

Supplementary Material

• Supplementary Tables

Supplementary Table 1. Summary of Ingenuity Pathway Analysis (IPA) for top biological functions regulated by melatonin and its metabolites based on the data obtained from primary human epidermal keratinocytes. (0 – lack of activation, Z – score in IPA)

Compound	Categories	Diseases or Functions Annotation	P-value	Activation Z-score	# Molecules
Melatonin	Cancer, Dermatological Diseases and Conditions, Organismal Injury and Abnormalities	Cutaneous melanoma	4.3×10^{-21}	0	1016
	Cancer, Dermatological Diseases and Conditions, Organismal Injury and Abnormalities	Skin tumor	4.64×10^{-18}	1.29	1052
	Dermatological Diseases and Conditions, Organismal Injury and Abnormalities	Skin lesion	5.6×10^{-18}	-0.14	1058
	Cancer, Dermatological Diseases and Conditions, Organismal Injury and Abnormalities	Skin cancer	5.93×10^{-18}	0.39	1046
	Organismal Injury and Abnormalities, Reproductive System Disease	Nonobstructive azoospermia	3.49×10^{-13}	0	21
	Endocrine System Disorders, Gastrointestinal Disease, Metabolic Disease, Organismal Injury and Abnormalities	Diabetes mellitus	9.57×10^{-13}	-1.06	215
	Cancer, Dermatological Diseases and Conditions, Organismal Injury and Abnormalities	Skin squamous cell carcinoma	5.5×10^{-12}	0	159
	Cancer, Organismal Injury and Abnormalities	Melanoma	3.44×10^{-11}	0.79	1119
	Metabolic Disease, Organismal Injury and Abnormalities	Glucose metabolism disorder	2.09×10^{-10}	-0.67	247
	Cancer, Dermatological Diseases and Conditions, Organismal Injury and Abnormalities	Skin carcinoma	1.05×10^{-9}	0	229
	Cell-To-Cell Signaling and Interaction	Communication of cells	2.19×10^{-9}	-1.66	217
	Cardiovascular Disease, Organismal Injury and Abnormalities	Stenosis of artery	2.25×10^{-9}	0	31
	Organismal Injury and Abnormalities	Discomfort	3.23×10^{-9}	-0.01	73
	Cell-To-Cell Signaling and Interaction	Signal transduction	4.42×10^{-9}	0	199
	Organismal Injury and Abnormalities	Chronic pain	7.71×10^{-9}	0	31
	Respiratory Disease	Chronic respiratory disorder	1.11×10^{-8}	0.37	55
	Connective Tissue Disorders, Inflammatory Disease, Inflammatory Response, Organismal Injury and Abnormalities, Skeletal and Muscular Disorders	Osteoarthritis	1.15×10^{-8}	0	59
	Psychological Disorders	Drug dependence	2.11×10^{-8}	0	36
	Organismal Injury and Abnormalities	Non-cancer pain	2.91×10^{-8}	0	38
	Psychological Disorders	Alcoholism	3.15×10^{-8}	0	32
	Cardiovascular Disease, Organismal Injury and Abnormalities	Vaso-occlusion	3.78×10^{-8}	0.50	112
	Cardiovascular Disease	Occlusion of blood vessel	4.49×10^{-8}	0.46	110

