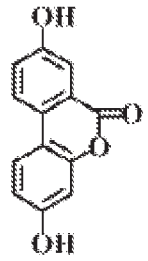
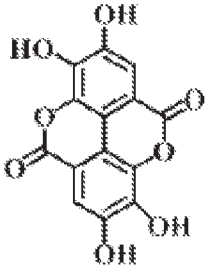
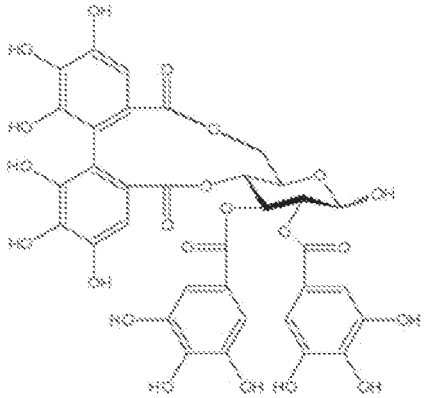
**Figure 1**



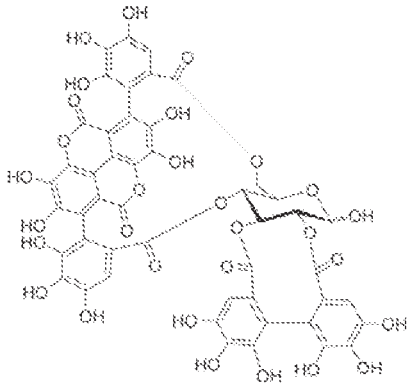
Urolithin A (UA)



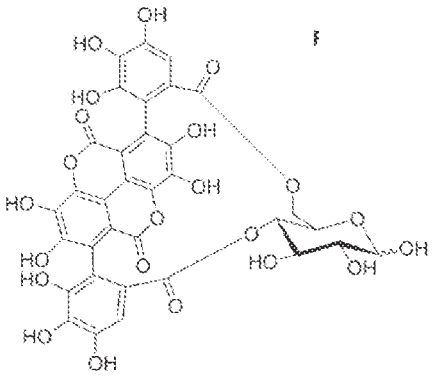
Ellagic Acid (EA)



Tellimagrandin (TL)



Punicalagin (PA)



Punicalin (PB)

