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RESEARCH ARTICLE

Metabolomic Insights into the Elite Rice Varieties Unveil Bioactive Resources for Enhancing Global Human Health

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Abstract

Rice (*Oryza sativa* L.), as a staple food, is a critical target for nutritional enhancement. Understanding the natural variation of the bioactive components in rice bran holds significant promise for improving public health. An untargeted metabolite profiling of elite rice varieties, Jyothi, Jaya and Swarna, by high-resolution liquid chromatography and mass spectrometry enabled mining plant metabolic diversity. The 135 metabolites of 16 bioactive compound classes revealed the unique metabolite profiles of rice varieties. Key metabolites with nutritional and therapeutic potential were identified in brown rice. Mapping of metabolites against the KEGG database identified upregulated primary metabolic pathways crucial for growth and stress response in Jaya. Jyothi exhibited an enhanced phenylpropanoid biosynthetic pathway associated with compounds beneficial for plant defense and human health. Cutin, suberin, and wax biosynthesis pathways were unique to Swarna, ensuring survival in diverse and challenging environments. Metabolomics-centered analysis highlighted the biochemical distinctness and diversity, essential for targeted breeding for enhancing nutritional value and health benefits.

Keywords: Rice, Metabolomics, Bioactive compound, Targeted breeding, Phenylpropanoid pathway

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Introduction

Cultivated rice (*Oryza sativa* L.) is one of the most important crops globally, feeding approximately half of the world's human population. Rice, typically brown rice or whole grain rice, contains numerous bioactive compounds with potent antioxidant activity, and integrating rice and rice bran into the diet has been suggested to offer significant health advantages (Limtrakul *et al*., 2019). Brown rice demonstrates several nutrigenomic benefits, including enhanced antioxidant defense via pathways involving AKT NF-κB, along with reduced oxidative stress and also aids in lowering blood glucose and improving lipid profiles by modulating genes linked to glucose metabolism and cholesterol regulation (Ravichanthiran *et al*., 2019). A comprehensive metabolite profiling study of non-pigmented, black, and red rice cultivars by Kim *et al.* (2021) found that black and red rice are particularly rich in flavonoids and terpenoids, highlighting complex interactions between nitrogen and carbon metabolism that could inform breeding programs for nutritionally enhanced rice varieties. Understanding the diversity of bioactive compounds in rice is essential for developing rice varieties with enhanced health benefits (Gani *et al*., 2012; Zhao *et al*., 2020).

Comprehensive profiling of entire metabolites can provide profound insights into important metabolic pathways and biochemical processes occurring in plants (Razzaq *et al*., 2019). The phenylpropanoid pathway generates a diverse range of secondary metabolites, such as flavonoids, monolignols, and phenolic acids.

These compounds not only play a crucial role in enhancing plant defense but also offer health benefits for humans, exhibiting properties like antioxidant, anti-inflammatory, and protective effects (Anwar *et al*., 2021). Pathways of sugar metabolism also play a central role in plant immune response by modulating flavonoid biosynthesis and through interaction with phytohormones (Jeandet *et al*., 2022). Pathway enrichment analyses provide vital perceptions into the potential use of rice varieties in breeding programs, focusing on enhancing health benefits and environmental adaptability.

Materials and Methods

The experimental material comprised three high-yielding rice varieties popular in India. Jyothi (PTB 39), released in 1972 by the Regional Agricultural Research Station (RARS) in Pattambi, Kerala, is a short-duration variety (115-120 days) with parentage of PTB 10 x IR 8. Jaya, released in 1968 by the Indian Institute of Rice Research (IIRR) in Hyderabad, is a medium-duration variety (125–130 days) with parentage of TN 1 x T 141. Swarna (MTU 7029), released in 1979 by Andhra Pradesh Rice Research Institute (APRRI) and the Regional Agricultural Research Station (RARS) in Maruteru, is a long-duration variety (140–145 days) with parentage of Vasistha x Mahsuri. These varieties are renowned for their high grain yield and good cooking quality; hence are preferred by farmers and consumers alike. Jaya and Swarna are non-pigmented varieties with a white kernel color, whereas Jyothi is a variety with a red kernel color (Figure 1). Jyothi and Jaya were collected from Pattambi, while Swarna was sourced from Maruteru. All rice varieties were grown under uniform conditions in the net house facility at RARS, Pattambi, during the Kharif season of 2021, and matured grains were dehusked manually to obtain brown rice.

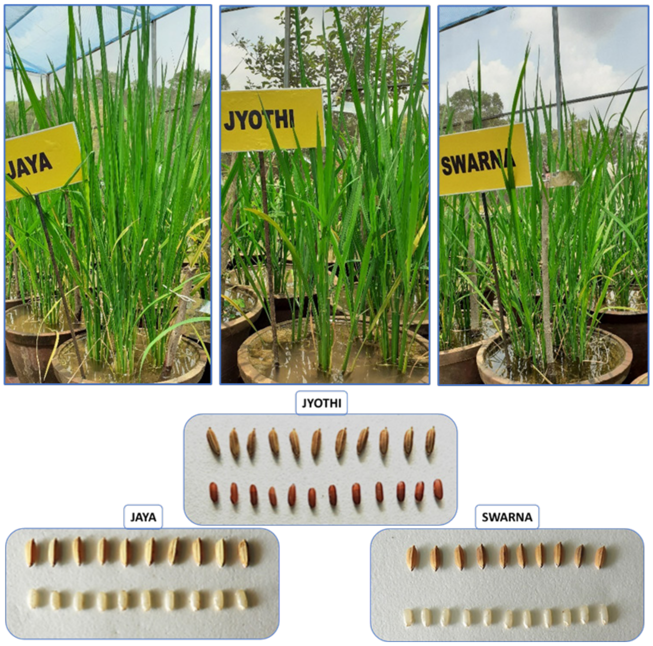

Figure 1: Plant and grain characteristics of the popular rice varieties Jyothi, Jaya, and Swarna

Untargeted Metabolite Profiling

Brown rice samples from the rice varieties were ground into fine powder, and 10 g of each sample was extracted with 50 mL of 98% methanol using a conventional rotary shaker. Samples were extracted three times at room temperature and filtered using Whatman no.1 filter paper, and the supernatants of the three extractions were combined and subjected to lyophilization using a vacuum rotary evaporator. The lyophilized extracts were reconstituted in 99% HPLC-grade methanol to a final volume of 1-mL. The samples were stored at -20°C. Metabolite profiling was performed using a Q-exactive plus biopharma-high resolution orbitrap liquid chromatograph mass spectrometer (Orbitrap-HRLCMS). Separation was carried out on a Hypersil Gold 3-micron 100 x 2.1 mm column (Thermo Scientific) with 0.1% formic acid in Milli-Q water (Solvent A) and methanol (Solvent B) as mobile phases. A gradient flow was used: 5% B at 2 minutes, gradually increasing to 95% at 25 minutes, and reduced to 5% at 30 minutes. The flow rate was 0.3 mL/min, and the total running time was 35 minutes with an injection volume of 5 µL. Data processing was conducted using Compound Discoverer 3.2 SP1 (Thermo Scientific) for compound identification. Data was screened and annotated using multiple databases. Metabolites from Orbitrap-HRLCMS were examined and classified into different compound classes based on *in-silico* analyses. The number of metabolites in each bioactive compound (BAC) class was determined. Unique bioactive compounds present in individual rice lines were identified. The area of the peaks of each metabolite was calculated from the chromatogram of Orbitrap-HRLCMS and tabulated as the relative abundance for quantitative data on the metabolites. The area of a peak is proportional to the concentration of the metabolite in the sample, which can be used to compare across different rice varieties.

