nih.gov/pubmed) and Google Scholar (http://scholar.google.co.jp/). This literature search using the keywords 'metabolite' and 'activity/function' provided 9,584 records of triplet relations (metabolite–biological activity–target species), including 2,356 metabolites, 140 activity categories, 2,963 specific descriptions of biological activities and 778 target species. The DB allows users to search for both metabolites using descriptions of biological activities and activities using the KNApSAcK compound ID, metabolite name, target species, molecular formula and CAS ID. Furthermore, the biological species that synthesize a target metabolite can be identified by connecting to the species–metabolite relational database KNApSAcK Core (Afendi et al. 2012).

Search options in the KNApSAcK Metabolite Activity DB

Fig. 1 shows the interfaces of the KNApSAcK Family DBs. The main window of the KNApSAcK Metabolite Activity DB (http://kanaya.naist.jp/MetaboliteActivity/top.jsp) can be accessed by clicking the Metabolite Activity button on the main page of the KNApSAcK Family DB (**Fig. 1A**; http://kanaya.naist.jp/KNApSAcK_Family/), which accesses the search type (b1 in **Fig. 1B**) and search conditions (b2). To specify the search type, users can select partial or exact string searches by clicking the corresponding radio button, i.e. Partial or Exact (b1), and other check boxes can be selected to specify different search conditions (b2). The descriptions of biological activity concerning medicine and human health care are classified into 92 activity categories (M01–M92 in **Table 1**) based on the KEGG DRUG DB (http:// www.genome.jp/kegg/drug/). The other descriptions, i.e. concerning chemical ecology, are classified into 48 categories (E01–E48 in **Table 1**) based on their biological activity. The total number of activity categories is 140. The activity categories and individual descriptions of the activities included in the DB are listed in the 'Dictionary of Metabolite Activity' at the bottom of the window [b3; 'Download of the dictionary of accumulated metabolite activities (PDF)'].

The search conditions comprise seven attributes, i.e. C_ID (which corresponds to the KNApSAcK compound ID), metabolite name, activity category in **Table 1**, individual biological activity, target species, molecular formula and CAS ID (b2 in **Fig. 1B**). If users input 'Enhance stem growth' in the text box for the activity category and select the corresponding check box, and then click the List button, the results retrieved are those shown in **Fig. 2A**. The attributes in the list are C_ID (a1 in **Fig. 2A**), metabolite name (a2 in **Fig. 2A**), activity category (a3 in **Fig. 2A**), biological activity (a4 in **Fig. 2A**), target species (a5 in **Fig. 2A**) and references (i.e. the source of the metabolite information, a6 in **Fig. 2A**), from left to right. For example, in the first five lines, gibberellin A1 has 'Enhance stem growth' in the activity category and this metabolite is available from four species, *Pisum sativum* cv. Progress No. 9, *Lactuca sativa*, *Oryza sativa* cv. Tanginbozu and *Zea mays* d1 and d3 (**Fig. 2A**). Information related to any of the metabolites shown in **Fig. 2A** can be obtained by clicking the C_ID. **Fig. 2B** shows the search results obtained by clicking the C_ID, C00000003 (**Fig. 2B**), which were retrieved from the KNApSAcK Core (Afendi et al. 2012).

Statistical Analysis of the Biological Activity DB

Fig. 3 represents as a pie chart the relative frequencies of the 21 metabolite activity general descriptions listed in **Table 1**. The metabolite activities are tentatively classified into two types of activities, i.e. chemical ecology, which involves metabolites related to interactions between species and the natural regulation of organisms, and human health care and medicine, which concerns metabolites utilized by human health care applications. In the current version of the Metabolite Activity DB, approximately 46% of the activities correspond to chemical ecology, mainly antimicrobial agents (19.5%) and plant