**Figure 2**

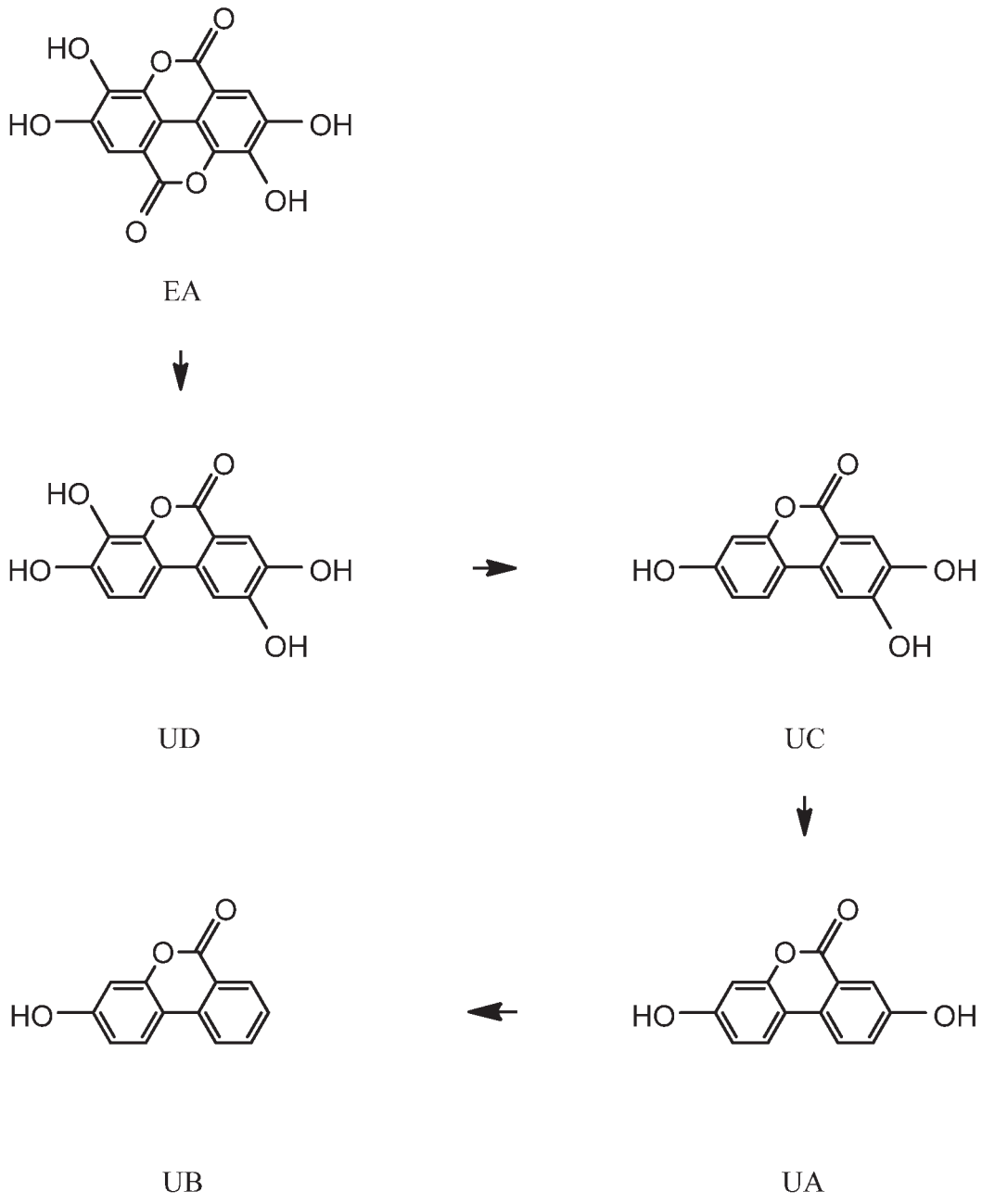


**Figure 3**

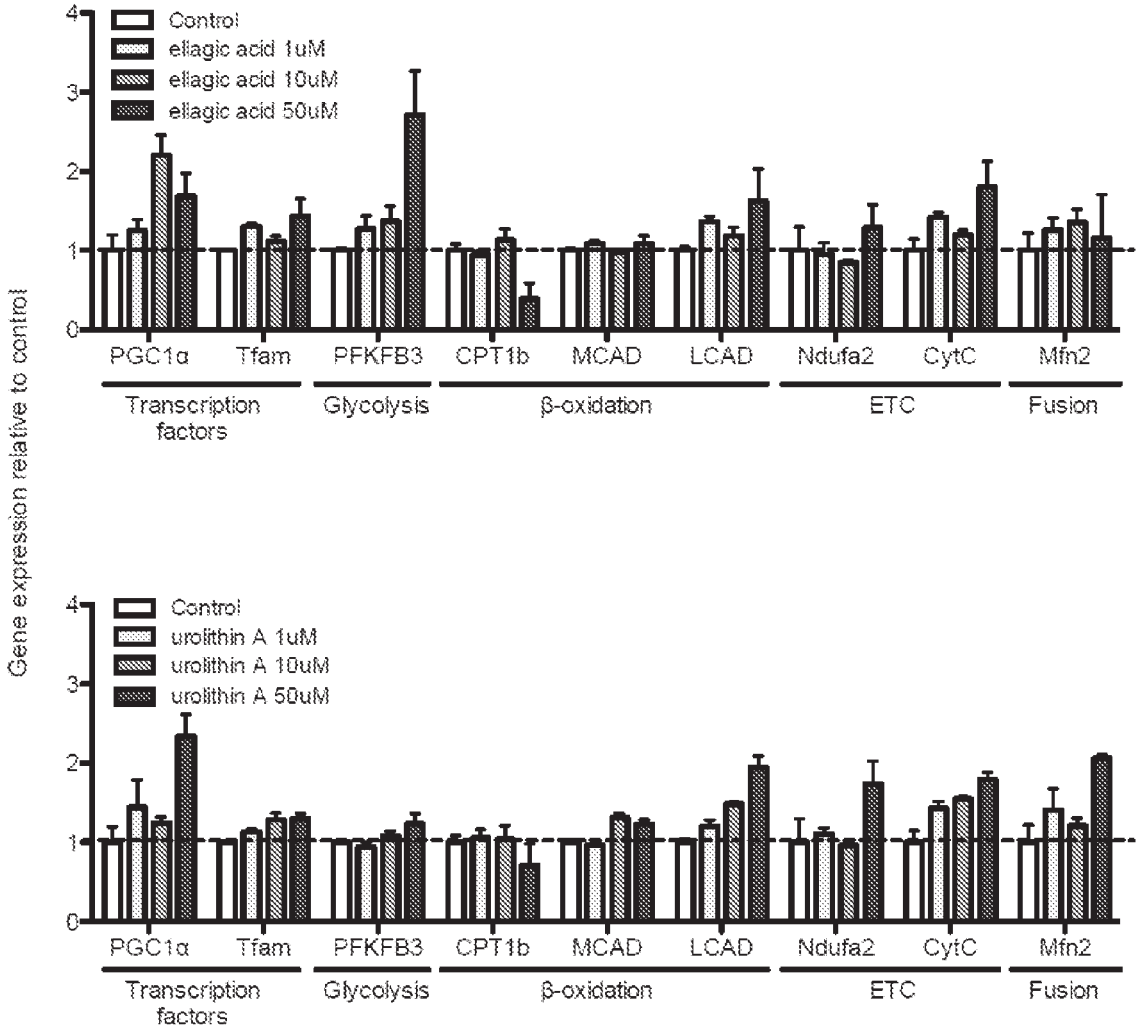

Gene expression relative to control
Control
ellagic acid 1uM
ellagic acid 10uM
ellagic acid 50uM
PGC1α
Tfam
PFKFB3
CPT1b
MCAD
LCAD
Ndufa2
CytC
Mfn2
Transcription factors
Glycolysis
β-oxidation
ETC
Fusion
Control
urolithin A 1uM
urolithin A 10uM
urolithin A 50uM
PGC1α
Tfam
PFKFB3
CPT1b
MCAD
LCAD
Ndufa2
CytC
Mfn2
Transcription factors
Glycolysis
β-oxidation
ETC
Fusion

**Figure 4**

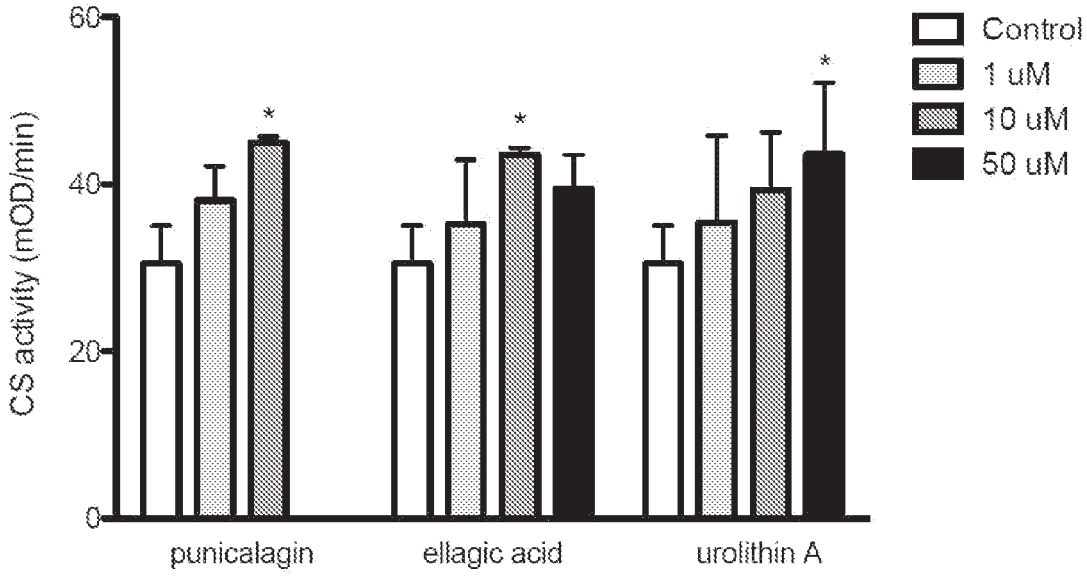
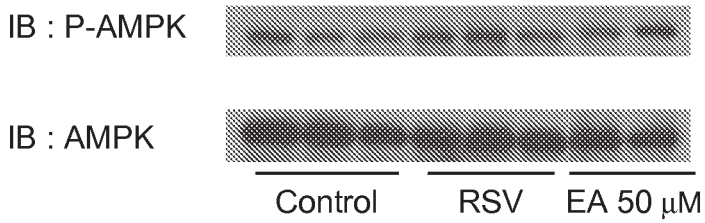
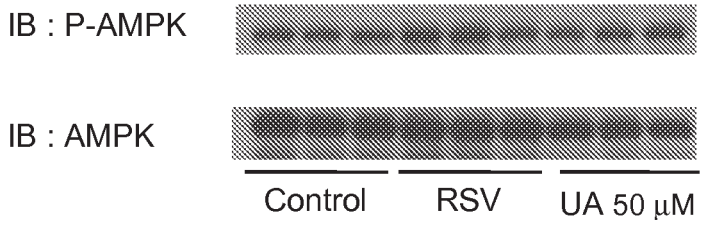