Comparison of varieties was done based on qualitative and quantitative data on metabolites. The qualitative distribution of each metabolite class was calculated as the number of metabolites in each metabolite class out of the total number of metabolites in the variety and expressed as a percentage. In quantitative distribution, total relative abundance and the percentage of relative abundance of metabolite classes were used for comparison of the different rice varieties investigated. The total metabolite abundance of a class is the sum of the relative abundance of all metabolites belonging to that metabolite class.

Pathway Analysis

The pathway analysis module merges results from pathway enrichment as well as topology analysis to recognize the most relevant pathways involved in the analysis. By using the metabolomics pathway analysis (MetPA) tool from metaboanalyst software 6.0, the identified metabolites were exposed to pathway enrichment analysis. This analysis module utilizes KEGG metabolic pathways and the pathway library chosen was osa (KEGG organisms abbreviation). MetPA applies one-tailed Fisher's exact test for over-representation analysis, which identifies if a specific group of metabolites is represented more than expected by chance in the metabolite list. The node importance measure employed for topological analysis was `relative betweenness centrality'. The outcome from the pathway analysis was tabulated with hit score which is the matched number from the uploaded data, *p*-value, as well as pathway impact calculated from topology analysis. Pathways present in rice samples were presented on a map and the color and size show the significance or impact of the pathway detected. Important pathways of metabolites in rice varieties Jyothi, Jaya, and Swarna were identified from enrichment analysis.

Results

Metabolomic Profile of High-yielding Rice Varieties

The untargeted metabolite profiling in the methanolic fraction of brown rice samples using Orbitrap-HRLCMS has identified 135 metabolites that covered 16 bioactive compound classes (Supplementary Table).

Qualitative Metabolomic Profile

The bioactive compounds identified (Table 1) included primary metabolites such as 28 amino acids and derivatives (AA), 16 carboxylic acids and derivatives (CA), 22 fatty acids and derivatives (FA), eight purine derivatives (PU), five pyrimidine derivatives (PY), one sphingolipid (SL), 11 sugars and derivatives (SU), and four vitamins (VM). Among the secondary metabolites, four alkaloids (AL), six flavonoids (FL), one heterocyclic compound (HC), four indole derivatives (IN), one piperidine derivative (PI), 12 polyphenols (PP), seven quinoline derivatives (QL), and five terpenoids (TP) were detected. The percentage of qualitative distribution in rice is presented in Figure 2. Varieties were almost similar in the total number of metabolites, the highest being Swarna (91), followed by Jaya (86). Jyothi (82) was detected with the lowest number of metabolites among the three varieties tested. A higher number of primary metabolites were present in all varieties (Figure 3). Secondary metabolites were comparatively higher in Jyothi, especially PP (12.2%), QL (6.1%), and FL (4.9%). Swarna variety was also detected with a good proportion of secondary metabolites such as PP (7.7%), TP (4.4%), and FL (4.4%).

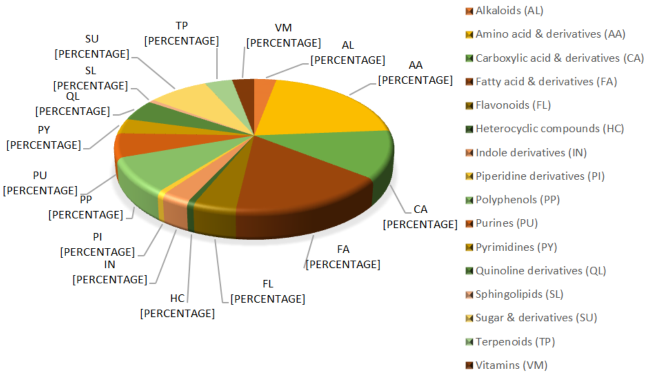

Figure 2: Qualitative distribution of metabolite classes in rice varieties
*Qualitative distribution refers to number of metabolites in each class

Quantitative Metabolomic Profile

Among the 16 bioactive compounds (BAC) classes detected, the relative abundance was the highest for CA (32%), followed by AA (19.6%), SU (14.8%), and FA (14.78%) as presented in Table 2. Among the secondary metabolites, AL was the most prevalent (7.8%), followed by IN (1.9%), PP (1.9%), FL (1%), TP (0.83%), and QL (0.6%). Percentage of relative abundance of metabolite class in each variety is given in parenthesis, which indicates the abundance of a specific metabolite class in a variety out of the total abundance of that metabolite class. This highlights each

Table 1: Distribution of different classes of bioactive compounds among rice varieties

Bioactive compound (BAC) class	*Total number of BAC*	*Jyothi*	*Jaya*	*Swarna*
Alkaloids (AL)	4	2	3	3
Amino acid & derivatives (AA)	28	15	20	20
Carboxylic acid & derivatives (CA)	16	11	12	9
Fatty acid & derivatives (FA)	22	9	16	13
Flavonoids (FL)	6	4	2	4
Heterocyclic compounds (HC)	1	1	1	1
Indole derivatives (IN)	4	3	3	4
Piperidine derivatives (PI)	1	1	0	1
Polyphenols (PP)	12	10	5	7
Purines (PU)	8	5	6	7
Pyrimidines (PY)	5	1	5	3
Quinoline derivatives (QL)	7	5	1	5
Sphingolipids (SL)	1	1	1	1
Sugar & derivatives (SU)	11	9	8	6
Terpenoids (TP)	5	1	2	4
Vitamins (VM)	4	4	4	3
Total	135	82	89	91

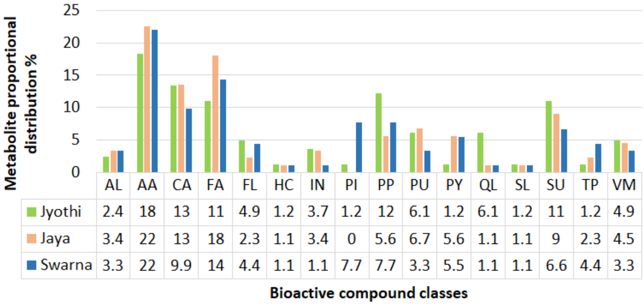

Figure 3: Qualitative distribution of primary and secondary metabolites in rice variety

*Metabolite proportional distribution (%) is the number of metabolites in each class out of total number of metabolites in a variety

variety's contribution towards the overall abundance of a specific metabolite class, as illustrated in Figure 4. Jyothi exhibited the highest abundance of CA (46.8%), VM (48.3%), PP (65.4%), and QL (48.4%), Jaya was detected with the highest abundance of FA (71.4%), PY (65.4%), and SL (60.1%). Swarna exhibited the highest abundance of SU (54.5%), IN (61.2%), TP (41.4%), and HC (43.8%).

