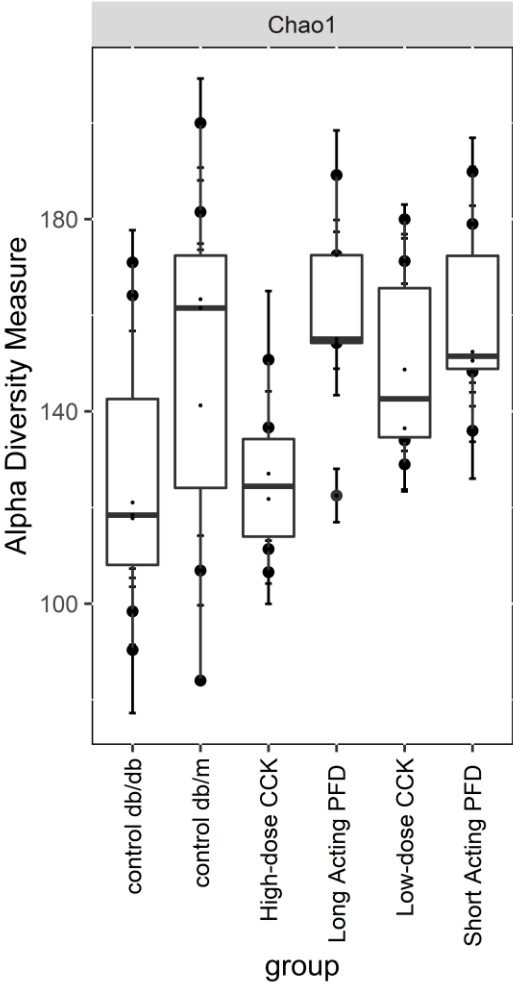
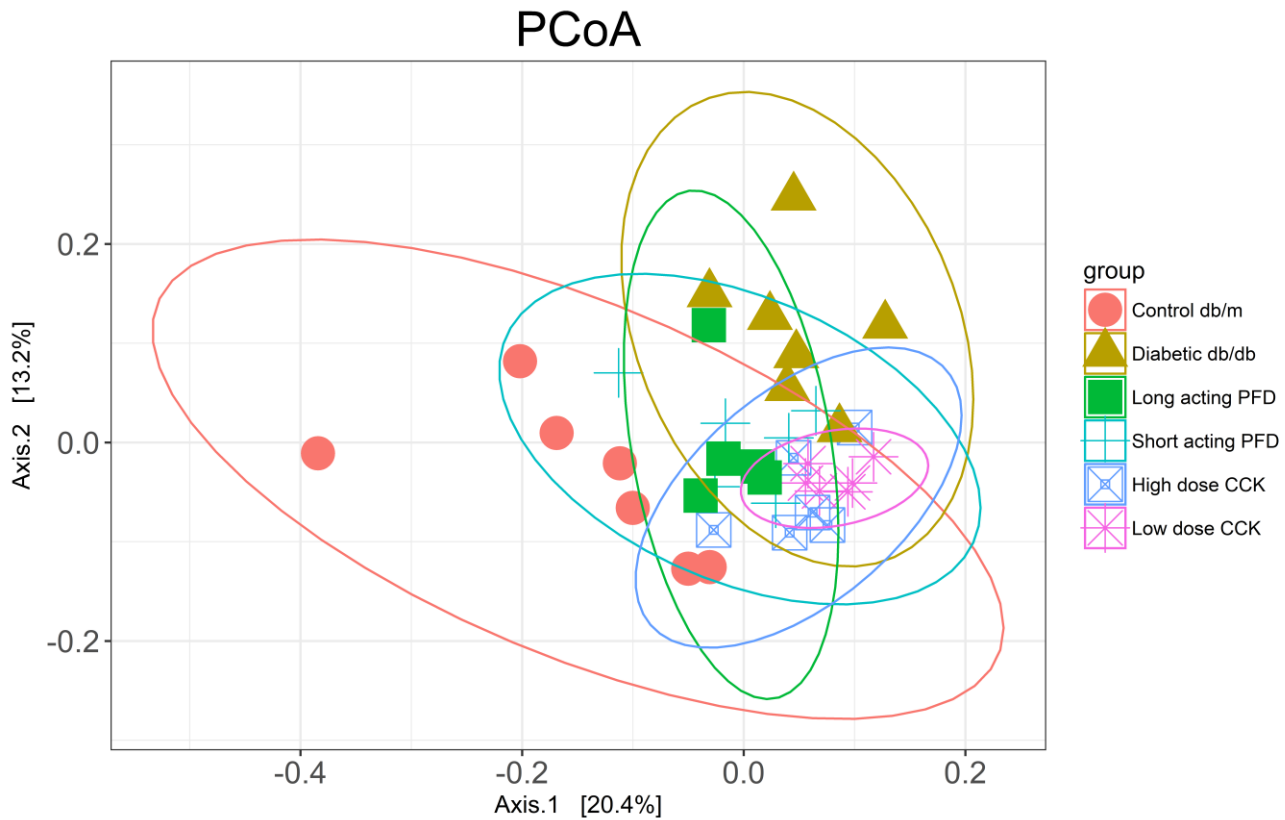


