Table S1. Primers sequences used for qRT-PCR.

Gene	Forward primer sequence (5'-3')	Reverse primer sequence (5'-3')
β-actin	CTATGCTCTCCCTCACGCCA	TCACGCACGATTTCCCTCTC
IL-1β	TGTGTTTTCCTCCTTGCCTCTGAT	TGCTGCCTAATGTCCCCTTGAAT

Table S2. The relative ratios of identified compounds in areca leaves in response to exogenous melatonin treatment. Data are expressed as mean ± SD (n = 3). The data statistics analysis was performed using one-way ANOVA with Bonferroni correction. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, and ****$P < 0.0001$: 20 or 200 μM melatonin treatment *vs* 0 μM melatonin treatment.

Compound Name	Formula	Mass	mzmed	rtmed (min)	0 μM Melatonin	20 μM Melatonin	200 μM Melatonin
Cucurbitacin B	$C_{32}H_{46}O_8$	558.7028	559.7273	0.8761	1.0000 ± 0.2194	106.9118 ± 3.6107****	71.6253 ±8.3717****
Ganoderic acid C1	$C_{30}H_{42}O_7$	514.6503	515.6310	0.7666	1.0000 ± 0.1544	72.7993 ± 1.0305****	55.8475 ± 12.4259***
Fluocinolone Acetonide	$C_{24}H_{30}F_2O_6$	452.4882	453.4899	3.2665	1.0000 ± 0.1081	44.6458 ± 1.8373****	23.9521 ± 7.9564**
Citronellyl beta-sophoroside	$C_{22}H_{40}O_{11}$	480.5464	481.5625	3.8608	1.0000 ± 0.1365	34.4771 ± 1.7565****	17.6708 ± 5.5666**
Deferoxamine	$C_{25}H_{48}N_6O_8$	560.6840	561.6798	4.4605	1.0000 ± 0.2242	28.8760 ± 1.9555***	14.9028 ± 5.0001**
Hexaethylene glycol	$C_{12}H_{26}O_7$	282.3306	305.3374	1.9489	1.0000 ± 0.1968	17.6805 ± 1.6780***	10.1492 ± 2.7769**
Pyrohyperforin	$C_{35}H_{50}O_4$	534.7691	557.7614	0.7303	1.0000 ± 0.9399	9.7319 ± 0.4411***	7.4547 ± 1.9964**
alpha-Terpineol propanoate	$C_{13}H_{22}O_2$	210.3126	211.3193	1.2316	1.0000 ± 0.1989	4.5469 ± 0.3824***	2.1964 ± 0.6396*
5'-Methylthioadenosine	$C_{11}H_{15}N_5O_3S$	297.3340	298.3268	1.3424	1.0000 ± 0.2029	3.6110 ± 0.3249**	2.5868 ± 1.0810
N1-Methyl-4-pyridone-3-carboxamide	$C_7H_8N_2O_2$	152.1506	153.1663	5.6500	1.0000 ± 0.1186	3.4053 ± 0.1685**	4.1770 ± 0.7367***
Ethosuximide	$C_7H_{11}NO_2$	141.1677	142.1762	6.7928	1.0000 ± 0.1223	3.3181 ± 0.1348**	3.7796 ± 1.3321*
1-Aminocyclohexanecarboxylic acid	C7H13NO2	143.0946	144.1018	6.6700	1.0000 ± 0.1229	3.2801 ± 0.1860**	2.6202 ± 0.6807**
Citrusinine II	$C_{15}H_{13}NO_5$	287.2674	288.2768	0.8576	1.0000 ± 0.0648	3.2766 ± 0.5009**	3.1282 ± 0.9593*
Vitexin	$C_{21}H_{20}O_{10}$	432.1056	433.1135	1.1504	1.0000 ± 0.2230	3.1122 ± 0.2529***	0.3220 ± 0.1472*
1,2-Diacylglycerol-Bile-PC-pool	$C_7H_8N_2O$	136.1512	137.1711	6.2773	1.0000 ± 0.1295	3.0505 ± 0.0218****	3.1085 ± 0.2129****
PE(18:3(6Z,9Z,12Z)/16:0)	$C_{39}H_{72}NO_8P$	713.4996	714.5067	5.0108	1.0000 ± 0.1499	2.9283 ± 0.1997****	1.9229 ± 0.2654**
(2Z)-2-[(2-hydroxyphenyl)methylidene]octanal	$C_{15}H_{20}O_2$	232.3230	255.3363	0.9352	1.0000 ± 0.3898	2.1808 ± 0.2910*	0.4313 ± 0.3740
Isopeonidin 3-glucoside	$C_{22}H_{23}O_{11}$	463.4114	463.4239	1.1515	1.0000 ± 0.2870	1.8458 ± 0.2382*	0.2533 ± 0.1577*
PG(16:1(9Z)/18:3(9Z,12Z,15Z))	$C_{40}H_{71}O_{10}P$	742.9595	765.9666	2.2542	1.0000 ± 0.0431	1.4286 ± 0.1021**	1.6428 ± 0.0868***