Partitioning of Metabolite Abundance

Table 3 presents the partitioning of total metabolite abundance (%) among 16 metabolite classes within each rice variety and is an indication of how the primary and secondary metabolites are distributed in each variety. According to this proportional quantitative distribution of metabolites, primary metabolites constituted 82 to 92% of the metabolome, in which the major primary metabolites (AA, CA, FA, SU, and VM) accounted for 80 to 86%, while minor (PU, PY, SL) contributed 2 to 5%. The secondary metabolite proportion was the lowest in Jaya (8.4%), while it was the highest in Jyothi (18%) and intermediate in Swarna (15.8%). Jyothi showed a higher proportion of FL (1.1%), PP (3.8%), and AL (9.9%). Both Jyothi and Swarna had higher proportions of QL (0.86 and 0.75%) and TP (0.92 and 0.98%), respectively. Additionally, Swarna exhibited a higher proportion of IN (3.33%).

The proportional quantitative distribution of metabolites within each rice variety is illustrated in Figure 5, highlighting the specific allocation of primary and secondary metabolites within the metabolome of each variety. In the Jyothi variety, the proportion of lipid metabolites was notably low (0.03 for FA and 1% for SL), whereas the Jaya exhibited the highest proportions of these metabolites (32.9% for FA and 1.4% for SL). A lower SU proportion was observed in Jaya (9.2%) compared to Swarna (22.9%) and Jyothi (11.8%). The proportion of CA in Jyothi was remarkably higher (45.9%) compared to Jaya (25.2%) and Swarna (25.4%). The AA proportion of elite rice varieties showed minimal variation (18.1–20.6%).

Table 2: Comparative analysis of rice varieties based on total relative abundance of metabolite classes

Bioactive compound (BAC) class	*Total relative abundance of BAC class*			*Abundance of BAC class (%)*
	Jyothi	*Jaya*	*Swarna*	
Amino acid & derivatives (AA)	5535 (33.40)	4905 (29.59)	6134 (37.01)	19.63
Carboxylic acid & derivatives (CA)	12637 (46.80)	6866 (25.43)	7500 (27.77)	31.99
Fatty acid & derivatives (FA)	277 (2.22)	8903 (71.35)	3299 (26.44)	14.78
Sugar & derivatives (SU)	3212 (25.71)	2476 (19.82)	6805 (54.47)	14.80
Vitamins (VM)	422 (48.29)	256 (29.28)	196 (22.43)	1.04
Purines (PU)	454 (23.70)	713 (37.22)	748 (39.08)	2.27
Pyrimidines (PY)	43 (10.41)	270 (65.42)	100 (24.12)	0.49
Sphingolipids (SL)	11 (1.76)	381 (60.07)	242 (38.19)	0.75
Alkaloids (AL)	2714 (41.09)	1281 (19.39)	2611 (39.52)	7.83
Flavonoids (FL)	301 (35.68)	247 (29.25)	296 (35.06)	1.00
Polyphenols (PP)	1032 (65.72)	246 (15.67)	293 (18.62)	1.86
Indole derivatives (IN)	372 (22.91)	258 (15.90)	994 (61.17)	1.92
Quinoline derivatives (QL)	236 (48.35)	31 (6.32)	222 (45.42)	0.58
Terpenoids (TP)	253 (35.85)	160 (22.69)	292 (41.44)	0.83
Heterocyclic compounds (HC)	37 (22.53)	56 (33.68)	72 (43.83)	0.20
Piperidine derivatives (PI)	11 (51.60)	0 (0.00)	11 (48.45)	0.03
Metabolite abundance per variety (%)	32.64	32.04	35.32	100.00

*Actual value of relative abundance is x10^6 times of table value. Percentage of relative abundance of each variety is given in parenthesis, which is the abundance of a specific metabolite class in a variety out of total abundance of that metabolite class in three varieties.

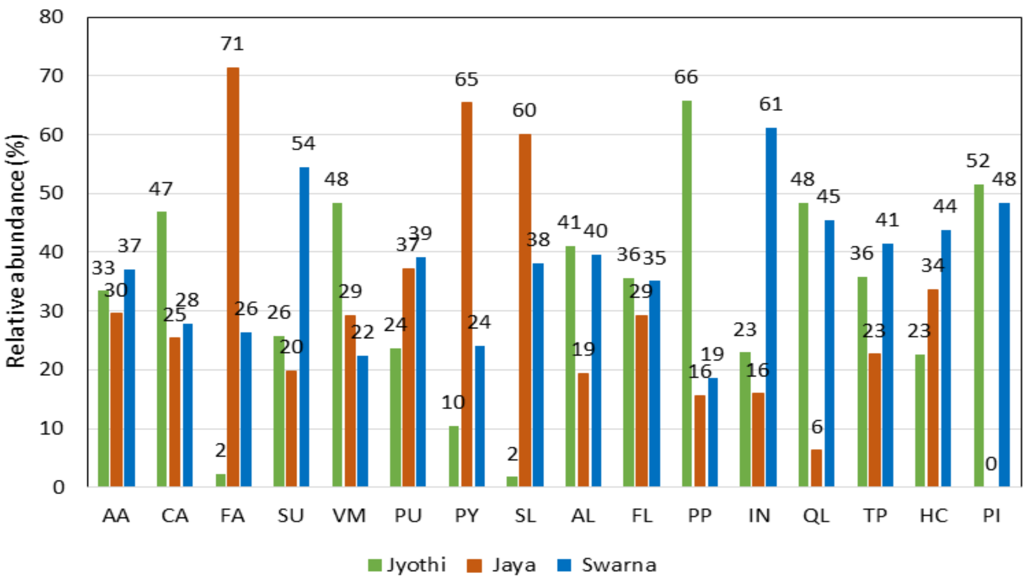

Figure 4: Comparison of varieties based on percentage of abundance of metabolite classes

Biological Pathways of Popular Rice Varieties

Mapping of the metabolites against the KEGG database revealed 39 pathways each in Jyothi and Swarna, whereas 49 pathways were revealed from Jaya. Out of the 39 pathways, four major pathways showed low *p-value* (≤ 0.5) in Jyothi (Table 4a), in which Galactose metabolism exhibited the lowest *p-value* (0.018). Ten major pathways with low *p*-values (<0.05) were noticed in Jaya, and that of Swarna was 6. The lowest *p-value* (0.003) was detected for alanine, aspartate and glutamate metabolism in Jaya (Table 4b), while the unsaturated fatty acid biosynthesis pathway exhibited the lowest *p-value* (0.002) in Swarna (Table 4c). The pathway view of varieties is displayed in Figure 6. Table 5 lists unique metabolites with nutraceutical potential identified from elite rice varieties belonging to major detected pathways.