60
40
20
0
CS activity (mOD/min)
*
*
*
punicalagin
ellagic acid
urolithin A
Control
1 uM
10 uM
50 uM

**Figure 5**

**A**


IB : P-AMPK
IB : AMPK
Control
RSV
EA 50 μM

**B**


IB : P-AMPK
IB : AMPK
Control
RSV
UA 50 μM

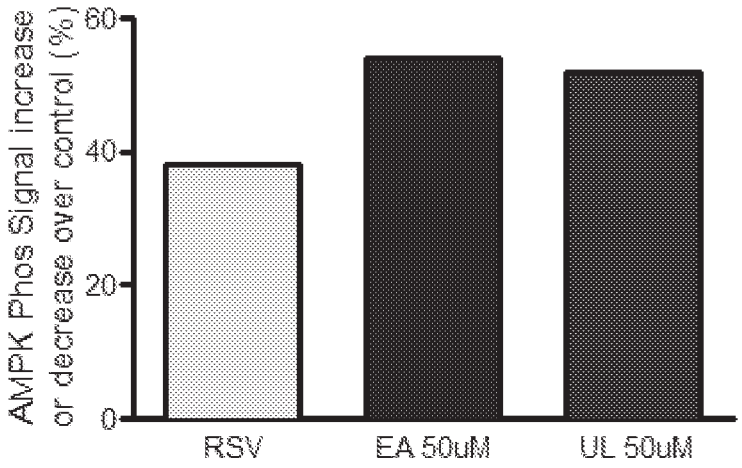
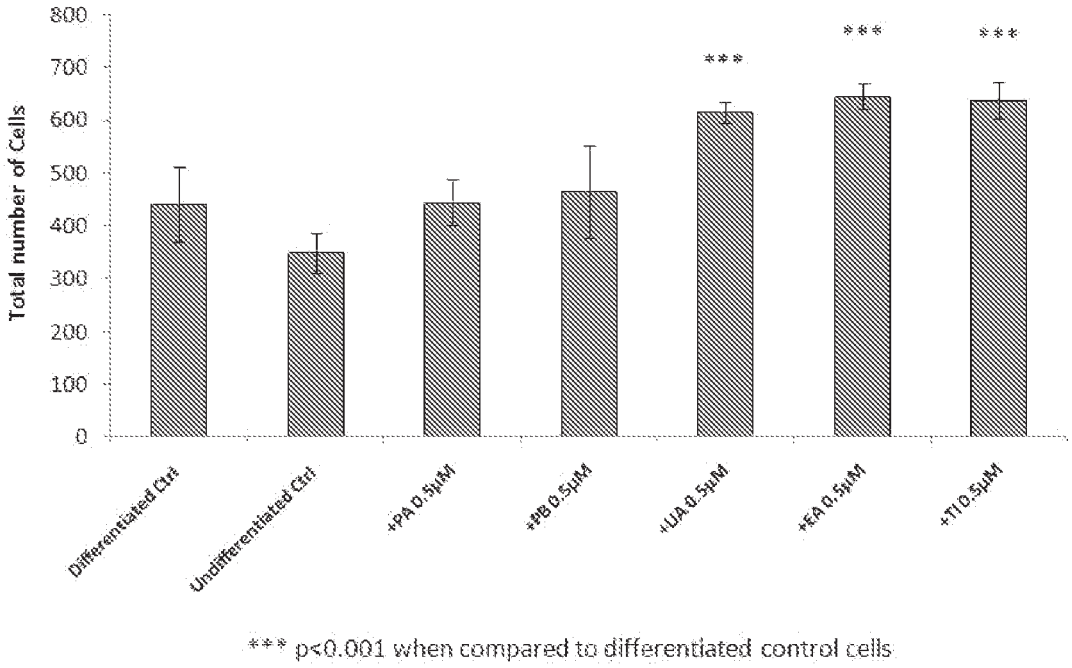
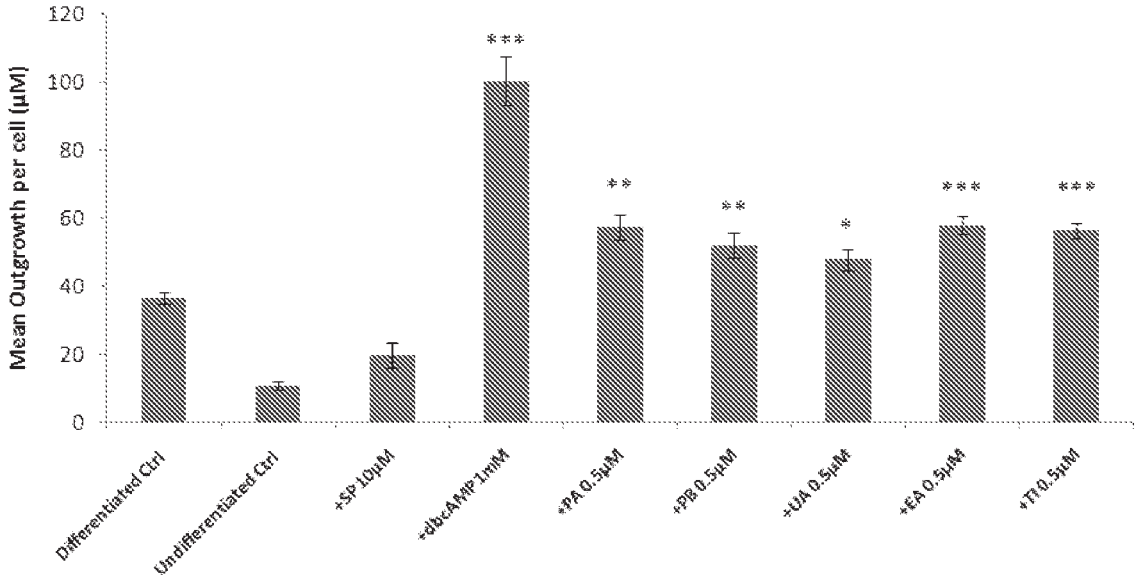