p-Aminobenzoic acid	$C_7H_7NO_2$	137.1360	138.1449	6.0704	1.0000 ± 0.0709	1.2614 ± 0.0252*	1.3586 ± 0.2384
Pipemidic acid	$C_{14}H_{17}N_5O_3$	303.3165	304.3191	1.3792	1.0000 ± 0.0414	1.1746 ± 0.0067**	0.1640 ± 0.0619***
(1S,16R)-5,6,7,11-tetrahydroxy-8,8,10,12,16 -pentamethyl-3-[1-(2-methyl-1,3-thiazol-4-yl) prop-1-en-2-yl]-17-oxa-4-azabicyclo[14.1.0] heptadec-4-en-9-one	$C_{27}H_{42}N_2O_6S$	522.2764	523.2826	0.9021	1.0000 ± 0.1725	1.1667 ± 0.1260	0.5506 ± 0.0777*
Labetalol	$C_{19}H_{24}N_2O_3$	328.4055	329.4062	0.9237	1.0000 ± 0.1674	1.0987 ± 0.1153	0.4579 ± 0.1418*
L-Acetylcarnitine	$C_9H_{17}NO_4$	203.2380	204.2231	6.6657	1.0000 ± 0.1570	1.0782 ± 0.0718	0.4624 ± 0.2085*
3-Methoxyanthranilate	$C_8H_9NO_3$	167.1620	168.1654	0.9687	1.0000 ± 0.0811	1.0567 ± 0.0102	0.6808 ± 0.1830*
Guvacoline/Arecaidine	$C_7H_{11}NO_2$	141.1677	142.1870	2.8365	1.0000 ± 0.0677	1.0456 ± 0.0279	0.9617 ± 0.1751
1-Phenylethylamine（HMDB、Metlin)	$C_8H_{11}N$	121.1796	122.1961	4.4503	1.0000 ± 0.1449	0.9041 ± 0.0698	0.4566 ± 0.1063**
Proline betaine	$C_7H_{13}NO_2$	143.1836	144.1718	6.0580	1.0000 ± 0.0995	0.8738 ± 0.0637	0.6847 ± 0.0409**
2,5-Dimethyl-1H-pyrrole	C_6H_9N	95.1424	96.1409	0.9149	1.0000 ± 0.1576	0.7914 ± 0.0739	0.3615 ± 0.0776**
Ethyl 2-pyrrolecarboxylate	$C_7H_9NO_2$	139.1519	140.1505	1.4755	1.0000 ± 0.2348	0.7539 ± 0.0906	1.9025 ± 0.5057*
D-Glutamine	$C_5H_{10}N_2O_3$	146.1445	147.1465	6.6102	1.0000 ± 0.2573	0.7065 ± 0.1050	0.0787 ± 0.0647**
Cohibin D	$C_{37}H_{68}O_4$	576.9334	577.9200	2.2624	1.0000 ± 0.1614	0.4626 ± 0.0120**	0.6373 ± 0.0775*
Harmaline	$C_{13}H_{14}N_2O$	214.2631	215.2579	4.8653	1.0000 ± 1.4377	0.1925 ± 0.2361	4.8572 ± 1.6056*