Table 3: Partitioning of metabolite abundance within rice variety

Bioactive compound (BAC)	*Jyothi (%)*	*Jaya (%)*	*Swarna (%)*
Amino acid & derivatives (AA)	20.09	18.13	20.60
Carboxylic acid & derivatives (CA)	45.87	25.38	25.19
Fatty acid & derivatives (FA)	1.00	32.91	11.08
Sugar & derivatives (SU)	11.66	9.15	22.86
Vitamins (VM)	1.53	0.95	0.66
Purines (PU)	1.65	2.64	2.51
Pyrimidines (PY)	0.16	1.00	0.33
Sphingolipids (SL)	0.04	1.41	0.81
Alkaloids (AL)	9.85	4.74	8.77
Flavonoids (FL)	1.09	0.91	1.00
Polyphenols (PP)	3.75	0.91	0.98
Indole derivatives (IN)	1.35	0.95	3.33
Quinoline derivatives (QL)	0.86	0.11	0.75
Terpenoids (TP)	0.92	0.59	0.98
Heterocyclic compounds (HC)	0.13	0.21	0.24
Piperidine derivatives (PI)	0.04	0.00	0.04
TOTAL	100	100	100
Primary metabolites	82.0	91.6	84.2
Secondary metabolites	18.0	8.4	15.8

*Highlighted cells display values that deviate from rest of the values in the respective metabolite class

Discussion

Metabolite Diversity and Abundance in Brown Rice

Rice, a staple food for a significant portion of the global population, holds critical importance in terms of nutritional quality. Typically consumed as refined white grain, rice loses many nutritious components present in the bran. Rice bran is a rich source of bioactive compounds (Das *et al.*, 2017; Ravichanthiran *et al.*, 2019), the biochemical profiles

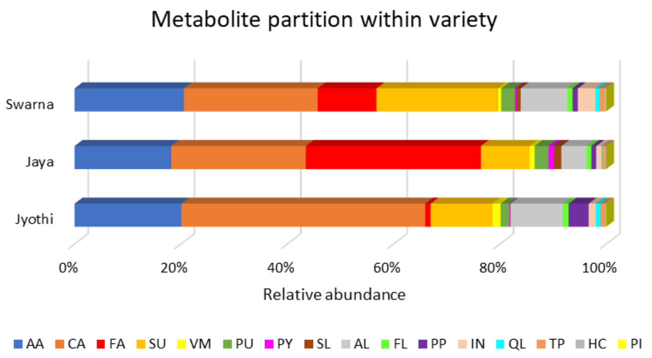

Figure 5: Comparison of rice varieties based on metabolite partition within each variety

Table 4a: Pathway analysis result of Jyothi variety

KEGG pathway- Jyothi variety	*Total*	*Hits*	*Raw p*	*-log10(p)*	*Impact*
Galactose metabolism	27	3	0.017784	1.75	0.06356
Phenylalanine metabolism	12	2	0.025076	1.6007	0.42308
Nicotinate and nicotinamide metabolism	13	2	0.029249	1.5339	0.0202
Phenylpropanoid biosynthesis	33	3	0.030456	1.5163	0.05294
Purine metabolism	70	4	0.056645	1.2468	0.01697
Phenylalanine, tyrosine and tryptophan biosynthesis	22	2	0.077031	1.1133	0.02152
Alanine, aspartate and glutamate metabolism	22	2	0.077031	1.1133	0.32374
Tryptophan metabolism	23	2	0.083282	1.0795	0.18605
Glutathione metabolism	27	2	0.10973	0.95969	0.06211

* KEGG pathway with high relevance is written in bold

Table 4b: Pathway analysis result of Jaya variety

KEGG Pathway- Jaya Variety	*Total*	*Hits*	*Raw p*	*-log10(p)*	*Impact*
Alanine, aspartate and glutamate metabolism	22	4	0.003029	2.5188	0.57914
Nicotinate and nicotinamide metabolism	13	3	0.00526	2.279	0.0202
Galactose metabolism	27	4	0.006542	2.1843	0.08003
Arginine and proline metabolism	28	4	0.007473	2.1265	0.12538
Arginine biosynthesis	18	3	0.013569	1.8674	0.16991
Biosynthesis of unsaturated fatty acids	22	3	0.023634	1.6265	<0.01
Valine, leucine and isoleucine biosynthesis	22	3	0.023634	1.6265	0.05721
Lysine biosynthesis	9	2	0.025861	1.5874	<0.01
Purine metabolism	70	5	0.047741	1.3211	0.03016
Glyoxylate and dicarboxylate metabolism	29	3	0.048769	1.3119	0.16405
Phenylpropanoid biosynthesis	33	3	0.067267	1.1722	0.05294
Glycine, serine and threonine metabolism	33	3	0.067267	1.1722	0.123
Butanoate metabolism	17	2	0.084477	1.0733	0.13636
beta-Alanine metabolism	18	2	0.09334	1.0299	<0.01
Pentose phosphate pathway	19	2	0.10246	0.98943	<0.01

*KEGG Pathway with high relevance is written in bold

Table 4c: Pathway result of Swarna variety

KEGG Pathway- Swarna Variety	*Total*	*Hits*	*Raw p*	*-log10(p)*	*Impact*
Biosynthesis of unsaturated fatty acids	22	4	0.001855	2.7317	<0.01
Purine metabolism	70	5	0.029061	1.5367	0.03016
Phenylalanine metabolism	12	2	0.035305	1.4522	0.42308
Nicotinate and nicotinamide metabolism	13	2	0.041066	1.3865	0.0202
Phenylpropanoid biosynthesis	33	3	0.048731	1.3122	0.05294
Cutin, suberine and wax biosynthesis	15	2	0.053556	1.2712	0.16667
Lysine degradation	20	2	0.089567	1.0479	<0.01
Citrate cycle (TCA cycle)	20	2	0.089567	1.0479	0.16079
Thiamine metabolism	22	2	0.10554	0.9766	<0.01
Phenylalanine, tyrosine and tryptophan biosynthesis	22	2	0.10554	0.9766	0.02152
Alanine, aspartate and glutamate metabolism	22	2	0.10554	0.9766	0.1295

* KEGG Pathway with high relevance is written in bold

of which vary greatly across different rice varieties. Several studies have focused on exploring these varietal differences in bioactive bran components for enhancing human health (Heuberger *et al*., 2010; Forster *et al*., 2013). In this study, untargeted metabolite profiling of methanolic extract from brown rice samples of three high-yielding rice varieties, Jyothi, Jaya, and Swarna, revealed a diverse array of bioactive compounds. The total 135 metabolites detected indicated a rich metabolomic landscape across these varieties. A deeper analysis revealed a distinct pattern of bioactive metabolite distribution for each variety, thus confirming the importance of characterizing each variety biochemically to identify superior varieties with higher nutritional values and health benefits (Nandhini *et al*., 2023; Rajagopalan *et al*., 2022).

Primary metabolites constituted the majority of the bioactive compounds, highlighting their essential role in nutrition (Frank *et al.,* 2012). Quantitative analysis revealed that the primary metabolites together accounted for a major portion (80–90%) of the metabolome in each variety. They play an important role in upholding cellular homeostasis and production of a series of lineage-specific secondary metabolites, which are vital for plant adaptation as well as human medicine and nutrition (Maeda, 2019). It is notable that the non-pigmented varieties exhibited a wider primary metabolite profile, Jaya being the highest (>90%), whereas pigmented type Jyothi had a richer secondary metabolite profile and remarkably elevated phenolic profile, as noticed in earlier studies (Hussein and El-Anssary, 2019; Kim *et al*., 2021). The Swarna variety was found to be an exception, with more secondary metabolite proportion compared to the non-pigmented variety, Jaya.

Comparison among Rice Varieties based on Metabolite Classes

A comprehensive comparison of metabolomic profiles of three elite rice varieties is helpful in uncovering the biochemical basis for their health-promoting properties and adaptability to various environmental conditions. It is evident from the results that primary metabolite profiles like lipid (FA, SL) and sugar derivatives have a crucial role, along with secondary metabolites, in the distinctness of rice varieties.