AMPK Phos Signal increase or decrease over control (%)
60
40
20
0
RSV
EA 50uM
UL 50uM

**Figure 6**



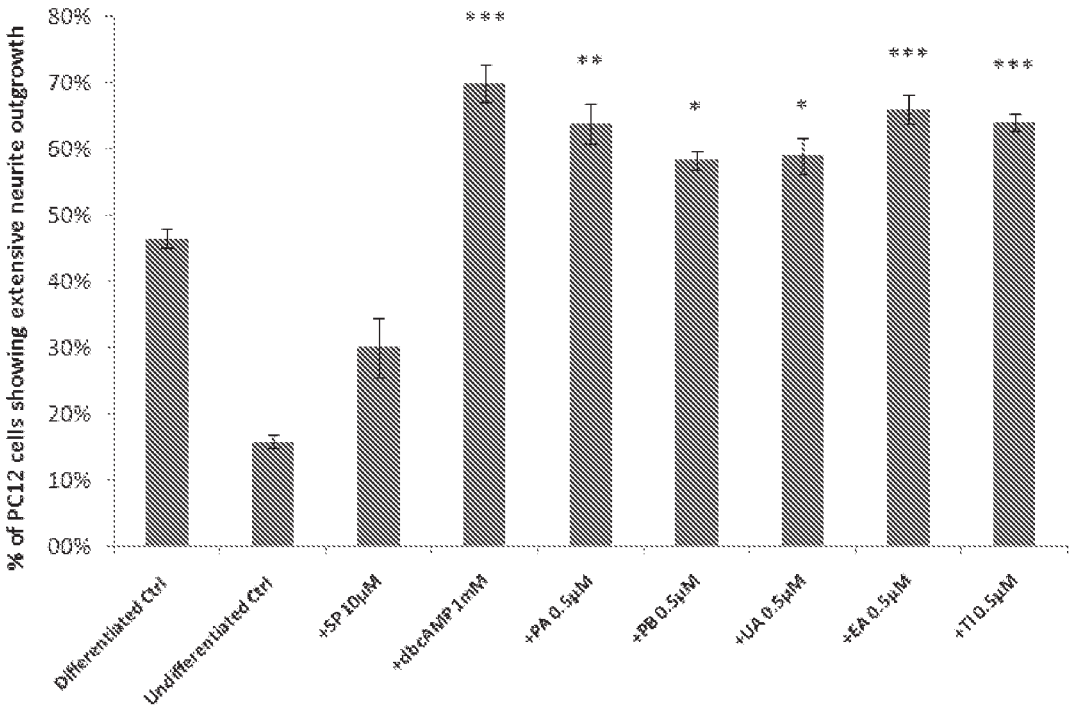

*** p<0.001 when compared to differentiated control cells

**Figure 7**



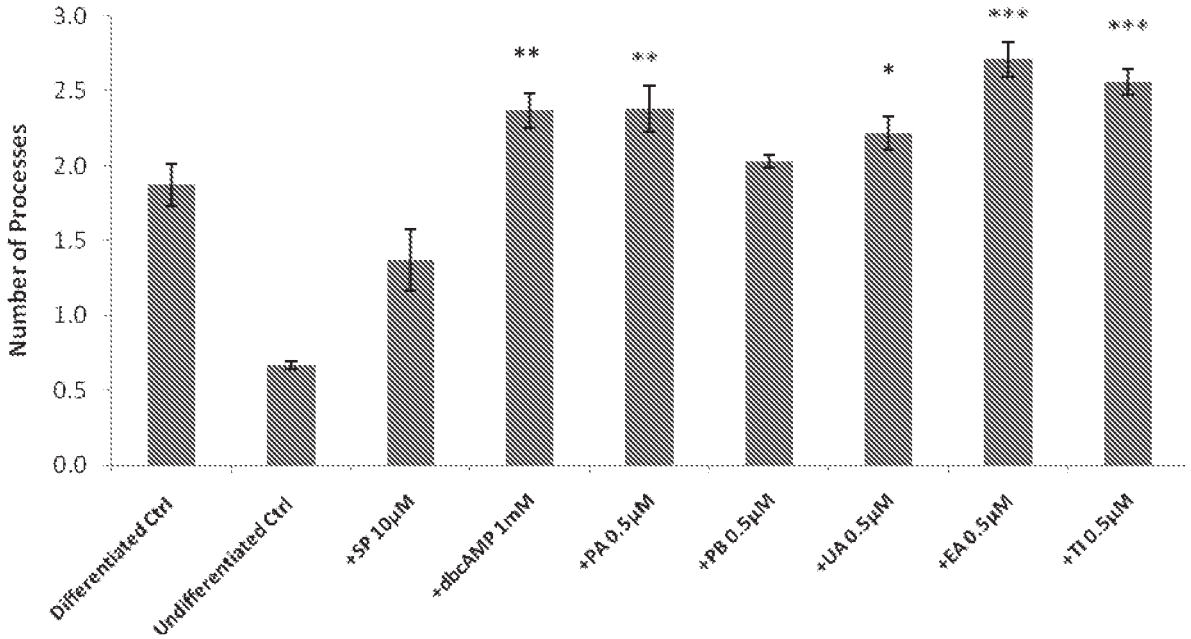

* p< 0.05, ** p<0.01, *** p<0.001 when compared to differentiated control cells

**Figure 8**



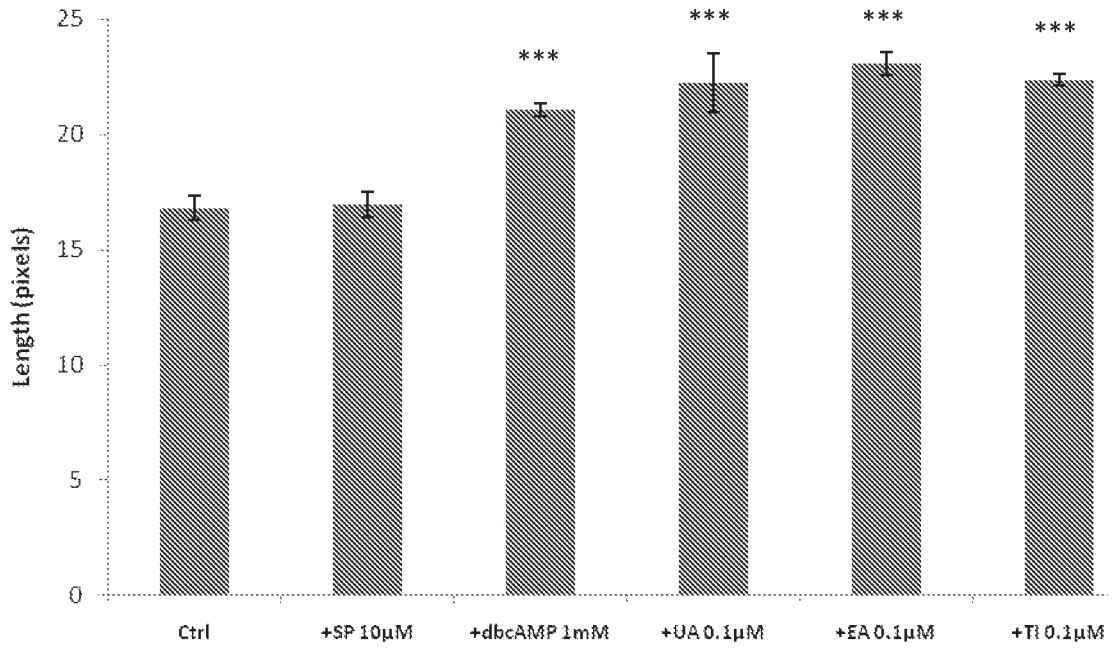