Table S3. The relative ratios of identified compounds in areca nuts in response to exogenous melatonin treatment. Data are expressed as mean ± SD (n = 3). LC-MS raw data files generated from the analyses were converted to mzData format using DA reprocessor (Agilent) with the threshold of the peak height set at 5000 counts. Peak finding, filtering and alignment were subsequently carried out using open-source R-Package XCMS. MetaboAnalyst 3.0 was then employed for the analysis of the data. Metabolites were identified based on their mass spectral data using HMDB (http://www.hmdb.ca) or Metlin (https://metlin.scripps.edu) database. The data statistics analysis was performed using one-way ANOVA with Bonferroni correction. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, and ****$P < 0.0001$: 20 or 200 μM melatonin treatment *vs* 0 μM melatonin treatment.

Compound Name	Formula	Mass	mzmed	rtmed (min)	0 μM Melatonin	20 μM Melatonin	200 μM Melatonin
Homoarecoline	$C_9H_{15}NO_2$	169.2209	170.2175	1.1930	1.0000 ± 0.0799	11.9064 ± 0.7576****	11.0625 ± 0.7313****
Arecoline	$C_8H_{13}NO_2$	155.0946	156.1020	2.7279	1.0000 ± 0.1465	10.4394 ± 1.0032****	5.9690 ± 0.4385***
Adenine	$C_5H_5N_5$	135.1267	136.1315	1.9373	1.0000 ± 0.4308	7.5523 ± 0.6466****	5.8742 ± 0.1346****
Adenosine	$C_{10}H_{13}N_5O_4$	267.0968	268.1040	1.9345	1.0000 ± 0.3970	6.5209 ± 0.6329****	5.2167 ± 0.1088****
Monocrotaline	$C_{16}H_{23}NO_6$	325.3569	343.3466	6.0387	1.0000 ± 0.4436	4.8195 ± 0.5607****	0.2332 ± 0.0615
2-Methyl-2-pentenoic acid	$C_6H_{10}O_2$	114.1424	132.1019	5.6852	1.0000 ± 0.1413	3.1287 ± 0.1225****	2.0923 ± 0.0604****
2-Furanmethanol	$C_5H_6O_2$	98.0999	116.0907	5.9754	1.0000 ± 0.2491	2.6833 ± 0.2071***	1.9507 ± 0.0779**
Benzyl beta-primeveroside	$C_{18}H_{26}O_{10}$	402.3930	425.3819	2.0334	1.0000 ± 0.3026	2.5150 ± 1.2273	0.4790 ± 0.0468*
1-(Hydroxymethyl)-5,5-dimethyl-2,4-imidazolidinedione	$C_6H_{10}N_2O_3$	158.1552	159.1767	6.5654	1.0000 ± 0.4675	2.0828 ± 0.4225*	2.6295 ± 0.2949**
Glucoconringiin	$C_{11}H_{21}NO_{10}S_2$	391.4150	392.4081	6.6373	1.0000 ± 0.2685	2.0178 ± 0.6358	2.8638 ± 0.1986**
Guvacine	$C_6H_9NO_2$	127.0633	128.0703	6.5220	1.0000 ± 0.1293	1.6169 ± 0.0949***	1.7221 ± 0.0359***
2-Methyl-5-propyloxazole	$C_7H_{11}NO$	125.1683	126.1710	6.5184	1.0000 ± 0.0705	1.2474 ± 0.0373**	1.3010 ± 0.0337***