The high-yielding pigmented rice variety Jyothi exhibited the highest levels of CA and VM. Its FA profile was notably low, while its SU profile was moderate. Jyothi's most remarkable feature is its robust polyphenolic profile and other bioactive metabolites such as FL, AL, QL, TP, and PI. The elevated secondary metabolite profile, attributed to its pigmentation (Oki *et al*., 2002), enhances Jyothi's potential nutritional and health benefits, making it an exceptional variety among elite cultivars.

The rice variety Jaya displayed a moderately higher abundance of most of the primary metabolites, except for low-sugar derivatives. Jaya was characterized by an upregulated lipid profile (FA and SL), a downregulated SU profile, and a notably higher PY content. Despite its lower secondary metabolite profile, Jaya was detected with a moderate level of AL, highlighting its distinct biochemical composition.

Swarna, a non-pigmented variety, was characterized by low FA and high SU profile, biochemically distinguishing it from Jaya. Swarna exhibited higher secondary metabolites, particularly AL, IN, PI, TP, and QL. Similar to Jyothi, secondary metabolites with several nutraceutical properties were also observed in Swarna. However key metabolites such as CA and PP were substantially lower than Jyothi. The nutritional profile of Swarna is distinctive due to its uniform distribution of phytochemicals in an intermediate range.

Metabolite partitioning within each rice variety revealed a characteristic bioactive profile of individual variety and showed the biochemical distinctness and diversity within rice varieties. This is also an indication of differential regulation of metabolic pathways to distinguish specific varieties.

Biological Pathways: Bridging Plant Metabolism and Human Health

Mapping of the metabolites identified by Orbitrap-HRLCMS against the KEGG database revealed major pathways in each variety (Figure 6a, b and c). The elevated pathways in each variety, as demonstrated by the lowest *p*-values, emphasize their distinctness. Among the major biological pathways, nicotinate and nicotinamide metabolic pathways is present in all varieties, confirming the relevance of primary metabolism. Nicotinate (niacin) and nicotinamide are precursors to NAD+ and NADP+, which are critical co-factors in cellular respiration and photosynthesis, DNA repair, regulation of gene expression by deacetylating histones and other proteins during stress responses, metabolism, and aging in rice plants (Wu *et al*., 2016; Wu *et al*., 2023).

Jaya variety displayed the majority of primary metabolic pathways in an upregulated manner (Supplementary Table 1), with alanine, aspartate, and glutamate metabolism as the lowest *p*-value. Glutamate is a precursor to GABA synthesis, which plays a crucial role in drought and salinity stress (Ramos-Ruiz *et al*., 2019). The upregulation of such pathways, especially arginine and proline metabolism in Jaya, indicates an adaptive response to optimize growth, development, and survival by mechanisms like efficient nitrogen assimilation and transport, polyamine production, osmotic regulation by proline accumulation during drought and salinity, regulation of various metabolic pathways, and ultimately contributing to overall health and productivity (Akula and Ravishankar, 2011; Maeda, 2019; Yang *et al*., 2022).

Jyothi and Jaya showed upregulated galactose metabolism (sugar derivatives), which serves as an essential

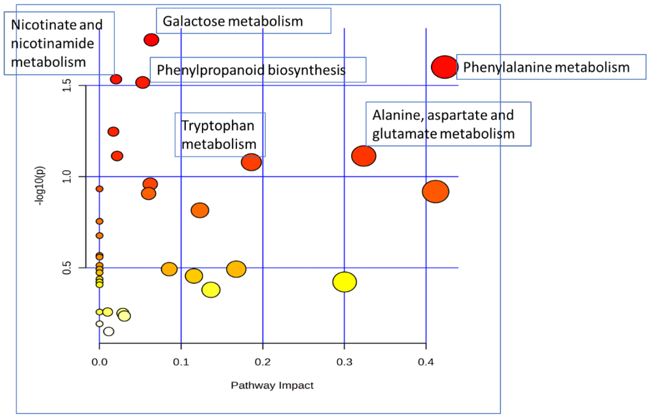

Figure 6a: Pathway view of Jyothi variety
*Major pathways are marked in text box

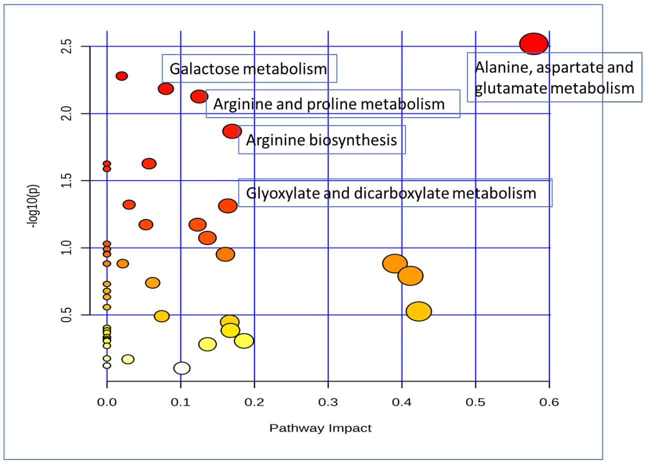

Figure 6b: Pathway view of Jaya variety
*Major pathways are marked in text box

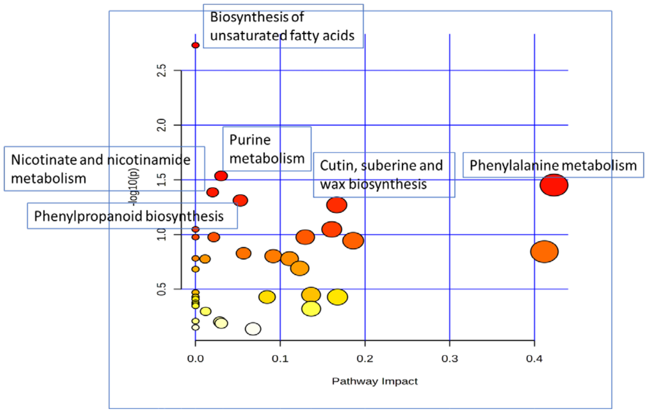

Figure 6c: Pathway view of Swarna variety
*Major pathways are marked in the text box

carbon source and enhances the mechanical strength of plants by improving cell wall integrity, especially during drought, salinity, and cold, as osmoprotectants (Jeandet *et al.*, 2022). This pathway contributes to better energy production, stress tolerance, and genomic stability.

Additionally, Jyothi showed upregulated secondary metabolite pathways like phenylalanine metabolism and phenylpropanoid biosynthesis (Supplementary Table 1). Lignin, a major product of the pathway, provides structural integrity, antimicrobial phytoalexins enhance plant defense mechanism, allelopathic phenolics give a competitive advantage, and most importantly, flavonoids and phenolics can detoxify reactive oxygen species (ROS), thus protecting plants from abiotic stress and harmful UV rays. These compounds contribute to the nutritional and medicinal value of the pigmented Jyothi variety. As detailed in several studies, these pathways significantly contribute to the overall fitness, yield, and quality of rice crops (Anwar *et al.*, 2021; Kim *et al.*, 2021; Lam *et al.*, 2022).

