

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 | |

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|-----------------|--|---|------------------------|-------|------|
| | 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 |
| | 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 |
| 6(OH)Mel | 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 |

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|---|-------------------------------------|------------------------|-------|------|
| 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 |

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|-------------|--|--|------------------------|-------|------|
| | 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 |

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|--|---|------------------------|-------|-----|
| 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 |

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|--|--|------------------------|-------|-----|
| 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).