trans-Isoasarone	$C_{12}H_{16}O_3$	208.2536	209.2673	1.8520	1.0000 ± 0.3317	1.1889 ± 0.2475	3.5138 ± 0.6131**
Niazirin	$C_{14}H_{17}NO_5$	279.2885	297.2759	6.6255	1.0000 ± 0.0691	1.1151 ± 0.0413	2.0835 ± 0.0585***
2-Methyl-5-propyloxazole	$C_7H_{11}NO$	125.1683	126.1712	1.7099	1.0000 ± 0.1428	1.0126 ± 0.0631	0.4211 ± 0.0346***
(S)-Homostachydrine	$C_8H_{15}NO_2$	157.1103	158.1176	1.7094	1.0000 ± 0.1209	1.0101 ± 0.0625	0.4059 ± 0.0190***
N1-Methyl-2-pyridone-5-carboxamide	$C_7H_8N_2O_2$	152.1506	153.1658	5.6713	1.0000 ± 0.1004	0.9306 ± 0.0184	1.7375 ± 0.0520***
Guvacoline/Arecaidine	$C_7H_{11}NO_2$	141.1677	142.1689	6.6229	1.0000 ± 0.0667	0.9168 ± 0.0344	1.3812 ± 0.0223***
D-1-Piperideine-2-carboxylic acid	$C_6H_9NO_2$	127.1412	113.1493	1.2587	1.0000 ± 0.0432	0.8855 ± 0.0340*	0.8135 ± 0.0331**
4-Aminophenol	C_6H_7NO	109.1259	110.1300	2.9381	1.0000 ± 0.1101	0.8366 ± 0.0467	0.7846 ± 0.0191*
Furanone A	$C_4H_4O_2$	84.0740	102.0546	6.4178	1.0000 ± 0.2633	0.8090 ± 0.1622	2.2514 ± 0.2279**
5-hydroxy-7-methoxy-3-(2,3,4-trihydroxyphenyl)-4H-chromen-4-one	$C_{16}H_{12}O_7$	316.2650	317.2658	2.0994	1.0000 ± 0.0381	0.7826 ± 0.0544**	0.7039 ± 0.0375***
PE-NMe(16:0/22:4(7Z,10Z,13Z,16Z))	$C_{44}H_{80}NO_8P$	782.0970	804.0922	5.1883	1.0000 ± 0.5301	0.7665 ± 0.2049	0.1919 ± 0.1094*
L-Glutamate	$C_5H_9NO_4$	147.0532	148.0603	6.4334	1.0000 ± 0.0373	0.7244 ± 0.0660*	1.6843 ± 0.1678*
2'-Hydroxyacetanilide	$C_8H_9NO_2$	151.1626	152.1710	5.3676	1.0000 ± 0.1652	0.5959 ± 0.0320**	0.4323 ± 0.0050**
Sulfametopyrazine	$C_{11}H_{12}N_4O_3S$	280.3030	298.2966	1.3379	1.0000 ± 0.2584	0.3321 ± 0.0456**	0.4419 ± 0.0395*
PS(14:1(9Z)/15:0)	$C_{35}H_{66}NO_{10}P$	691.8840	709.8787	1.5040	1.0000 ± 0.2318	0.3040 ± 0.0936**	0.3297 ± 0.0252**
Cohibin D	$C_{37}H_{68}O_4$	576.9334	577.9189	1.5095	1.0000 ± 0.4295	0.2836 ± 0.2541	0.0707 ± 0.0232*