Swarna was detected with upregulated primary metabolite pathways like biosynthesis of unsaturated fatty acids and purine metabolism. Similar to pigmented rice, phenylalanine and phenylpropanoid biosynthesis were detected as major pathways, as also indicated by a high QL, TP, PI, and AL profile in its metabolome (Supplementary Table 1). Cutin, suberin, and wax biosynthesis is a unique pathway detected in Swarna, and the metabolites of this pathway enhance the ability to withstand drought, salinity, and extreme temperatures (Bakan and Marion, 2017). These compounds also provide barriers against pathogens and pests. Cuticular layers are composed of an insoluble hydrophobic cutin, a complex mixture of derivatives of long-chain FA and TP (Bakan and Marion, 2017). By linking the higher abundance of TP as well as long chain FA, with the upregulated cutin, suberin, and wax biosynthesis pathway, it becomes evident that Swarna has developed a robust cuticular structure. Upregulated primary and secondary metabolites, as well as cutin, suberine and wax pathways in the metabolome, Swarna ensures survival in diverse and often challenging environments.

Enhancing Health Through Bioactive Metabolite Resources in Rice

The study reveals the unique metabolite profiles of rice varieties and several bioactive compounds with therapeutic potential were detected in elite varieties, as presented in Table 5. It is of utmost importance to conduct further validation of each of these compounds identified in rice varieties by thorough targeted metabolite profiling (Perng and Aslibekyan, 2020).

Metabolomics-centred mining of varieties and identification of bioactive resources are key to the utilization of plant metabolic diversity towards metabolomic-assisted breeding (Shen *et al.*, 2023). The study emphasizes that diverse and differential bioactive profiles of Jyothi, Jaya, and Swarna (Table 5) offer significant opportunities for targeted breeding programs aimed at enhancing health benefits, such as, antioxidant, anti-inflammatory, anticancer, antidiabetic, antimicrobial, neuroprotective, hepatoprotective and cardioprotective properties and adaptability to specific environments. Pigmented rice variety

Table 5: Distinct health-promoting metabolites identified in elite rice varieties

Property	*Metabolite and variety*	*Reference*
Antioxidant	(-)-Epicatechin and Catechin in Jyothi; Proline in Jaya; Caffeic acid, Citral and Ursolic acid in Swarna	Shay *et al*., 2015; Hayat *et al*., 2012; Biswas *et al*., 2021
Anti-inflammatory	12-Oxophytodienoic acid, (±)9(10)-DiHOME, and Acetyl-α-D-glucosamine in Jyothi; 3-dihydroxy propyl 12-methyltridecanoate in Jaya; Caffeic acid, Citral, and Ursolic acid in Swarna	Bernatoniene and Kopustinskiene, 2018; Wang *et al*., 2017
Anticancer	(-)-Epicatechin, Catechin, and 6-Methoxyquinoline N-oxide in Jyothi; α-Eleostearic acid in Jaya; Tricin 5-O-β-D-glucoside and Citral in Swarna	Singha *et al*., 2022; Eom *et al*., 2010; Jiang *et al*., 2020
Antidiabetic	(-)-Epicatechin, Catechin, and 2-Hydroxyquinoline in Jyothi; Citral in Swarna	Lee and Lee, 2015; Sharma *et al*., 2021
Antimicrobial	12-Oxophytodienoic acid, (+/-)12(13)-DiHOME, 2,5-Dihydroxybenzaldehyde, and Catechol in Jyothi; 3,5,5-trimethylhexyl) phthalate, (+/-)9-HpODE, and 9,12,13-Trihydroxy-15-octadecenoic acid in Jaya; Tricin 5-O-β-D-glucoside, 6,18,19-Trihydroxytrachyloban-2-one, Citral, and Ursolic acid in Swarna	Liu and Park, 2021; Schabauer *et al*., 2018; Adigun *et al*., 2023; Donadio *et al*., 2022
Neuroprotective	Catechin and Acetyl-α-D-glucosamine in Jyothi; Methoxypuerarin, Xanthurenic acid, and Ursolic acid in Swarna	Bernatoniene and Kopustinskiene, 2018
Hepatoprotective and cardioprotective	Catechin in Jyothi	Bernatoniene and Kopustinskiene, 2018
Antidepressant	Proline in Jaya	Hayat *et al*., 2012

Jyothi, with its elevated polyphenolic profile (Catechins, 6-Methoxyquinoline N-oxide, 2,5-Dihydroxybenzaldehyde *etc*.) and galactose metabolism (sugar derivatives) can be used in breeding programs to develop new varieties with enhanced antioxidant properties (Anwar *et al*., 2021) and better adaptability to abiotic stresses and harsh environments (Jeandet *et al*., 2022). Meanwhile, Jaya's high levels of essential primary metabolites, such as proline, α-eleostearic acid, and (+/-)9-HpODE, support its suitability for breeding programs focused on enhancing nutritional quality, with adaptability to diverse growing conditions due to its moderate duration. A balanced profile of both primary and secondary metabolites (Lysine, Histidine, Caffeic acid, Citral, Tricin 5-O-β-D-glucoside and Ursolic acid) and long duration makes Swarna the right candidate to develop rice varieties that provide a well-rounded nutritional profile, particularly suited for sustainability in challenging environments (Rathinasabapathi *et al*., 2015).

Future research should explore deeper into the specific metabolic pathways responsible for the production of key bioactive compounds. The integration of different multi-omics data can remarkably accelerate the process towards a complete understanding of the pathway structure and regulation of primary and secondary metabolism (Zhu *et al*., 2023). By harnessing the power of plant bioactive resources and pathway analysis, targeted breeding approaches can create rice varieties that not only feed the world but also nourish it.

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Declaration of Conflicting Interests

The authors declare no conflict of interest in the conduct of the study.

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SUPPLEMENTARY TABLE:

Supplementary Table 1: Bioactive compounds identified from methanolic fraction of brown rice by Orbitrap-HRLCMS