* p< 0.05, ** p<0.01, *** p<0.001 when compared to differentiated control cells

**Figure 9**



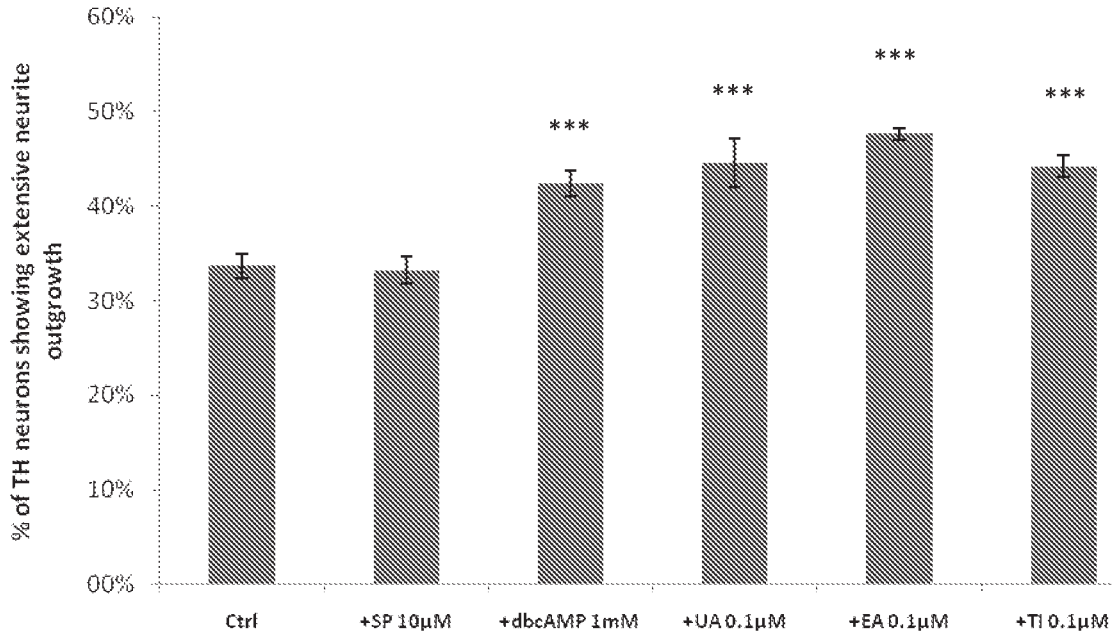

* p< 0.05, ** p<0.01, *** p<0.001 when compared to differentiated control cells

**Figure 10**



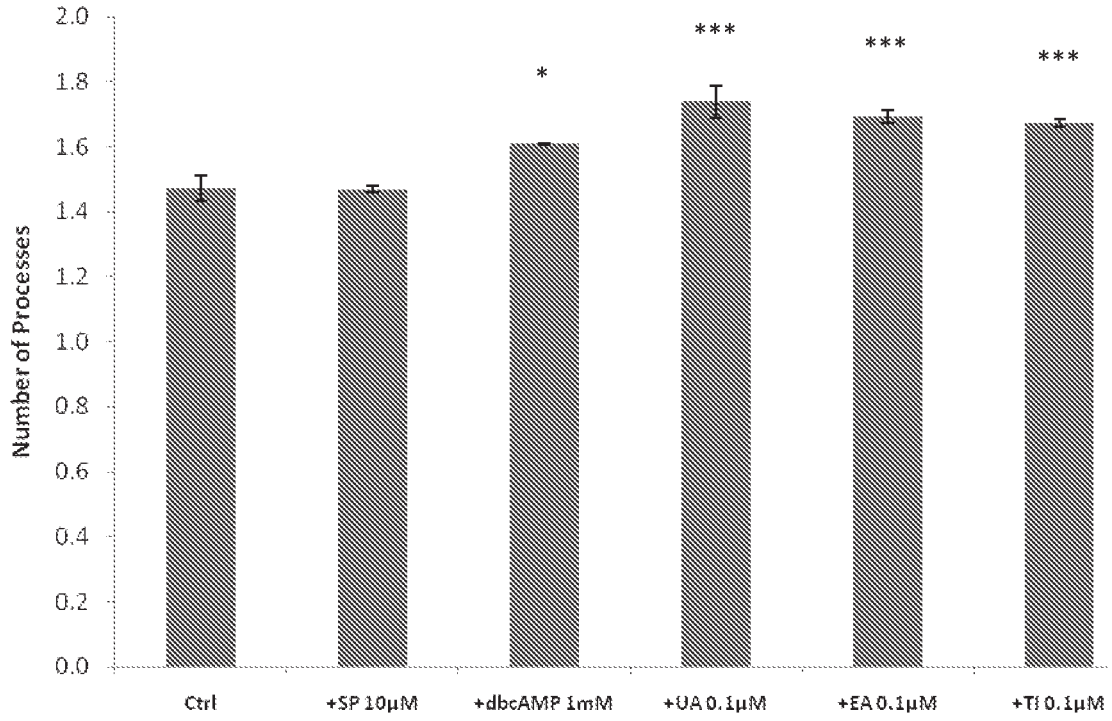

*** p<0.001 when compared to differentiated control cells

**Figure 11**



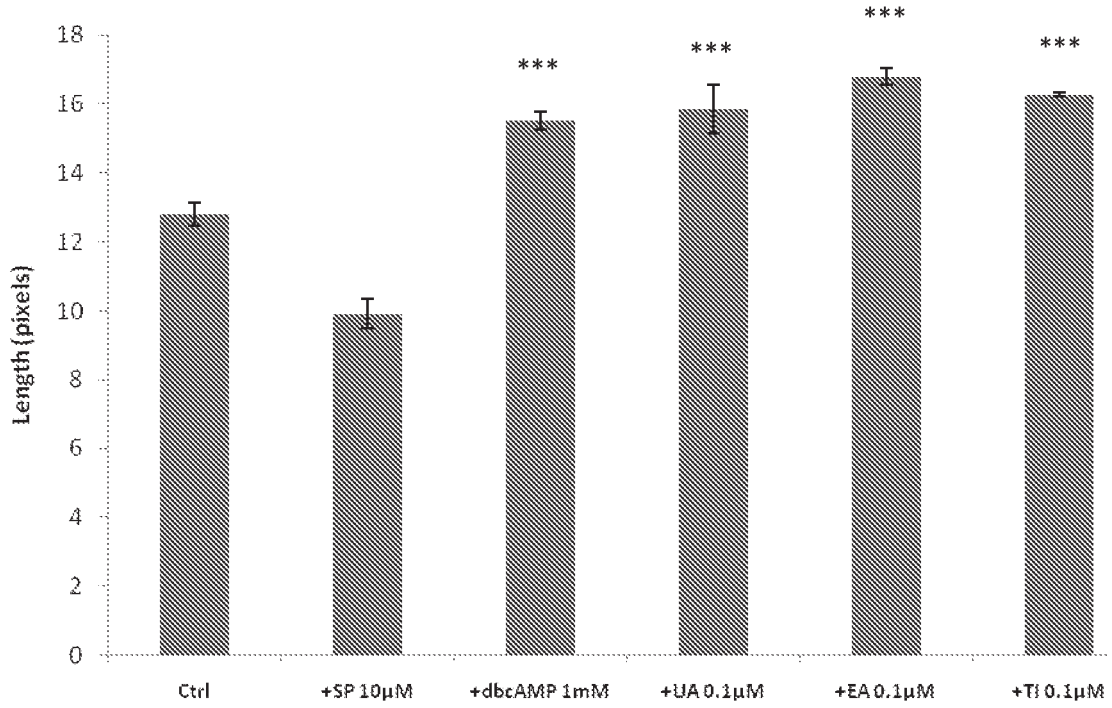