	Gene Expression	Gene silencing	5.8×10^{-08}	0	25
	Gastrointestinal Disease	Nausea	6.37×10^{-08}	0	26
	Cardiovascular Disease, Organismal Injury and Abnormalities	Stenosis of aorta	7.15×10^{-08}	0	24
	Cancer, Organismal Injury and Abnormalities, Reproductive System Disease	Early stage invasive cervical squamous cell carcinoma	8.41×10^{-08}	0	11
	Cardiovascular Disease, Organismal Injury and Abnormalities	Infarction of heart	1.16×10^{-07}	-2.23	56
	Cardiovascular Disease, Organismal Injury and Abnormalities	Occlusion of artery	1.21×10^{-07}	0.10	107
	Neurological Disease, Psychological Disorders	Mania	1.7×10^{-07}	0	18
	Developmental Disorder, Hereditary Disorder, Ophthalmic Disease, Organismal Injury and Abnormalities	Recessive congenital stationary night blindness	1.94×10^{-07}	0	8
	Cell-To-Cell Signaling and Interaction, Nervous System Development and Function	Action potential of cells	2.08×10^{-07}	0.60	39
	Organismal Injury and Abnormalities	Backache	2.37×10^{-07}	0	23
	Cardiovascular Disease, Neurological Disease, Organismal Injury and Abnormalities, Psychological Disorders	Vascular dementia	2.78×10^{-07}	0	17
	Cardiovascular Disease, Organismal Injury and Abnormalities, Skeletal and Muscular Disorders	Myocardial infarction	2.9×10^{-07}	-1.80	54
	Cardiovascular Disease, Organismal Injury and Abnormalities	Acute coronary syndrome	3.2×10^{-07}	0	40
	Gastrointestinal Disease	Vomiting	3.63×10^{-07}	0	27
	Cardiovascular Disease, Organismal Injury and Abnormalities	Ischemia of heart	3.71×10^{-07}	0	46
	Developmental Disorder, Hereditary Disorder, Ophthalmic Disease, Organismal Injury and Abnormalities	Congenital stationary night blindness	4.27×10^{-07}	0	9
	Neurological Disease, Organismal Injury and Abnormalities	Subarachnoid hemorrhage	4.35×10^{-07}	0	20
	Cell-To-Cell Signaling and Interaction	Activation of cells	4.73×10^{-07}	0.04	183
	Cardiovascular Disease, Organismal Injury and Abnormalities	Infarction	5.89×10^{-07}	-1.96	80
	Cardiovascular Disease, Organismal Injury and Abnormalities	Disorder of coronary artery	6.36×10^{-07}	1.97	65
6(OH)Mel	Cell Signaling, Molecular Transport, Vitamin and Mineral Metabolism	Mobilization of Ca^{2+}	7.55×10^{-07}	0.66	66
	Inflammatory Response, Respiratory Disease	Inflammation of respiratory system component	8.61×10^{-07}	-0.30	118
	Cancer, Dermatological Diseases and Conditions, Organismal Injury and Abnormalities	Cutaneous melanoma	8.62×10^{-21}	0	1012
	Cancer, Dermatological Diseases and Conditions, Organismal Injury and Abnormalities	Skin cancer	1.07×10^{-17}	1.17	1042
	Dermatological Diseases and Conditions, Organismal Injury and Abnormalities	Skin lesion	2.37×10^{-17}	-0.53	1052
	Cancer, Dermatological Diseases and Conditions, Organismal Injury and Abnormalities	Skin tumor	3.04×10^{-17}	0.84	1045

Cancer, Dermatological Diseases and Conditions, Organismal Injury and Abnormalities	Skin squamous cell carcinoma	1.46×10^{-14}	0	167
Cancer, Dermatological Diseases and Conditions, Organismal Injury and Abnormalities	Non-melanoma skin cancer	2.15×10^{-14}	0	169
Cancer, Organismal Injury and Abnormalities	Melanoma	1.49×10^{-12}	0.28	1125
Cancer, Dermatological Diseases and Conditions, Organismal Injury and Abnormalities	Skin carcinoma	3.69×10^{-11}	0	235
Molecular Transport	Quantity of metal	3.08×10^{-10}	1.88	109
Molecular Transport	Quantity of metal ion	3.11×10^{-10}	1.95	98
Organismal Injury and Abnormalities	Discomfort	4.77×10^{-10}	-0.41	75
Cell-To-Cell Signaling and Interaction	Communication of cells	1.71×10^{-09}	-0.46	217
Organismal Injury and Abnormalities, Reproductive System Disease	Nonobstructive azoospermia	6.37×10^{-09}	0	17
Cell-To-Cell Signaling and Interaction	Signal transduction	9.67×10^{-09}	0	197
Cell Signaling, Molecular Transport, Vitamin and Mineral Metabolism	Quantity of Ca^{2+}	1.23×10^{-08}	1.25	85
Molecular Transport	Transport of ion	1.87×10^{-08}	0.66	113
Molecular Transport	Transport of cation	2.58×10^{-08}	0.69	86
Cell-To-Cell Signaling and Interaction, Nervous System Development and Function	Neurotransmission	2.67×10^{-08}	0.81	93
Organismal Injury and Abnormalities, Psychological Disorders	Anxiety Disorders	4.25×10^{-08}	0	35
Endocrine System Disorders, Gastrointestinal Disease, Metabolic Disease, Organismal Injury and Abnormalities	Diabetes mellitus	6.1×10^{-08}	-1.64	194
Psychological Disorders	Alcoholism	1.09×10^{-07}	0	31
Endocrine System Disorders, Gastrointestinal Disease, Immunological Disease, Metabolic Disease, Organismal Injury and Abnormalities	Insulin-dependent diabetes mellitus	1.6×10^{-07}	-1.89	86
Cardiovascular Disease, Neurological Disease, Organismal Injury and Abnormalities	Stroke	2.03×10^{-07}	1.09	58
Psychological Disorders	Drug dependence	2.23×10^{-07}	0	34
Cell Morphology, Cellular Function and Maintenance	Depolarization of cells	2.51×10^{-07}	-2.63	18
Nucleic Acid Metabolism, Small Molecule Biochemistry	Biosynthesis of cyclic nucleotides	2.91×10^{-07}	0.92	46
Cardiovascular Disease, Organismal Injury and Abnormalities	Stenosis of aorta	3.1×10^{-07}	0	23
Cellular Function and Maintenance	Ion homeostasis of cells	3.82×10^{-07}	-0.51	116
Cardiovascular Disease, Organismal Injury and Abnormalities	Stenosis of artery	5.74×10^{-07}	0	27
Behavior	Emotional behavior	6.13×10^{-07}	0.92	64
Organismal Injury and Abnormalities	Non-cancer pain	8.32×10^{-07}	0	35
Molecular Transport	Transport of inorganic cation	1.03×10^{-06}	0.02	74