METABOLITES	*Compound class and number of metabolites*		*Molecular formula*	*KEGG ID*	*Jyothi (Peak area)*	*Jaya (Peak area)*	*Swarna (Peak area)*
Arecoline	AL	1	$C_8H_{13}NO_2$	C10129	ND	185454909.1	ND
Isoquinoline	AL	2	C_9H_7N	C06323	100478873.2	51149713.4	85433245.33
Oxymorphone	AL	3	$C_{17}H_{19}NO_4$	C08019	ND	ND	7975791.46
Trigonelline	AL	4	$C_7H_7NO_2$	C01004	2613674492	1044346152	2517106610
1-Aminocyclohexanecarboxylic acid	AA	1	$C_7H_{13}NO_2$	C09822	ND	ND	9904682.331
2,3,4,9-Tetrahydro-1H-β-carboline-3-carboxylic acid	AA	2	$C_{12}H_{12}N_2O_2$	C01021	ND	ND	48960540.53
4-Guanidinobutyric acid	AA	3	$C_5H_{11}N_3O_2$	C01035	107147448.9	ND	ND
4-Oxoproline	AA	4	$C_5H_7NO_3$	C01877	20035617.78	37957916.62	ND
Asparagine	AA	5	$C_4H_8N_2O_3$	C16438	26360684.84	58253302.78	46126450.97
DL-Arginine	AA	6	$C_6H_{14}N_4O_2$	C02385	ND	58127054.19	55443212.46
DL-Lysine	AA	7	$C_6H_{14}N_2O_2$	C16440	ND	ND	7115935.953
DL-Tryptophan	AA	8	$C_{11}H_{12}N_2O_2$	C00806	826811827.9	74640269.63	3897382.821
Isoleucine	AA	9	$C_6H_{13}NO_2$	D00065	ND	386634894.1	ND
L-Aspartic acid	AA	10	$C_4H_7NO_4$	C00049	ND	22599324.3	ND
L-Glutamic acid	AA	11	$C_5H_9NO_4$	C00025	34517891.61	55753401.64	ND
L-Histidine	AA	12	$C_6H_9N_3O_2$	C00135	ND	ND	14140744.4
L-Lysine	AA	13	$C_6H_{14}N_2O_2$	C00135	ND	3779134.942	ND
L-Norleucine	AA	14	$C_6H_{13}NO_2$	C01933	419724946.3	ND	521519453.9
L-Phenylalanine	AA	15	$C_9H_{11}NO_2$	C00079	143807903.5	202212986.9	8324930.636
L-Threonine	AA	16	$C_4H_9NO_3$	C00188	13292805.65	18149560.93	37395097.22
L-Tyrosine	AA	17	$C_9H_{11}NO_3$	C00082	63660508.53	11023108.39	13404428.23
Proline	AA	18	$C_5H_9NO_2$	C00148	ND	239093927.4	ND
Prolyl leucine	AA	19	$C_{11}H_{20}N_2O_3$	C00107	1163081447	754138330.5	1535553002
Y-Aminobutyric acid (GABA)	AA	20	$C_4H_9NO_2$	C00334	ND	28028021.8	96537466.45
D- (+)-Pipecolinic acid	AA	21	$C_6H_{11}NO_2$	C00408	ND	48509861.32	12394297.55
D- (+)-Pyroglutamic Acid	AA	22	$C_5H_7NO_3$	C02237	53851678.93	186992208	44051183.02
Choline	AA	23	$C_5H_{13}NO$	C00114	2421430358	2506748908	3558719817
DL-Carnitine	AA	24	$C_7H_{15}NO_3$	C00487	23108510.85	ND	25008746.72
DL-Stachydrine	AA	25	$C_7H_{13}NO_2$	C10172	201506127.3	130378350.6	74772520.75
L-Methionine sulfoxide	AA	26	$C_5H_{11}NO_3S$	C02989	ND	4726753.2	9776355.235
N, N-Diisopropylethylamine (DIPEA)	AA	27	$C_8H_{19}N$	C00797	ND	76957793.33	ND
Phenylacetaldehyde	AA	28	C_8H_8O	C00601	16576333.4	ND	10747726.85
1,2,3-cyclopropane tricarboxylic acid	CA	1	$C_6H_6O_6$	C16267	8097419.849	ND	ND
2-Isopropylmalic acid	CA	2	$C_7H_{12}O_5$	C02504	ND	11028730.14	ND
4-oxododecanedioic acid	CA	3	$C_{12}H_{20}O_5$	C02678	47438373.34	20291848.28	62550830.31
Azelaic acid	CA	4	$C_9H_{16}O_4$	C08261	71235147.32	12557312.06	37413704.2
Benzoic acid	CA	5	$C_7H_6O_2$	C00180	8129834.569	ND	ND

Citric acid	CA	6	C6 H8 O7	C00158	335648096.5	17532100.01	65300278.94
D- (+)-Malic acid	CA	7	C4 H6 O5	C00497	65341686.26	63725581.76	10570346.6
Gluconic acid	CA	8	C6 H12 O7	C00257	256677205.1	200581620.8	197624929.5
Isocitric acid	CA	9	C6 H8 O7	C00311	ND	14979003.73	13793919.76
Methylmalonic acid	CA	10	C4 H6 O4	C02170	7171654.992	ND	ND
Bis(3,5,5-trimethylhexyl) phthalate	CA	11	C26 H42 O4	C15221	ND	24621094.17	ND
Dibutyl maleate	CA	12	C12 H20 O4	C01384	ND	306437837.1	ND
Dibutyl phthalate	CA	13	C16 H22 O4	C14214	ND	32159086.33	ND
Didodecyl-3,3-thiodipropionate (DLTDP)	CA	14	C30 H58 O4 S	C00163	11795656504	6129664771	7046873010
Erucamide	CA	15	C22 H43 N O	C08316	29113997.35	32788139.63	58221910.97
Methyl dihydrojasmonate	CA	16	C13 H22 O3	C11512	12256983.93	ND	7728598.738
2,3-dihydroxypropyl 12-methyltridecanoate	FA	1	C17 H34 O4	C17076	ND	625501866.1	ND
9(Z),11(E)-Conjugated linoleic acid	FA	2	C18 H32 O2	C04056	ND	949720430.3	474427107.3
9S,13R-12-Oxophytodienoic acid	FA	3	C18 H28 O3	C22503	11093597.12	ND	ND
Lignoceric acid	FA	4	C24 H48 O2	C08320	ND	6010053.134	ND
NP-000124	FA	5	C12 H20 O4	R07639	24919437.39	17402186.69	125779138.5
NP-014287	FA	6	C18 H32 O3	C04056	95364186.59	ND	ND
Oleic acid	FA	7	C18 H34 O2	C00712	ND	157478259.7	133022646.4
Palmitic acid	FA	8	C16 H32 O2	C00249	9051707.756	ND	48606398.28
Stearic acid	FA	9	C18 H36 O2	C01530	ND	13854107.94	14661964.64
α-Eleostearic acid	FA	10	C18 H30 O2	C08315	ND	72026659.69	ND
(+/-)12(13)-DiHOME	FA	11	C18 H34 O4	C14829	8945915.686	ND	ND
(±)9(10)-DiHOME	FA	12	C18 H34 O4	C14828	20625997.82	ND	ND
(+/-)9,10-dihydroxy-12Z-octadecenoic acid	FA	13	C18 H34 O4	C14828	ND	7939755.346	15245858.74
(+/-)9-HpODE	FA	14	C18 H32 O4	C14827	ND	92734858.95	ND
(15Z)-9,12,13-Trihydroxy-15-octadecenoic acid	FA	15	C18 H34 O5	C14833	ND	ND	418519154.8
13(S)-HOTrE	FA	16	C18 H30 O3	C16316	59628543.33	47930111.86	73619011.22
1-Linoleoyl glycerol	FA	17	C21 H38 O4	C21529	ND	5078878844	191497838
9(Z),11(E),13(E)-Octadecatrienoic Acid methyl ester	FA	18	C19 H32 O2	C08315	ND	6484039.217	13298221.35
Caprolactam	FA	19	C6 H11 N O	C06593	29929134.74	17107152.41	32230921.64
Ethyl myristate	FA	20	C16 H32 O2	C06424	ND	43643226.8	ND
Monoolein	FA	21	C21 H40 O4	C01203	ND	1749267118	1741624757
Myristyl sulfate	FA	22	C14 H30 O4 S	C02593	16987620.56	16739038.48	16360213.8
(-)-Epicatechin	FL	1	C15 H14 O6	C09727	6829396.446	ND	ND
5,7-dihydroxy-2-(4-hydroxyphenyl)-6,8-bis(3,4,5-trihydroxyoxan-2-yl)-4H-chromen-4-one	FL	2	C25 H26 O13	C01477	86048952.59	63529437.21	29234496.12
Catechin	FL	3	C15 H14 O6	C06562	23057622.85	ND	ND
Corymboside	FL	4	C26 H28 O14	C20462	185531979	183660515.9	249198074.7
NP-018731	FL	5	C22 H22 O10	C10524	ND	ND	9176740.844
Tricin 5-O-β-D-glucoside	FL	6	C23 H24 O12	C10193	ND	ND	8684595.706