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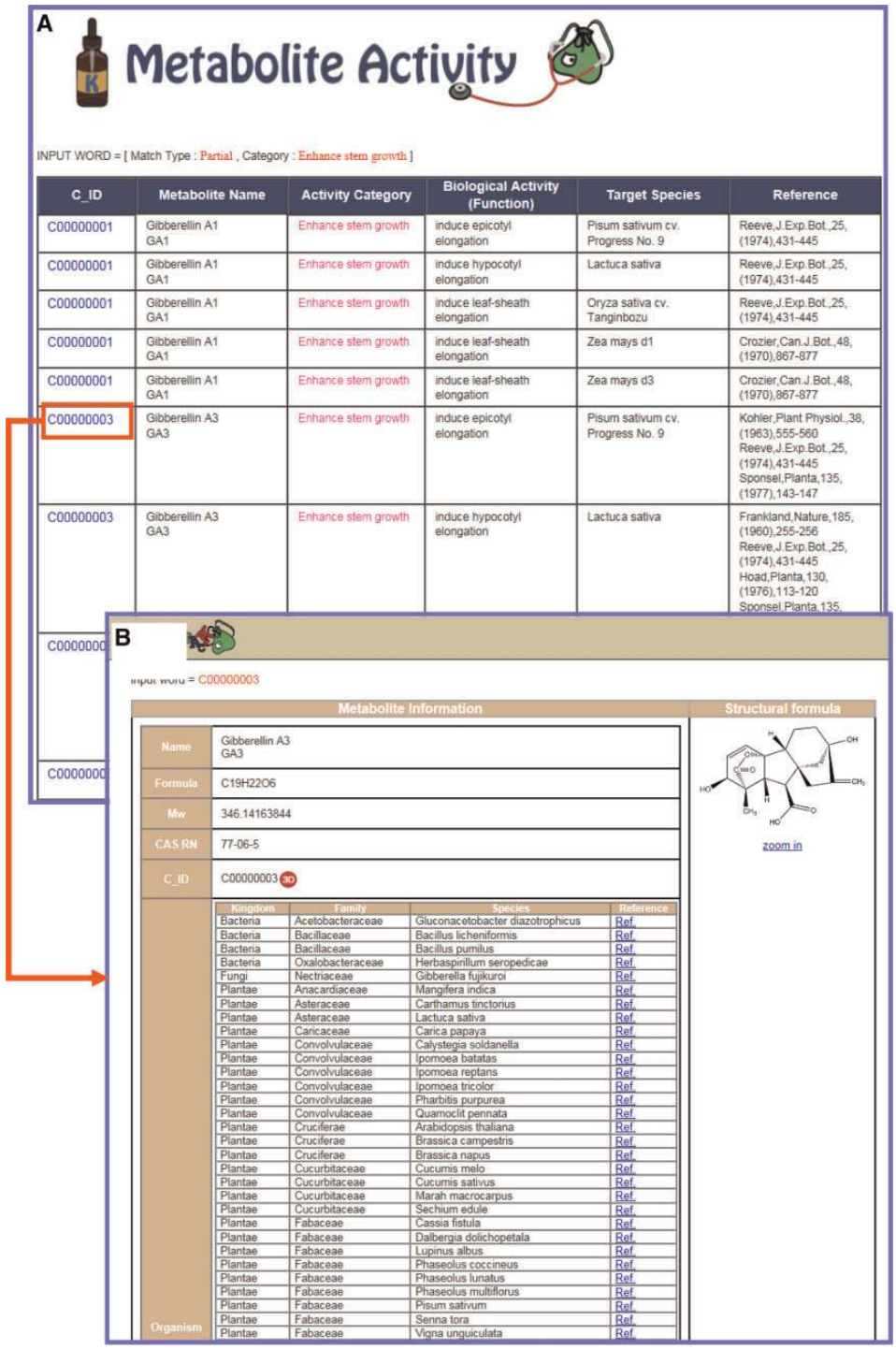

Fig. 2 Metabolite Activity DB search results. (A) An example of a search results window. There are six items in the list: C_ID (a1), metabolite name (a2), activity category (a3), biological activity (a4), target species (a5) and references (a6). (B) An example of a metabolite information window generated by clicking a C_ID string in the search results window.

growth regulators (14.9%) (**Fig. 3**). Most of the metabolites with roles as antimicrobial agents are flavonoids, such as amentoflavone, daidzein, formononetin, pinosylvin and resveratrol, and phenylpropanoids, such as marmesin, eugenol and gallic acid, which are effective against 151 bacterial species and 90 fungi. The Metabolite Activity DB includes 192 metabolites with plant growth regulatory effects, including plant hormones such as auxins, gibberellins, cytokinins and ABA, which have effects on 202 plant species.