*** p<0.001 when compared to differentiated control cells

**Figure 12**



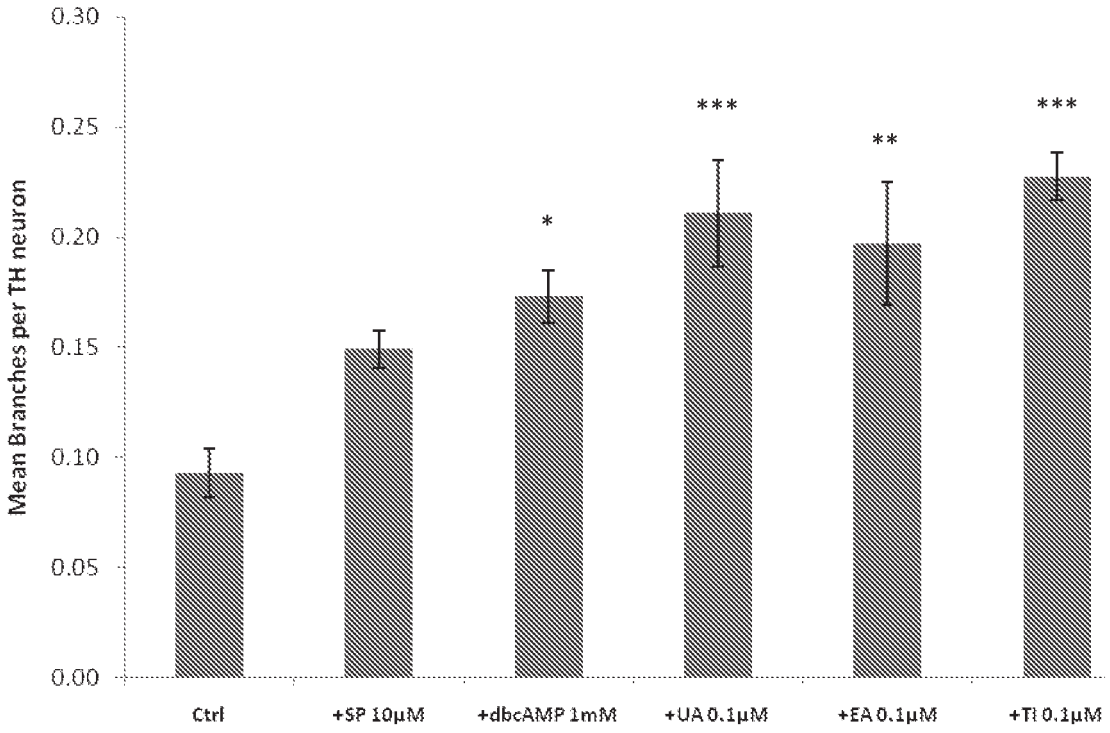

* p< 0.05, *** p<0.001 when compared to differentiated control cells

**Figure 13**



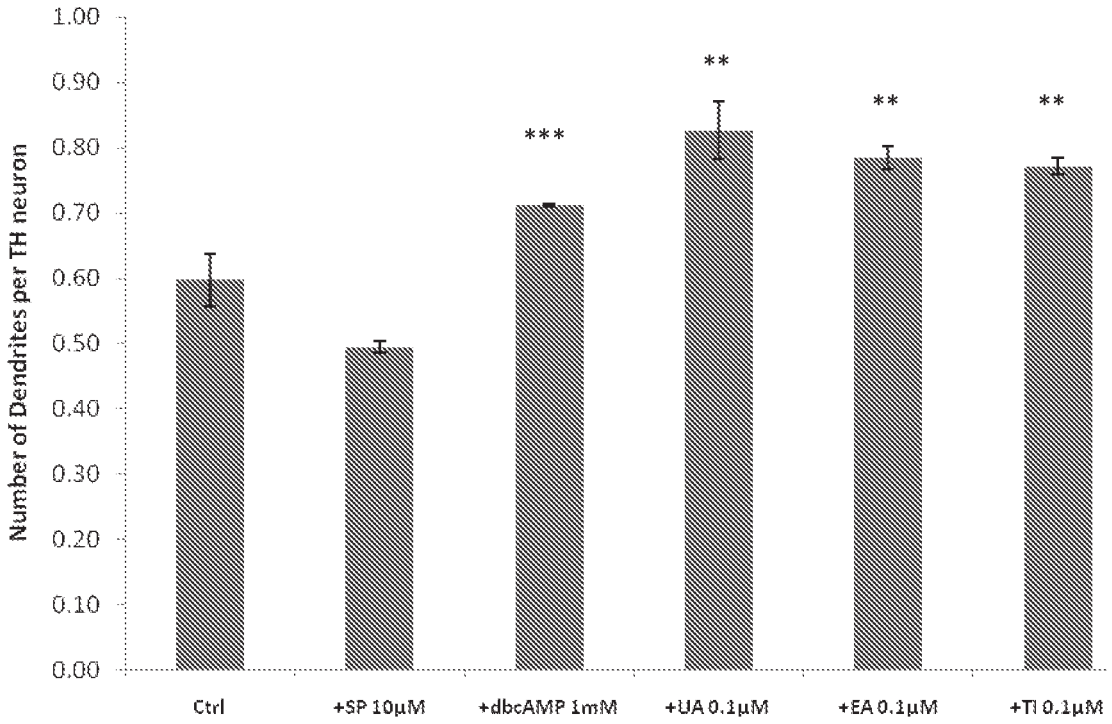

*** p<0.001 when compared to differentiated control cells

**Figure 14**



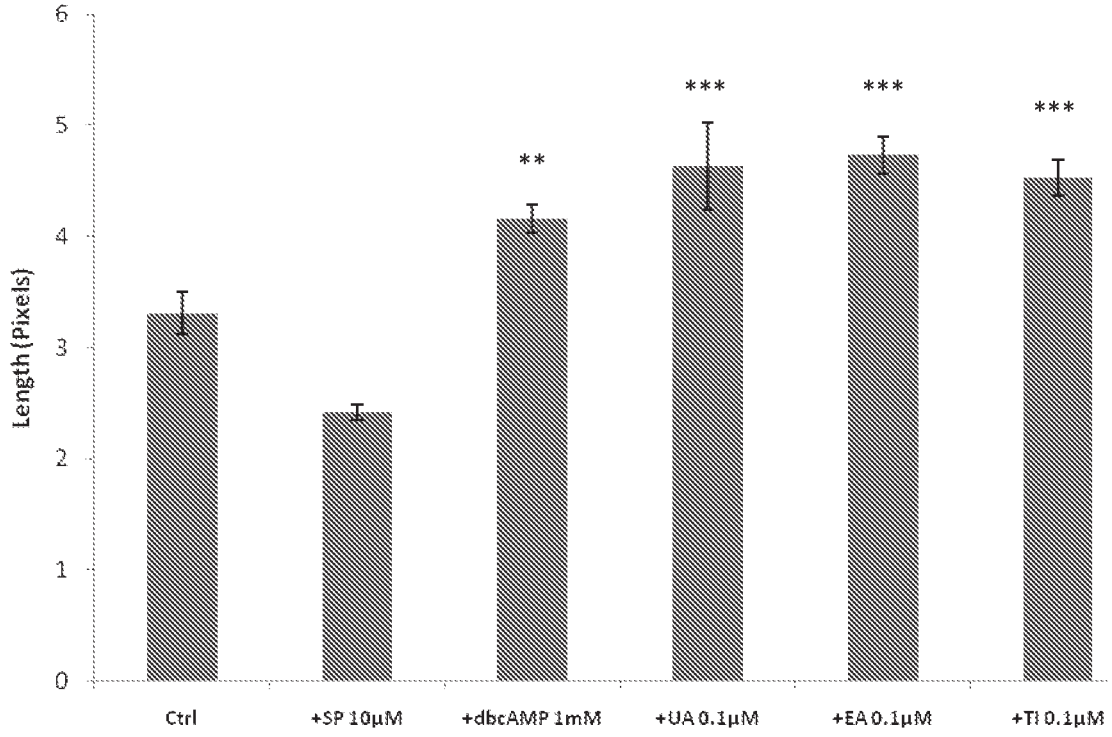

