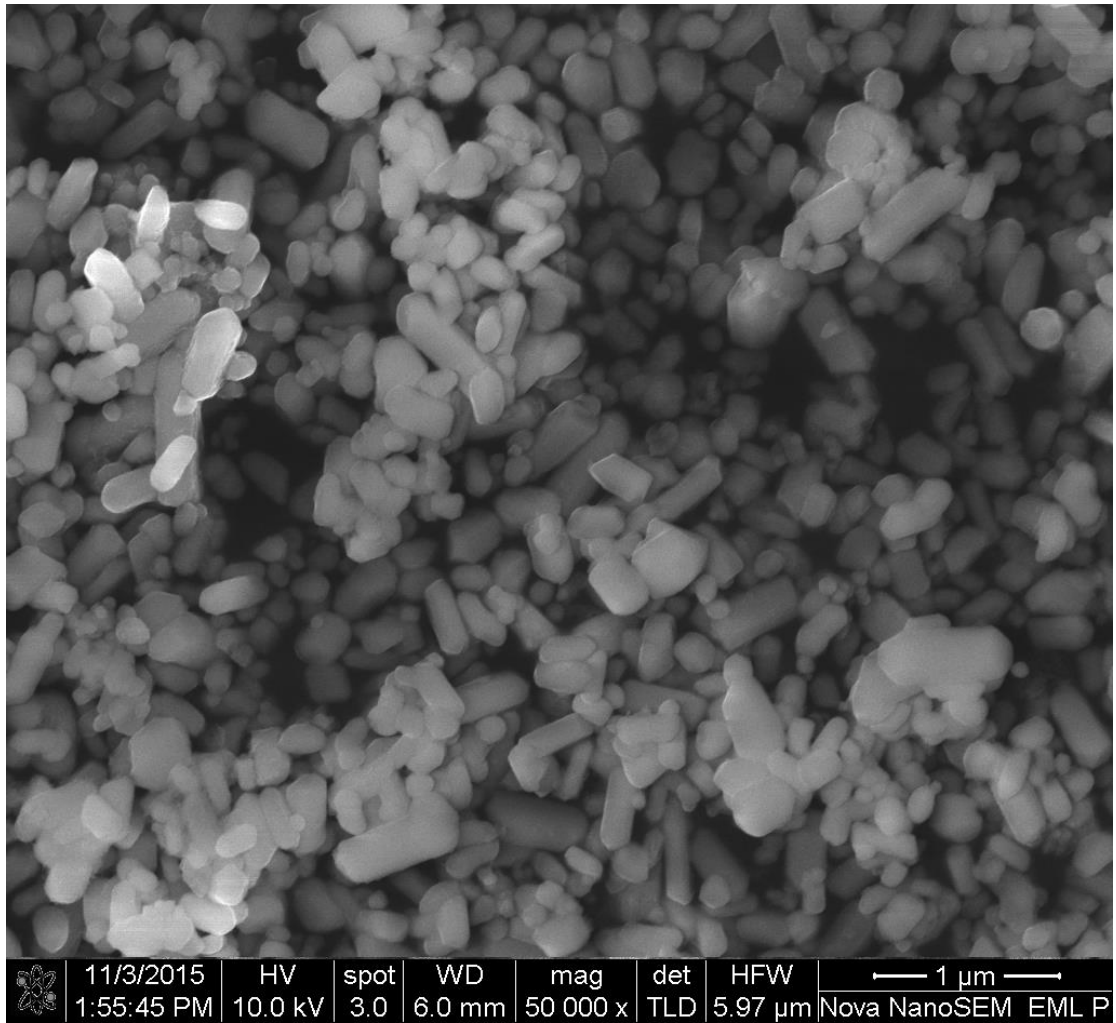


**Figure S1.** The network diagram of the pathway enrichment analysis. Each node represents a metabolic pathway in the database. If 25% or more of the metabolites are shared between the two metabolic pathways, then there will be a gray line connecting the two metabolic pathways. The thicker the connecting line, the larger the proportion of shared metabolites. The color of the node reflects the P value of the pathway enrichment analysis. The smaller P value, the darker color of the node. The size of the node reflects the Fold Change of the pathway. The network diagram can provide a systematic perspective on the overall impact of differential metabolites from metabolomics.