*Supplementary Material*



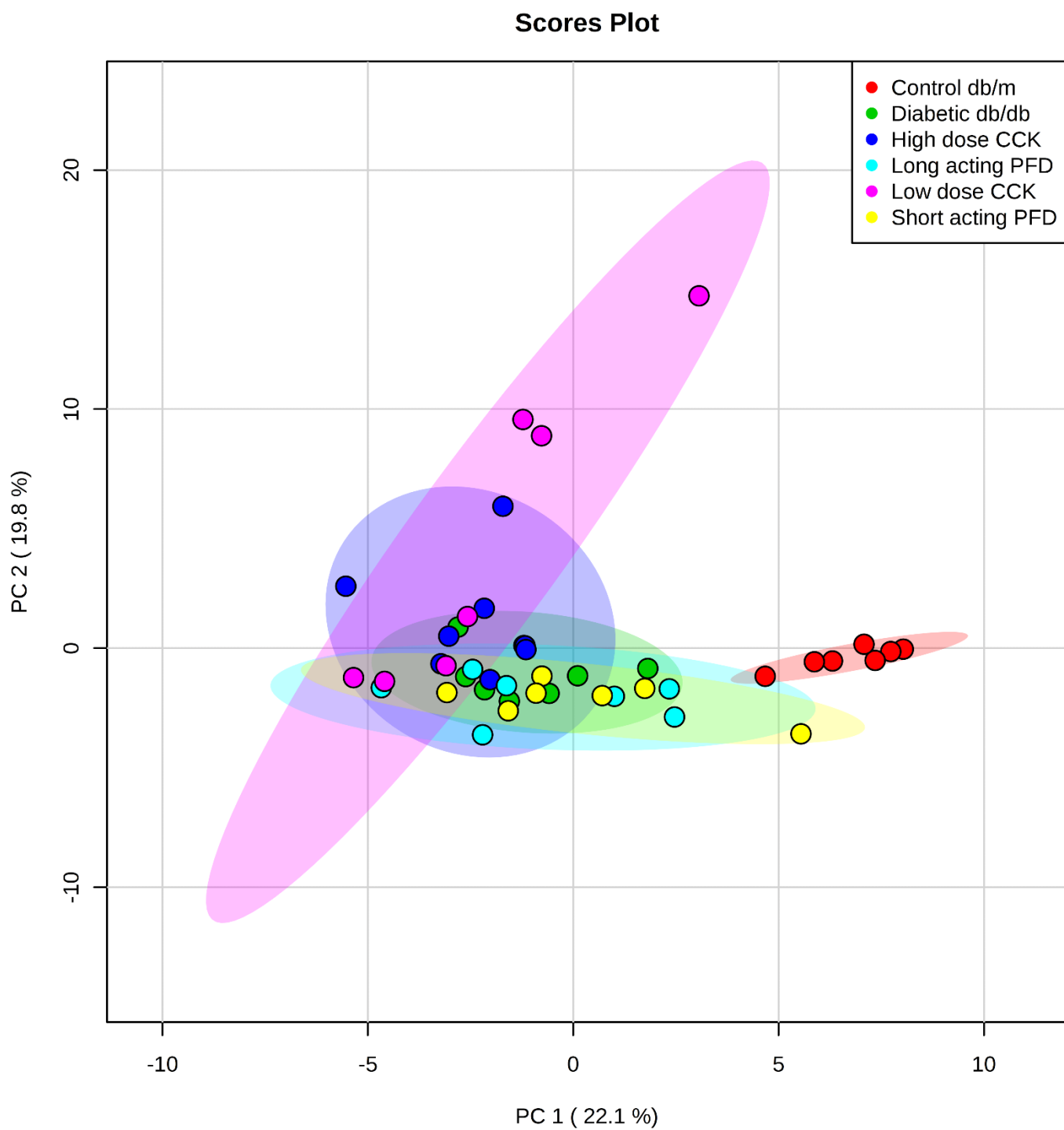
Supplementary Figure S1: The alpha diversity in terms of Chao1 comparison between diabetic db/db mice and control mice as well as the four treated control db/db mice with various drugs.