* p< 0.05, ** p<0.01,*** p<0.001 when compared to differentiated control cells

**Figure 15**



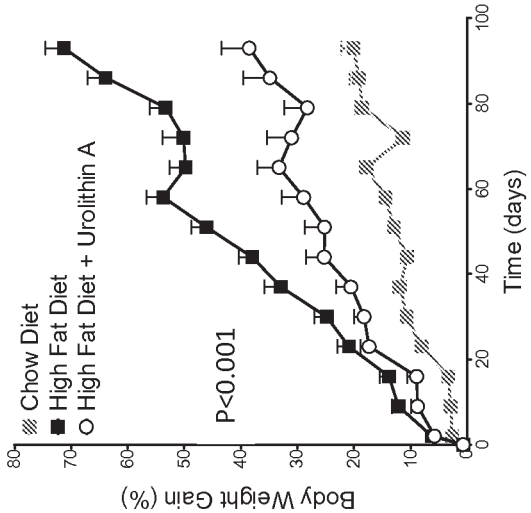

** p<0.01,*** p<0.001 when compared to differentiated control cells

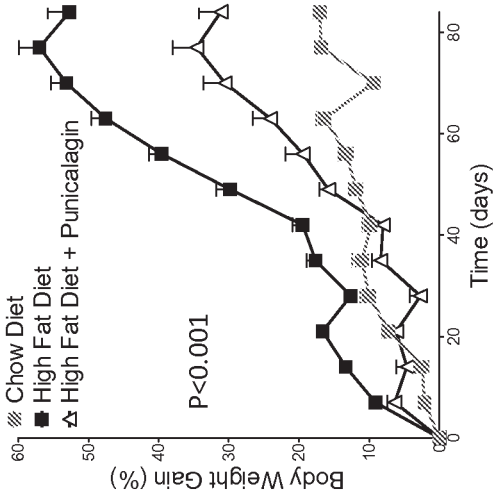
**Figure 16**




** p<0.01,*** p<0.001 when compared to differentiated control cells

Figure 17A


Body Weight Gain (%)