Secondary metabolites also have important roles in human health care because of their medicinal effects (Diplock 1999, Krzyzanowska et al. 2010, Wahle et al. 2010), and over half of the

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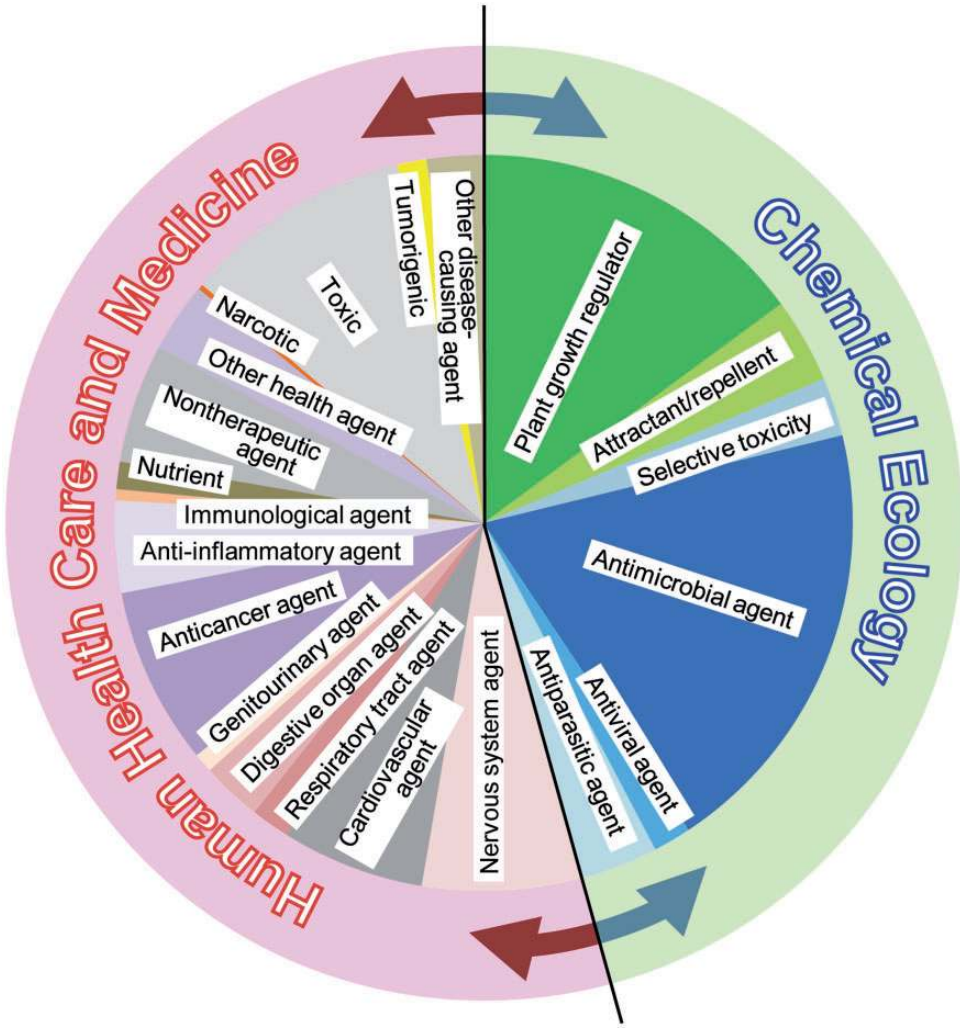

Fig. 3 Pie chart showing the relative frequencies of the 21 metabolite activity general descriptions listed in **Table 1**.