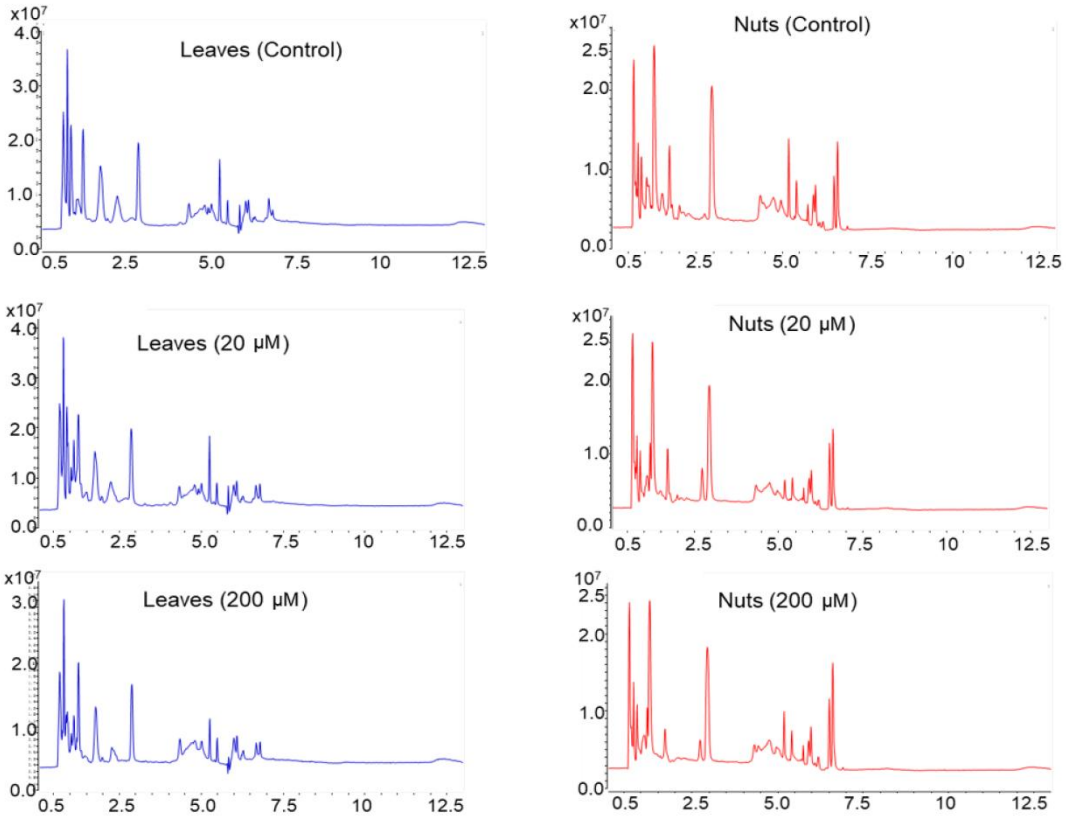

Fig. S1 Total ion chromatograms of leaves and nuts of areca. Areca was treated with or without 20 μM or 200 μM melatonin, respectively, and metabolites were extracted using 70% methanol dilution with deionized water. Metabolites were determined using UPLC-Q/TOF-MS. The total ions were counted within 12.5 min.