	Respiratory Disease	Sleep disordered breathing	1.76×10^{-06}	0	24
	Metabolic Disease, Organismal Injury and Abnormalities	Glucose metabolism disorder	2.57×10^{-06}	-1.97	225
	Organismal Injury and Abnormalities	Progressive fibrosis	2.67×10^{-06}	0	10
	Connective Tissue Disorders, Organismal Injury and Abnormalities, Respiratory Disease	Progressive interstitial lung disease	2.67×10^{-06}	0	10
	Cellular Function and Maintenance, Molecular Transport	Flux of ion	2.75×10^{-06}	-0.41	68
	Connective Tissue Disorders, Inflammatory Disease, Inflammatory Response, Organismal Injury and Abnormalities, Respiratory Disease	Slowly progressive idiopathic pulmonary fibrosis	2.83×10^{-06}	0	8
	Cardiovascular Disease, Organismal Injury and Abnormalities	Aortic occlusive disease	3.35×10^{-06}	-1.38	30
	Cell Signaling, Nucleic Acid Metabolism, Small Molecule Biochemistry	Synthesis of cyclic AMP	3.69×10^{-06}	1.64	40
	Cellular Function and Maintenance, Molecular Transport	Flux of cation	3.83×10^{-06}	-0.79	65
	Cell-To-Cell Signaling and Interaction, Nervous System Development and Function	Action potential of cells	4.32×10^{-06}	0.11	36
	Gastrointestinal Disease	Vomiting	4.44×10^{-06}	0	25
	Cellular Function and Maintenance, Molecular Transport	Flux of inorganic cation	4.59×10^{-06}	-0.89	64
AFMK	Cancer, Dermatological Diseases and Conditions, Organismal Injury and Abnormalities	Cutaneous melanoma	2.06×10^{-23}	0	1059
	Dermatological Diseases and Conditions, Organismal Injury and Abnormalities	Skin lesion	8.72×10^{-22}	0.20	1111
	Cancer, Dermatological Diseases and Conditions, Organismal Injury and Abnormalities	Skin tumor	1.03×10^{-21}	0.46	1104
	Cancer, Dermatological Diseases and Conditions, Organismal Injury and Abnormalities	Skin cancer	1.24×10^{-21}	-0.15	1098
	Cancer, Dermatological Diseases and Conditions, Organismal Injury and Abnormalities	Skin squamous cell carcinoma	5.19×10^{-16}	0	176
	Cancer, Organismal Injury and Abnormalities	Melanoma	9.45×10^{-16}	1.09	1184
	Cancer, Dermatological Diseases and Conditions, Organismal Injury and Abnormalities	Skin carcinoma	4.42×10^{-15}	0	258
	Endocrine System Disorders, Gastrointestinal Disease, Metabolic Disease, Organismal Injury and Abnormalities	Diabetes mellitus	1.56×10^{-12}	-1.24	220
	Metabolic Disease, Organismal Injury and Abnormalities	Glucose metabolism disorder	4.72×10^{-11}	-0.78	257
	Organismal Injury and Abnormalities, Reproductive System Disease	Nonobstructive azoospermia	1.13×10^{-10}	0	19
	Molecular Transport	Transport of ion	7.72×10^{-10}	-0.21	121
	Cellular Function and Maintenance	Ion homeostasis of cells	1.06×10^{-09}	-0.15	129
	Organismal Injury and Abnormalities	Discomfort	2.56×10^{-09}	-0.43	75
	Molecular Transport	Transport of cation	3.46×10^{-09}	-0.27	91