records in the Metabolite Activity DB are related to human health care and medicine (**Fig. 3**). The five largest groups are toxins (10.1%), anticancer agents (7.79%), nervous system agents (6.98%), cardiovascular agents (6.26%) and non-therapeutic agents (5.22%), such as flavors and fragrances. Most of these are related to medicinal drugs, but metabolites with roles as nutrients (1.20%) are also included. The integration of the human genome and nutrition has led to the emergence of nutrigenetics and nutrigenomics (Fenech et al. 2011). Similarly, the integration of food and health has resulted in the emergence of foodomics, because food is now considered as a nutrient and as an affordable way of preventing future disease (García-Cañas et al. 2012). The enrichment of records in the Metabolite Activity DB plays key roles in health care and medicinal applications, such as nutrigenetics, nutrigenomics and foodomics, as well as medical genomics.

To examine relationships between chemical structure and bioactivity, we tentatively classified the metabolites into 11 structural groups according to KEGG BRITE DB (http://www.genome.jp/kegg/brite.html) and assessed the similarity of metabolites based on 140 activities shown in **Table 1**. **Fig. 5** shows two-dimensional clustering. Similarities between metabolites are represented in the horizontal axis, and similarities in co-occurrence of activities are represented in the vertical axis. We then provisionally classified metabolites into nine clusters (**Fig. 5**) whose major activities are antibacterial (E32 in **Table 1**) in cluster 1, toxic (M82) in cluster 2, antifungal (E35) in cluster 3, antihypertensive (M26) in cluster 4, fragrance and feeding attractant (M65, M66 and E17) in cluster 5, pigment (M67) in cluster 6, antitumor (M46 and M47) in cluster 7, growth enhancement of stem, leaf, fruiting, germination and flowering (E02, E07, E04, E06, E01 and E05) in cluster 8 and broad effects in cluster 9. Though most of the chemical groups in the nine clusters are characterized by flavonoids and/or alkaloids, most of the metabolites belong to glucosinolates in cluster 5, many metabolites are quinones and betalains in cluster 6, and almost all the metabolites belong to terpenoids in cluster 8. Thus, relationships between fundamental chemical structures and

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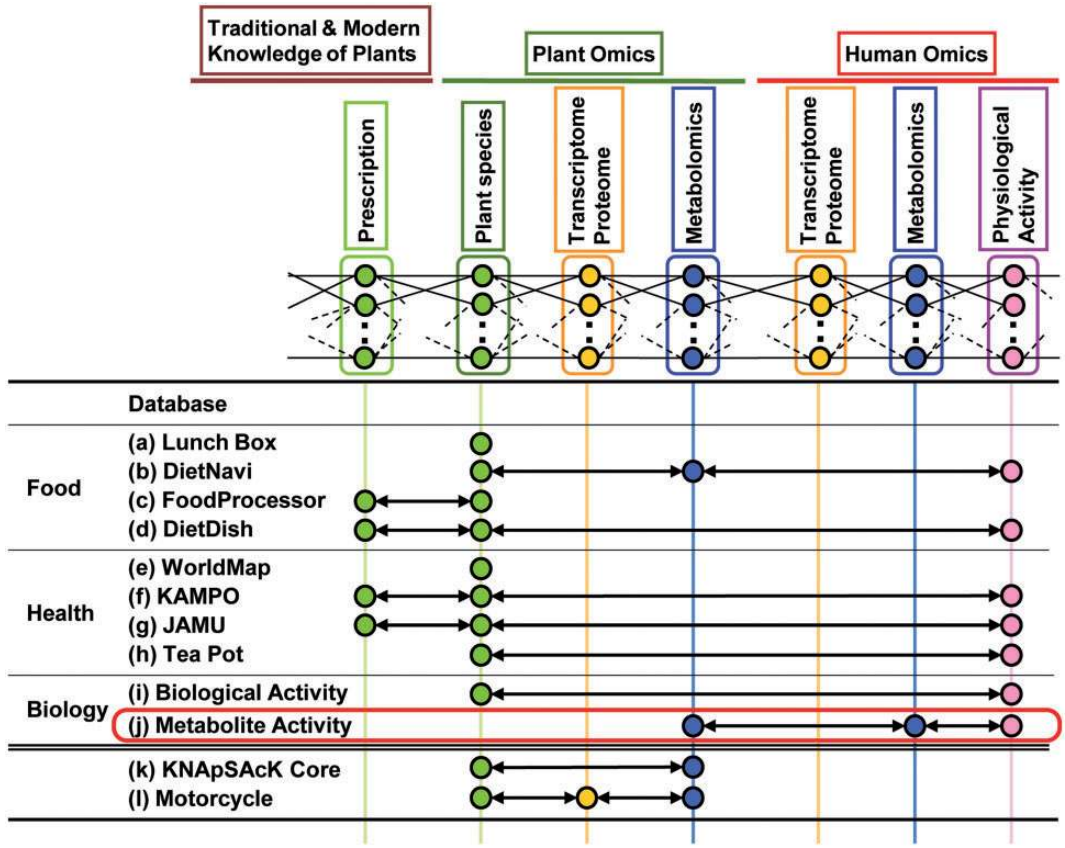