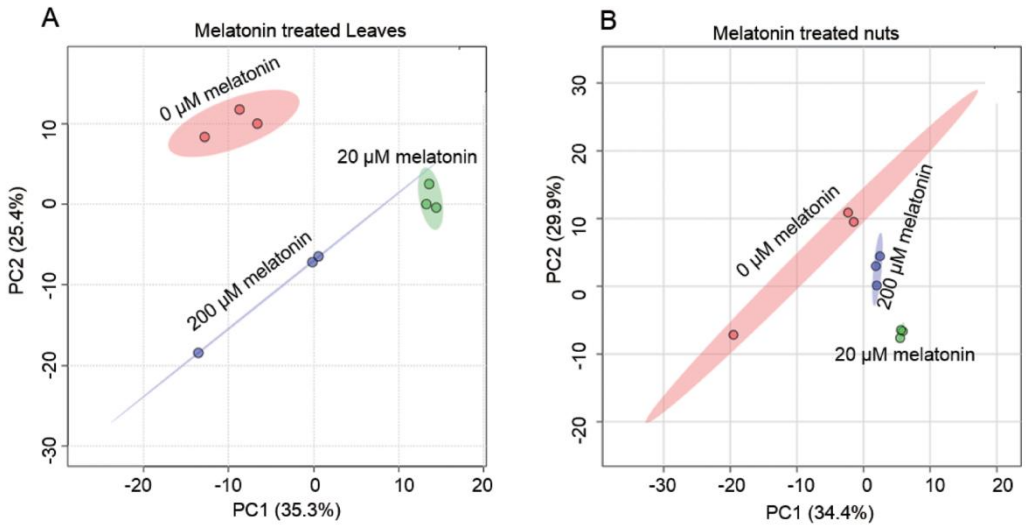

Fig. S2 Principal component analysis (PCA) of identified ions in different concentration of melatonin treated samples. (A) PCA of identified ions in 0, 20, 200 µM melatonin treated leaves of areca. (B) PCA of identified ions in 0, 20, 200 µM melatonin treated nuts of areca.

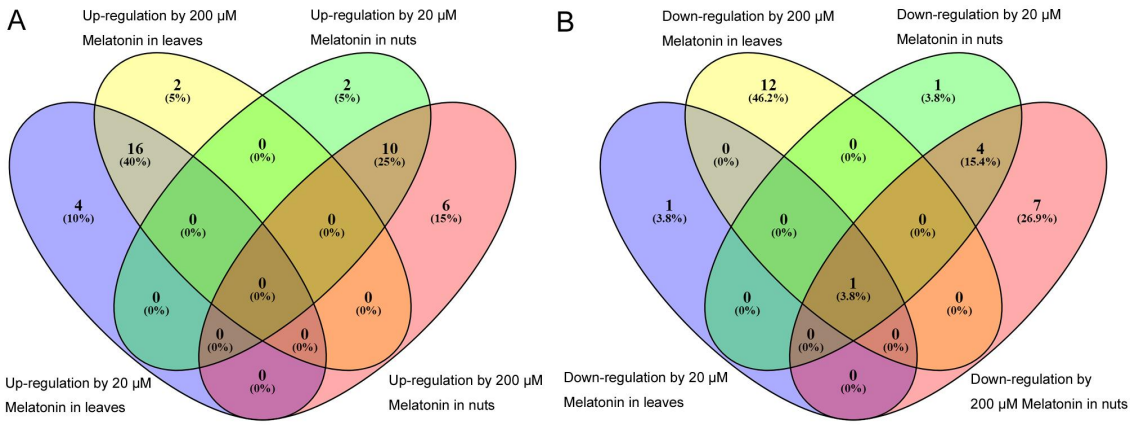

Fig. S3 The significantly changed metabolites in leaves or nuts of areca by different concentrations of melatonin. (A) Venn diagrams show the numbers of up-regulated metabolites in leaves or nuts by 20 μM or 200 μM melatonin. (B) Venn diagrams identify the number of down-regulated metabolites in leaves or nuts by 20 μM or 200 μM melatonin.