	Respiratory Disease	Chronic respiratory disorder	1.4×10^{-08}	1.35	56
	Organismal Injury and Abnormalities, Respiratory Disease	Chronic obstructive pulmonary disease	2.06×10^{-08}	1.35	48
	Molecular Transport	Transport of K^+	5.21×10^{-08}	-0.15	30
	Molecular Transport	Transport of inorganic cation	1.26×10^{-07}	-0.59	79
	Cellular Function and Maintenance, Molecular Transport	Flux of ion	1.38×10^{-07}	0.007	74
	Cellular Function and Maintenance, Molecular Transport	Flux of inorganic cation	2.04×10^{-07}	-0.53	70
	Cell Signaling, Molecular Transport, Vitamin and Mineral Metabolism	Mobilization of Ca^{2+}	2.71×10^{-07}	-0.27	69
	Molecular Transport	Transport of monovalent inorganic cation	4.09×10^{-07}	-0.15	49
	Nervous System Development and Function	Olfactory response	4.41×10^{-07}	0	18
	Cellular Movement, Hematological System Development and Function, Immune Cell Trafficking, Inflammatory Response	Chemotaxis of antigen presenting cells	4.56×10^{-07}	0.28	40
	Inflammatory Response, Respiratory Disease	Inflammation of respiratory system component	5.71×10^{-07}	-0.35	122
	Molecular Transport	Transport of metal ion	6.42×10^{-07}	-0.37	71
	Nervous System Development and Function	Olfaction	6.58×10^{-07}	-0.43	24
	Molecular Transport	Quantity of metal	9.31×10^{-07}	-0.54	100
	Molecular Transport	Quantity of metal ion	1.16×10^{-06}	-0.34	89
	Cellular Movement, Hematological System Development and Function, Immune Cell Trafficking, Inflammatory Response	Chemotaxis of phagocytes	1.43×10^{-06}	-0.14	66
	Inflammatory Response, Organismal Injury and Abnormalities	Inflammation of organ	1.56×10^{-06}	-0.04	247
	Cancer, Organismal Injury and Abnormalities, Reproductive System Disease	Early stage invasive cervical squamous cell carcinoma	1.73×10^{-06}	0	10
	Inflammatory Response	Inflammation of body cavity	1.92×10^{-06}	-0.25	186
	Gene Expression	Gene silencing	1.96×10^{-06}	0	23
	Cell Signaling, Cellular Function and Maintenance, Molecular Transport, Vitamin and Mineral Metabolism	Flux of Ca^{2+}	1.97×10^{-06}	-0.27	64
	Cardiovascular Disease, Organismal Injury and Abnormalities	Ischemia of heart	2.45×10^{-06}	0	45
	Connective Tissue Disorders, Organismal Injury and Abnormalities, Respiratory Disease	Progressive interstitial lung disease	3.76×10^{-06}	0	10

	Connective Tissue Disorders, Inflammatory Disease, Inflammatory Response, Organismal Injury and Abnormalities, Respiratory Disease	Slowly progressive idiopathic pulmonary fibrosis	3.76×10^{-06}	0	8
	Organismal Injury and Abnormalities	Stenosis of vasculature	3.92×10^{-06}	0.93	27
	Inflammatory Response	Inflammation of absolute anatomical region	3.94×10^{-06}	-0.66	211
	Cardiovascular Disease, Organismal Injury and Abnormalities	Vaso-occlusion	3.96×10^{-06}	0.26	107
	Cell-To-Cell Signaling and Interaction	Communication of cells	4.11×10^{-06}	-0.65	206
	Cardiovascular Disease, Organismal Injury and Abnormalities	Stenosis of artery	4.12×10^{-06}	1.40	26
	Inflammatory Disease, Inflammatory Response, Organismal Injury and Abnormalities, Respiratory Disease	Inflammation of lung	4.28×10^{-06}	-0.43	86

- **Supplementary Figures**

Supplementary Figure 1. Volcano Plot diagram of differentially expressed genes for melatonin vs EtOH (A), 6-hydroxymelatonin vs EtOH (B), and AFMK vs EtOH (C).