Fig. 4 Integrated platforms of knowledge for plants, and plant and human omics.

activities are observed in **Fig. 5**. This can be associated with the evolutionary strategies of metabolic pathways to create novel metabolites in species–species relationships via secondary metabolites in ecological systems and can be also be extended to human heath care.

Relationships between the Metabolite Activity DB and the KNApSAcK Family

At present, omics biology is experiencing an explosive increase in data, i.e. the so-called big data biology, including large-scale DNA sequencing, expression analyses, the mass spectra of metabolites and phenotype studies (Birney 2012). One of our goals is to facilitate a comprehensive understanding of the interactions between medicinal/edible plants and human health care and medicine, as well as the interactions that occur between species via metabolites. To achieve this goal, it is necessary to develop DBs that include the relationships among these omics data, as shown in **Fig. 4**. For health care and pharmacology applications, we have developed four DBs (Lunch Box, DietNavi, FoodProcessor and DietDish) related to the effects of popular Japanese foodstuffs on health. We have also developed four DBs to systematize crude drugs, i.e. WorldMap (relationships between geographic zones and the usage of edible and medicinal plants), KAMPO (prescription of crude drugs in Japan), JAMU (prescription of crude drugs in Indonesia) and Tea Pot (relationships between herbal tea and health care).

Users can search metabolites based on the molecular weights estimated from their mass spectra and according to the enzyme-catalyzed reactions of the metabolites using the KNApSAcK Core DB (Afendi et al. 2012) and Motorcycle DB (Ikeda et al. 2013), respectively. The KNApSAcK Core DB has been utilized extensively in omics science and it has about 100 citations in the scientific literature (Ikeda et al. 2013). Users can also search activity information with the Metabolite Activity DB. The Metabolite Activity DB and other KNApSAcK Family DBs play important roles in data-intensive or data-driven biological discovery because a large open pool of data that covers the full breadth of the life sciences is required to facilitate comprehensive research (Pennisi 2005, Thessen and Patterson 2011, Callebaut 2012). Thus, the metabolome needs to be connected to multifaceted information, such as species names, the utilization of crude drugs and edible plants, health care, and the proteome, such as enzyme reactions and activities. The KNApSAcK Family DBs have been enriched by addition of the Metabolite Activity DB, and the system now provides more systematized information related to metabolites in various fields, such as 'omics' sciences, particularly metabolomics, nutrigenomics and foodomics.