**Figure S2.** Scanning electron microscope (SEM) image of TiO<sub>2</sub> particles.

**Table S1.** Differential metabolites in urine between the TiO<sub>2</sub> NPs exposure group and the control group.

No.	Metabolite	Class	P value	FDR	log <sub>2</sub> Fold Change	VIP
1	(S)-5,7-Dihydroxy-6-prenylflavanone	Flavonoids	4.60E-16	9.47E-15	1.58	2.04
2	(Z)-3-(1-Butenyl)-1H-2-benzopyran-1-one	Isocoumarins and derivatives	2.61E-14	2.59E-13	-2.66	2.15
3	1-Methoxy-1-(2,4,5-trimethoxyphenyl)-2-propanol	Benzene and substituted derivatives	7.40E-18	7.08E-16	1.16	2.10
4	1-Methylguanosine	Purine nucleosides	2.93E-15	4.18E-14	-2.77	2.03
5	1-Methylinosine	Purine nucleosides	9.71E-16	1.74E-14	1.69	2.15
6	1,2,10-Trihydroxydihydro-trans-linalyl oxide 7-O-beta-D-glucopyranoside	Organooxygen compounds	3.27E-15	4.55E-14	1.51	2.06
7	2',4'-Dihydroxy-7-methoxy-8-prenylflavan	Flavonoids	8.02E-17	2.85E-15	-3.26	2.07
8	2-Octenedioic acid	Fatty Acyls	1.55E-12	8.56E-12	-3.29	2.15
9	3-Oxooctanoic acid glycerides	Unknown	3.13E-13	2.11E-12	-3.78	2.15
10	4-Hydroxycitrulline	Carboxylic acids and derivatives	1.97E-14	2.07E-13	-3.10	2.13
11	5-Methoxytryptophol	Indoles and derivatives	6.45E-20	3.36E-17	1.58	2.14
12	6-O-Acetylaustroinulin	Prenol lipids	8.34E-17	2.91E-15	-3.40	2.15
13	7-(4-Hydroxyphenyl)-1-phenyl-4-hepten-3-one	Diarylheptanoids	4.27E-14	3.86E-13	-2.55	2.26
14	7-beta-D-Glucopyranosyloxybutylidenephthalide	Organooxygen compounds	2.62E-16	6.36E-15	-2.71	2.14
15	Acetylcholine	Organonitrogen compounds	3.84E-14	3.55E-13	-2.59	2.10
16	Adenylsuccinic acid	Purine nucleotides	8.67E-15	1.05E-13	1.72	2.02
17	Amisulpride	Benzene and substituted derivatives	3.42E-19	6.80E-17	0.88	2.03
18	Ampicillin	Lactams	3.28E-19	6.80E-17	1.64	2.14
19	Arginyl-Proline	Carboxylic acids and derivatives	3.56E-17	1.70E-15	-2.40	2.04
20	Bacampicillin	Lactams	3.33E-18	3.67E-16	1.16	2.07
21	Carteolol	Quinolines and derivatives	1.75E-15	2.74E-14	-2.05	2.14
22	Carvedilol	Indoles and derivatives	1.66E-16	4.62E-15	-2.98	2.12
23	CDP-glucose	Pyrimidine nucleotides	1.22E-16	3.96E-15	1.54	2.01
24	Cysteinyl-Valine	Carboxylic acids and derivatives	2.34E-20	3.36E-17	1.92	2.35
25	D-Fructosazine	Diazines	5.83E-15	7.42E-14	-2.64	2.01
26	Dibenzyl ether	Benzene and substituted derivatives	1.16E-19	4.10E-17	1.54	2.07
27	Dihydrodioscorine	Azaspirodecane derivatives	4.11E-16	8.79E-15	-2.93	2.25
28	Dihydropteridine	Pteridines and derivatives	7.02E-20	3.36E-17	1.20	2.16
29	Famciclovir	Imidazopyrimidines	1.05E-15	1.83E-14	-3.08	2.05
30	Galactosyl 4-hydroxyproline	Carboxylic acids and derivatives	2.23E-17	1.29E-15	1.63	2.09