4-Methyl-5-thiazoleethanol	HC	1	C6 H9 N O S	C04294	37174599.75	55578113.49	72319434.36
4-Indolecarbaldehyde	IN	1	C9 H7 N O	C08493	74926857.55	12753175.27	45286840.34
5-Hydroxyindole-3-acetic acid	IN	2	C10 H9 N O3	C05635	32004419.61	ND	8656333.197
Indole-3-acetic acid	IN	3	C10 H9 N O2	C00954	265377347.5	129993308.6	245178075.9
trans-3-Indoleacrylic acid	IN	4	C11 H9 N O2	C21283	ND	115570436.5	694994237.7
2,2,6,6-Tetramethyl-1-piperidinol (TEMPO)	PI	1	C9 H19 N O	C01746	11351779.47	ND	10658648.44
2,5-Dihydroxybenzaldehyde	PP	1	C7 H6 O3	C05585	149230890.3	ND	ND
3-Methoxy-4-(3-methyl-2-buten-1-yl)-5-[(E)-2-phenylvinyl] phenol	PP	2	C20 H22 O2	C14679	119543400.8	109557804.5	68189126.69
5-methyl-4-{[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl] oxy}-2H-chromen-2-one	PP	3	C16 H18 O8	C03081	23751320.94	22110937.61	11484123.86
5-Methoxysalicylic acid	PP	4	C8 H8 O4	C00805	186917462.8	ND	ND
Caffeic acid	PP	5	C9 H8 O4	C01481	ND	ND	25652543.25
Catechol	PP	6	C6 H6 O2	C00090	104912341.9	ND	ND
Ferulic acid	PP	7	C10 H10 O4	C01494	38435882.28	23406537.84	55605004.99
Gentisic acid	PP	8	C7 H6 O4	C00628	285847069.3	19222575.16	ND
Pyrogallol	PP	9	C6 H6 O3	C01108	70033728.98	ND	80203343.38
Salicylamide	PP	10	C7 H7 N O2	C00805	ND	71922266.78	19637876.84
Salicylic acid	PP	11	C7 H6 O3	C00805	38686229.84	ND	ND
Vanillin	PP	12	C8 H8 O3	C00755	15050733.74	ND	31808225.14
2'-Deoxyadenosine	PU	1	C10 H13 N5 O3	C00559	13092132.96	ND	ND
2'-O-Methyladenosine	PU	2	C11 H15 N5 O4	C04779	ND	ND	21109467.92
Adenine	PU	3	C5 H5 N5	C00147	95793636.88	46011306.45	112994571
Adenosine	PU	4	C10 H13 N5 O3	C00212	317902086.2	589138541.7	526887466.6
Guanine	PU	5	C5 H5 N5 O	C00242	15199623.95	38502033.95	55598377.84
Guanosine	PU	6	C10 H13 N5 O5	C00387	ND	10267765.23	13718360.19
Olomoucine	PU	7	C15 H18 N6 O	C22439	11934662.48	12143992.69	5899377.027
Hypoxanthine	PU	8	C5 H4 N4 O	C00262	ND	16752145.25	12149285.49
Cytidine	PY	1	C9 H13 N3 O5	C00475	42999030.98	55606689.85	58306095.95
Cytosine	PY	2	C4 H5 N3 O	C00380	ND	23902463.76	18291977.83
Dihydrothymine	PY	3	C5 H8 N2 O2	C00906	ND	128722958.8	ND
Thiamine	PY	4	C12 H16 N4 O S	C00378	ND	36608625.73	23018141.09
Uridine	PY	5	C9 H12 N2 O6	C00299	ND	25344692.12	ND
2,4-Quinolinediol	QL	1	C9 H7 N O2	C16716	120463799.4	30902759.78	61444930.21
2-Hydroxyquinoline	QL	2	C9 H7 N O	C06338	25331378.06	ND	ND
6-Methylquinoline	QL	3	C10 H9 N	C06413	ND	ND	14572751
6-Methoxyquinoline N-oxide	QL	4	C10 H9 N O2	C04284	43981863.07	ND	ND
8-Hydroxyquinoline	QL	5	C9 H7 N O	D05321	25943578.73	ND	10963528.67
Kynurenic acid	QL	6	C10 H7 N O3	C01717	20710682.73	ND	114854823.8
Xanthurenic acid	QL	7	C10 H7 N O4	C02470	ND	ND	20287940.4
2-Aminooctadec-4-yne-1,3-diol	SL	1	C18 H35 N O2	C00319	11130894.37	380871517.3	242102985.7
D- (-)-Ribose	SU	1	C5 H10 O5	C00121	ND	104152081.3	ND
D- (+)-Glucose	SU	2	C6 H12 O6	C00031	43082689.95	29841087.45	ND
α-Lactose	SU	3	C12 H22 O11	C00243	33978152.92	33970639	6525563033

Bis(4-ethylbenzylidene) sorbitol	SU	4	C24 H30 O6	C00794	53843132.65	83480332.33	64041301.79
D- (-)-Mannitol	SU	5	C6 H14 O6	C00392	46009256.75	ND	33981589.16
Glucose 1-phosphate	SU	6	C6 H13 O9 P	C00103	ND	24489014.9	ND
L-Iditol	SU	7	C6 H14 O6	C01507	39518521.32	12535905.79	81592148.79
Maltotriose	SU	8	C18 H32 O16	C01835	7098999.185	11558622.12	ND
N-Acetyl-α-D-glucosamine	SU	9	C8 H15 N O6	C03878	22480756.18	ND	ND
NP-013538	SU	10	C12 H16 O8	C11918	23440534.52		17940150.68
α, α-Trehalose	SU	11	C12 H22 O11	C01083	2942317049	2176287471	81879559.42
6,18,19-Trihydroxytrachyloban-2-one	TP	1	C20 H30 O4	C06090	ND	ND	25061649.4
Citral	TP	2	C10 H16 O	C01499	ND	ND	7019539.655
NP-005196	TP	3	C15 H22 O5	C15971	ND	20281015.88	ND
Sibiricose A1	TP	4	C23 H32 O15	C17536	252745406.7	139663799.2	224133248.8
Ursolic acid	TP	5	C30 H48 O3	C08988	ND	ND	35927385.21
4-Pyridoxic acid	VM	1	C8 H9 N O4	C00847	40858940.92	31854986.21	ND
Nicotinamide	VM	2	C6 H6 N2 O	C00153	18144680.46	19344058.6	19634390.61
Nicotinic acid	VM	3	C6 H5 N O2	C00253	215738715.9	103617249.4	119400270.9
Pantothenic acid	VM	4	C9 H17 N O5	C00864	147313618.3	101102754.6	56978946.94

* ND-not detected; metabolites not available in KEGG database are denoted with the closely related KEGG compound ID of same pathway.