Supplementary Figure S2. Unweighted PCoA plot for all the groups along with 95% confidence interval.

Supplementary Table T1: Alpha diversity with Shannon and Chao1 diversity index differences using Wilcoxon test of the between control db/m and diabetic db/db and the four treated groups.

|                  | Shannon Diversity Index |                | Chao1 Diversity Index |                |
|------------------|-------------------------|----------------|-----------------------|----------------|
|                  | Control db/m            | Diabetic db/db | Control db/m          | Diabetic db/db |
| Diabetic db/db   | 0.03                    | NA             | 0.76                  | NA             |
| Long acting PFD  | 0.27                    | 0.07           | 0.94                  | 0.22           |
| Short acting PFD | 0.06                    | 1.00           | 0.95                  | 0.22           |
| High dose CCK    | 0.07                    | 0.56           | 0.50                  | 0.94           |
| Low dose CCK     | 0.07                    | 0.27           | 0.94                  | 0.22           |



Supplementary Figure S3: PCA plot with ellipse denotes 95% confidence interval. This data was generated using 61 metabolites values from control db/m, diabetic db/db and the four drug-treated db/db mice.

Supplementary Table T2: Log fold change of various metabolites in diabetic db/db mice and four treated groups in comparison with control db/m mice.

|                                | db/db mice |          | Long acting PFD |          | Short acting PFD |          | High dose CCK |          | Low dose CCK |          |
|--------------------------------|------------|----------|-----------------|----------|------------------|----------|---------------|----------|--------------|----------|
| Metabolite                     | FC         | P.values | FC              | P.values | FC               | P.values | FC            | P.values | FC           | P.values |
| 3-Hydroxybutyric acid          | 8.5        | 0.01     | 8.0             | 0.01     | 8.8              | 0.00     | 7.8           | 0.00     | 8.4          | 0.03     |
| Acetoacetic acid               | 8.3        | 0.03     | 7.2             | 0.02     | 8.7              | 0.01     | 7.2           | 0.03     | 8.6          | 0.09     |
| 2-Hydroxybutyric acid          | 3.8        | 0.07     | 9.4             | 0.33     | 2.0              | 0.40     | 3.7           | 0.01     | 6.5          | 0.12     |
| 3-keto-2-Methylbutyrate        | 3.7        | 0.03     | 2.9             | 0.01     | 4.0              | 0.00     | 2.6           | 0.04     | 4.1          | 0.11     |
| 3-Hydroxymethylglutaric acid   | 2.9        | 0.00     | 1.4             | 0.01     |                  |          | 3.1           | 0.00     | 3.4          | 0.00     |
| Glyceric acid                  | -2.7       | 0.00     | -2.0            | 0.00     | -2.2             | 0.00     | -2.8          | 0.00     | -2.3         | 0.00     |
| Pyruvic acid                   | 2.5        | 0.01     | 3.2             | 0.00     | 3.2              | 0.00     | 3.4           | 0.00     | 3.7          | 0.00     |
| 2-Ketobutyric acid             | 2.5        | 0.01     | 3.2             | 0.00     | 3.2              | 0.00     | 3.3           | 0.00     | 3.6          | 0.00     |
| L-Lactic acid                  | 2.4        | 0.00     | 2.7             | 0.04     | 2.6              | 0.02     | 4.1           | 0.00     | 4.5          | 0.00     |