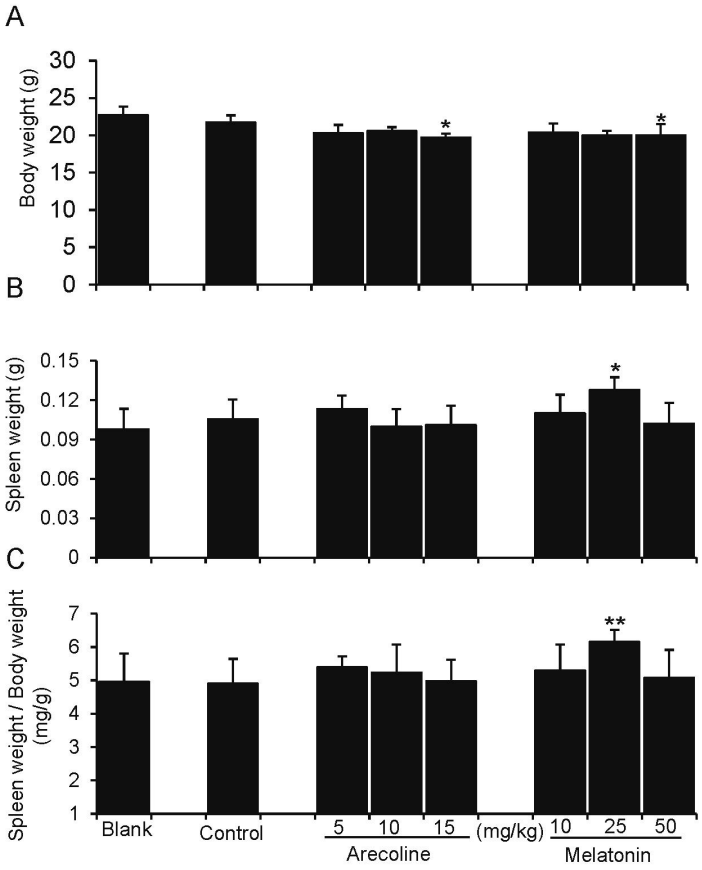

Fig. S4 Measurement of mice immune phenotype. The body weight (A), spleen weight (B), and spleen index (C) were measured. Results are expressed as mean ± SD (n = 7). The mice were pretreated with or without different concentration of arecoline or melatonin for 3 weeks. After the treatment period, mice were intraperitoneally treated with or without lipopolysaccharide (LPS) for 4 h before being killed. The statistics analysis was performed using one-way ANOVA with Bonferroni correction. *$P < 0.05$ and **$P < 0.01$: arecoline or melatonin treatment *vs* control group.

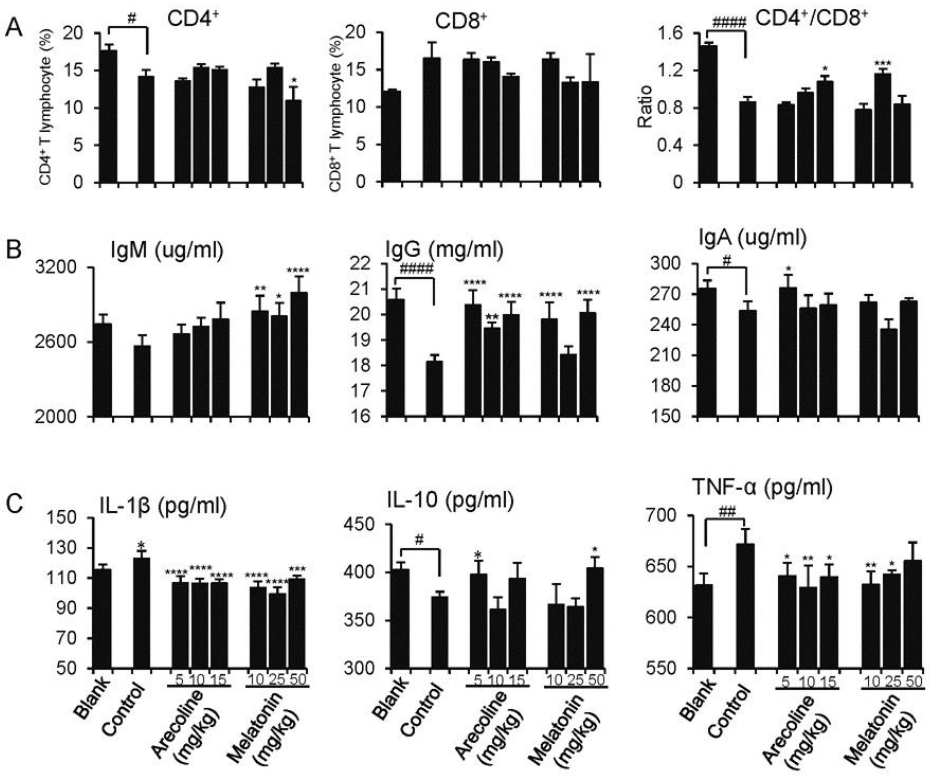

Fig. S5 Measurement of immune parameters. (A) After LPS treatment, $CD4^+$ and $CD8^+$ T lymphocytes in spleen were detected using Flow Cytometer with relative antibodies. (B) The levels of immune globulins (IgM, IgG, and Ig A) in plasma were determined using ELISA kits. (C) The content of inflammatory factors including IL-1β, TNF-α, and IL-10 in plasma were measured using ELISA kits. Results are expressed as mean ± SD (n = 5). The statistics analysis was performed using one-way ANOVA with Bonferroni correction. $^*P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$: arecoline or melatonin treatment *vs* control group; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, and $^{\#\#\#}P < 0.001$: blank group *vs* control group.