**Table S1.** Differential metabolites in urine between the TiO<sub>2</sub> NPs exposure group and the control group. (**Continued**)

No.	Metabolite	Class	P value	FDR	log <sub>2</sub> Fold Change	VIP
31	gamma-L-Glutamyl-L-pipecolic acid	Carboxylic acids and derivatives	2.72E-16	6.36E-15	1.42	2.07
32	Glutaminy-Lysine	Carboxylic acids and derivatives	6.13E-17	2.33E-15	-3.11	2.22
33	Glutamyl-Phenylalanine	Carboxylic acids and derivatives	3.56E-17	1.70E-15	1.49	2.09
34	Ipomeatetrahydrofuran	Prenol lipids	1.60E-16	4.62E-15	-3.00	2.14
35	Isosorbide Mononitrate	Furofurans	2.93E-17	1.61E-15	1.78	2.11
36	L-Carnitine	Organonitrogen compounds	9.71E-16	1.74E-14	-3.64	2.21
37	Tryptophan	Amino Acids	6.07E-18	6.07E-16	-2.34	2.05
38	Lipoamide	Dithiolanes	7.64E-20	3.36E-17	-3.22	2.21
39	Marshrin	Coumarins and derivatives	1.27E-18	1.74E-16	1.32	2.09
40	Methyl 3,4-dihydroxy-5-prenylbenzoate 3-glucoside	Tannins	5.35E-16	1.06E-14	-3.33	2.20
41	Methylguanidine	Organonitrogen compounds	9.35E-16	1.72E-14	-2.51	2.12
42	Musanolone F	Naphthalenes	1.49E-19	4.10E-17	1.62	2.26
43	Myrigalone A	Prenol lipids	1.49E-19	4.10E-17	1.46	2.07
44	N-(3-Methylbutyl)acetamide	Carboxylic acids and derivatives	1.27E-16	4.00E-15	-3.20	2.09
45	N-Carboxyethyl-g-aminobutyric acid	Carboxylic acids and derivatives	1.43E-16	4.24E-15	-3.42	2.17
46	Norspermidine	Organonitrogen compounds	6.21E-16	1.18E-14	-3.73	2.27
47	p-Octopamine	Phenols	1.27E-18	1.74E-16	1.87	2.29
48	Pandamarilactonine A	Dihydrofurans	1.98E-17	1.28E-15	0.97	2.01
49	Phenylalanyl-Histidine	Carboxylic acids and derivatives	1.09E-13	8.55E-13	-1.36	2.01
50	Prasugrel	Thienopyridines	4.21E-15	5.65E-14	-2.32	2.16
51	Prolylhydroxyproline	Carboxylic acids and derivatives	4.53E-15	5.97E-14	-3.06	2.04
52	Quassamarin	Prenol lipids	2.67E-19	6.52E-17	1.36	2.11
53	Romucosine H	Aporphines	1.08E-18	1.69E-16	1.65	2.23
54	Sinigrin	Organooxygen compounds	9.03E-18	7.64E-16	1.50	2.07
55	Suberic acid	Fatty Acids	4.27E-16	8.95E-15	-3.89	2.31
56	Tridecyl phloretate	Fatty Acyls	4.00E-17	1.80E-15	-3.53	2.26
57	Valaciclovir	Carboxylic acids and derivatives	6.13E-13	3.85E-12	-3.37	2.16
58	Xylometazoline	Benzene and substituted derivatives	1.66E-16	4.62E-15	-3.11	2.08
59	Yangonin	Kavalactones	2.14E-18	2.58E-16	1.37	2.15
60	Zalcitabine	Pyrimidine nucleosides	2.23E-18	2.58E-16	1.87	2.18