| 2-Hydroxy-3-methylbutyric acid | 2.3        | 0.01     | 2.1             | 0.07     | 1.9              | 0.05     | 3.6           | 0.00     | 4.1          | 0.00     |
| Uracil                         | -2.3       | 0.00     | -1.8            | 0.00     | -1.6             | 0.00     | -2.0          | 0.00     | -1.7         | 0.00     |
| 2-Ethylhydracrylic acid        | 2.1        | 0.00     | 1.9             | 0.00     | 1.9              | 0.00     | 1.7           | 0.00     | 1.4          | 0.09     |
| S-3-Hydroxyisobutyric acid     | 2.0        | 0.00     | 2.4             | 0.00     | 2.2              | 0.00     | 2.2           | 0.00     | 2.4          | 0.00     |
| Palmitic acid                  | -1.7       | 0.00     | -2.9            | 0.00     | -2.2             | 0.00     | -1.7          | 0.00     | -3.3         | 0.00     |
| Malonic acid                   | 1.6        | 0.13     | 1.7             | 0.15     | 1.6              | 0.00     |               |          |              |          |
| Oxoglutaric acid               | 1.6        | 0.00     | 1.6             | 0.00     | 1.5              | 0.00     | 1.8           | 0.00     | 2.2          | 0.00     |
| L-Octanoylcarnitine            | -1.5       | 0.00     | -1.1            | 0.02     | -2.0             | 0.00     | -1.7          | 0.00     | -1.5         | 0.00     |
| Benzoic acid                   | 1.5        | 0.25     | 2.4             | 0.01     |                  |          | 3.5           | 0.01     | 3.9          | 0.01     |
| Fumaric acid                   | 1.4        | 0.01     |                 |          | 1.0              | 0.07     | -1.2          | 0.00     | -1.9         | 0.00     |
| L-2-Hydroxyglutaric acid       | -1.4       | 0.00     |                 |          |                  |          |               |          |              |          |
| Glutaric acid                  | -1.4       | 0.00     | -1.1            | 0.00     |                  |          |               |          |              |          |
| Leucinic acid                  | 1.4        | 0.00     | 1.1             | 0.00     | 1.4              | 0.00     | 1.3           | 0.04     | 2.5          | 0.05     |
| 3-Hydroxyadipic acid           | 1.3        | 0.01     |                 |          |                  |          | 1.0           | 0.05     |              |          |
| Orotic acid                    | -1.3       | 0.00     |                 |          |                  |          | -1.3          | 0.00     |              |          |
| Succinic acid                  | -1.2       | 0.00     |                 |          |                  |          |               |          |              |          |
| Hippuric acid                  | -1.2       | 0.00     | -1.6            | 0.00     | -2.1             | 0.00     | -1.9          | 0.00     |              |          |
| Stearic acid                   | -1.2       | 0.00     | -6.6            | 0.00     | -6.4             | 0.00     |               |          | -1.8         | 0.00     |
| Alpha-ketoisovaleric acid      | -1.2       | 0.00     |                 |          |                  |          |               |          |              |          |
| p-Hydroxyphenylacetic acid     | -1.0       | 0.00     | -1.9            | 0.00     | -1.6             | 0.00     | -1.8          | 0.00     | -2.3         | 0.00     |