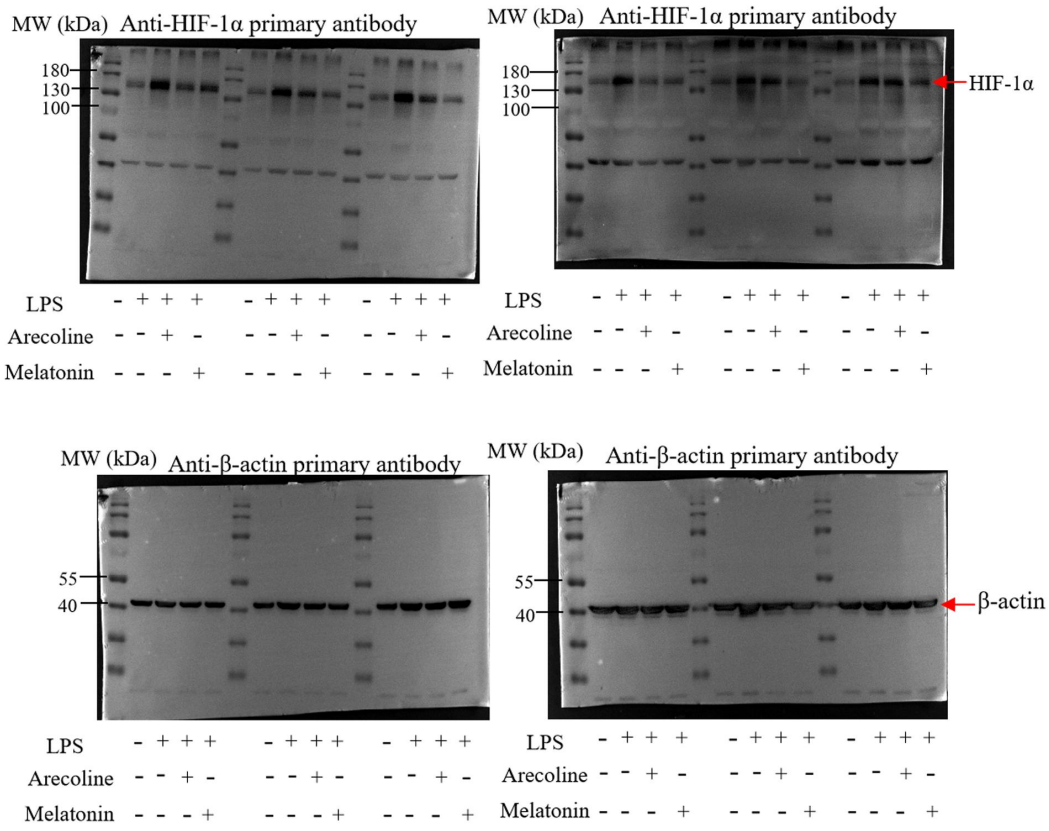

Fig. S6 The full blots of the repeated experiment of Fig. 7B. RAW 264.7 macrophages were cultured in DMEM (containing 10% heat-inactivated FBS and 1% (v/v) penicillin/streptomycin) at 37°C with 95% humidity and 5% CO_2. RAW 264.7 macrophages were treated with LPS (1 μg mL^{-1}) for 24 h to set up the inflammation model (control). To check the anti-inflammatory effects of melatonin and arecoline, RAW 264.7 cells were treated with melatonin (40 μM) or arecoline (40 μM) along with LPS stimulation.