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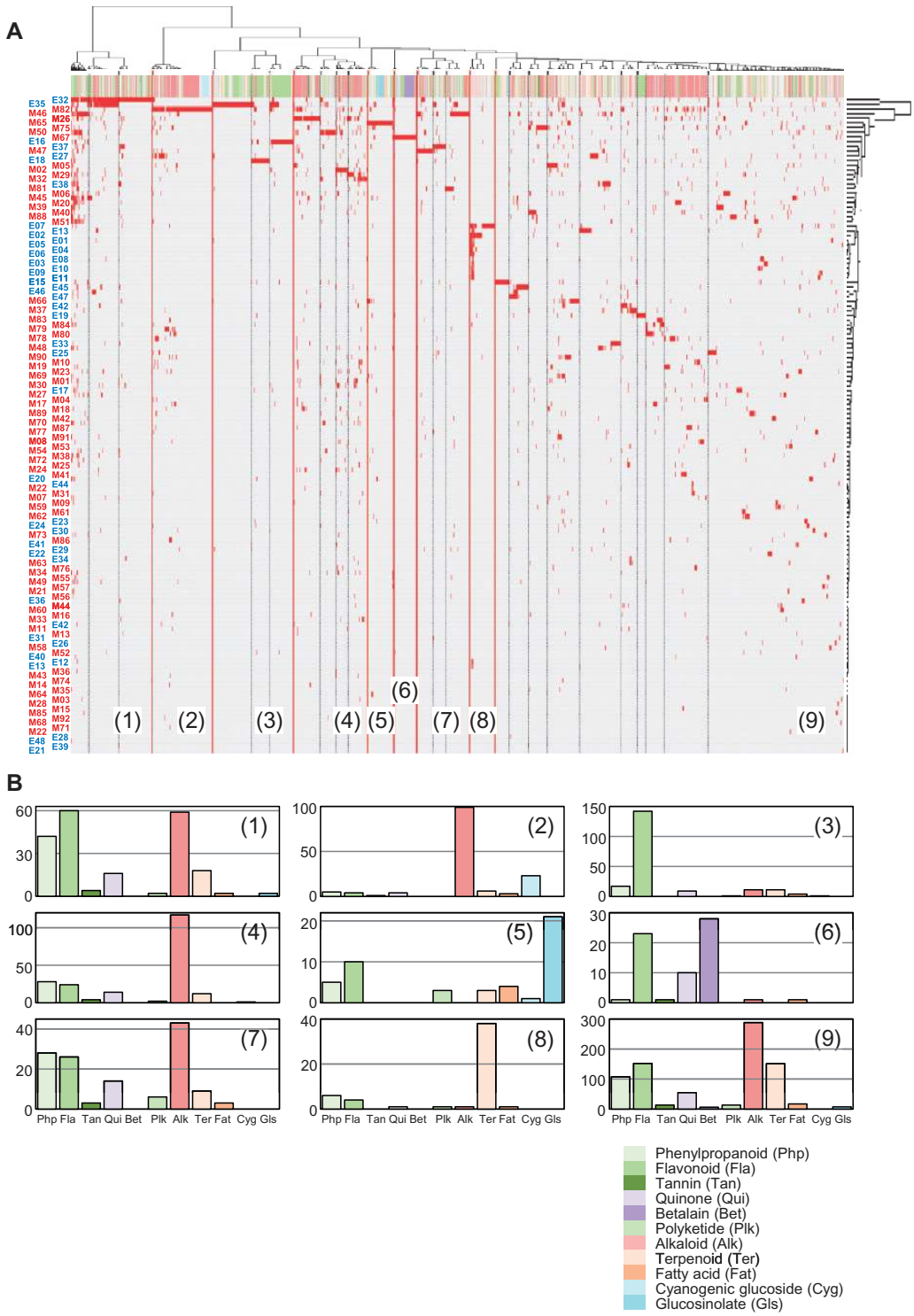

Fig. 5 Cluster analysis of metabolites in the Metabolite Activity DB according to their similarity of biological activity. (A) Overview of the two-dimensional clustering. Character strings in the left two columns describe the activity categories that are shown in **Table 1**. (B) Sum of metabolites in each structural group in each of the nine clusters.

Conclusion

The KNApSAcK Metabolite Activity DB provides triplet relationships between the metabolites of organisms, their biological activity and their target species. This DB facilitates the comprehension of the relationships and interactions between metabolites of organisms and the chemical-level contribution of metabolites to human health. Apart from metabolite activities

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related to chemical ecology, more than half of the biological activities listed in the Metabolite Activity DB are associated with medicine and human health. In future, the Metabolite Activity DB may therefore be utilized to develop novel drugs and to find viable resources for pharmacologically or nutritionally useful compounds.

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Disclosures

The authors have no conflicts of interest to declare.

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