Time (days)
Chow Diet
High Fat Diet
High Fat Diet + Urolithin A
P<0.001


Body Weight Gain (%)
Time (days)
Chow Diet
High Fat Diet
High Fat Diet + Punicalagin
P<0.001

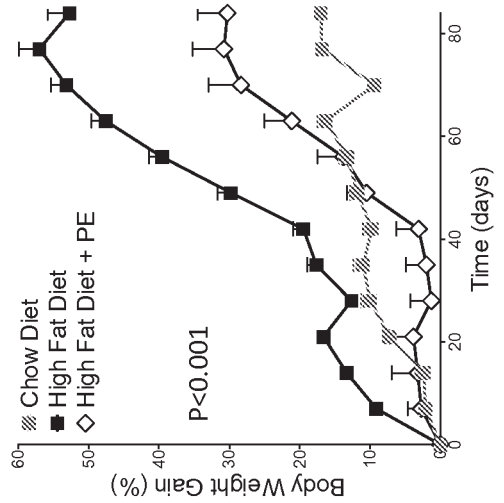

Body Weight Gain (%)
Time (days)
Chow Diet
High Fat Diet
High Fat Diet + PE
P<0.001

Figure 17B

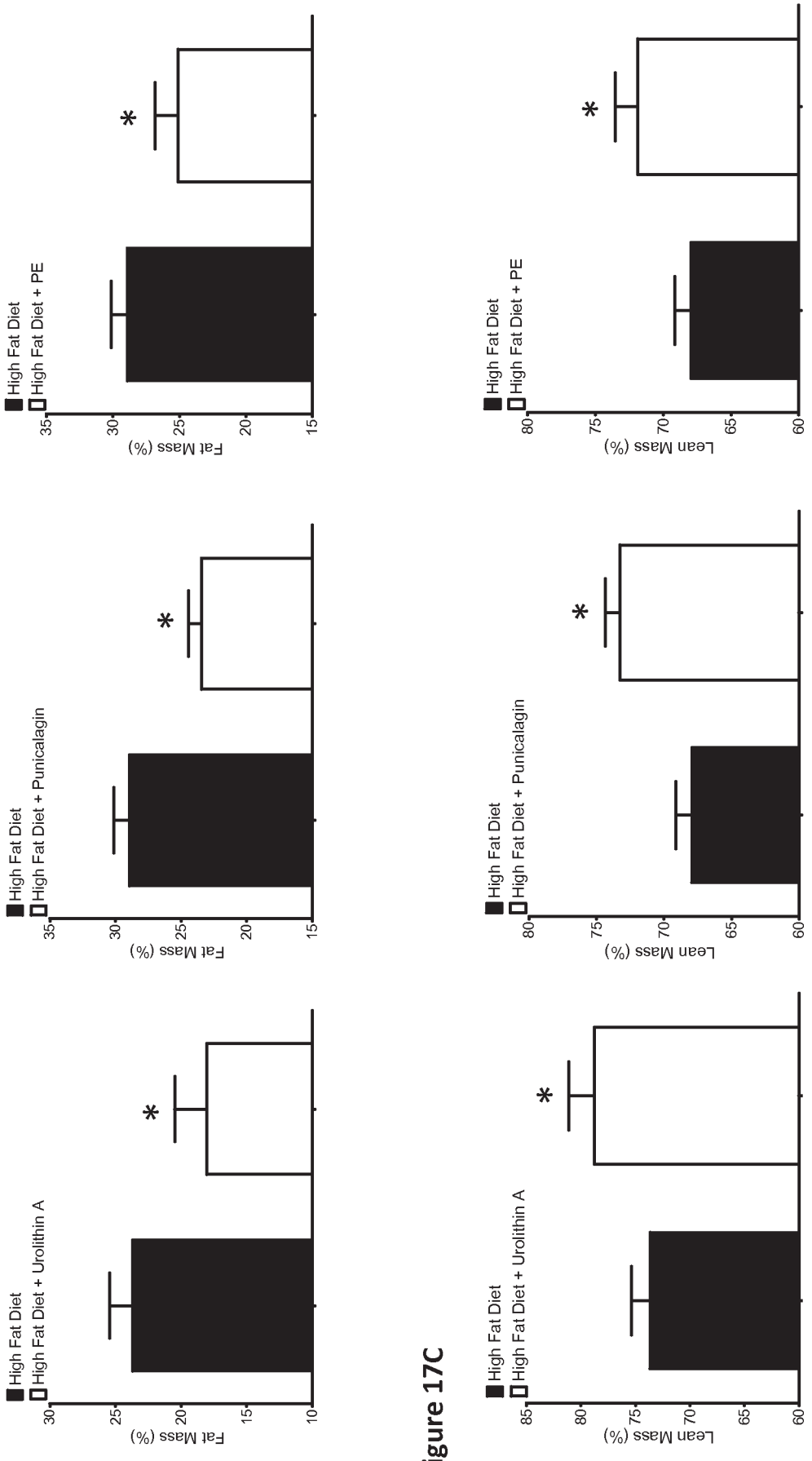



Figure 17C

Figure 18

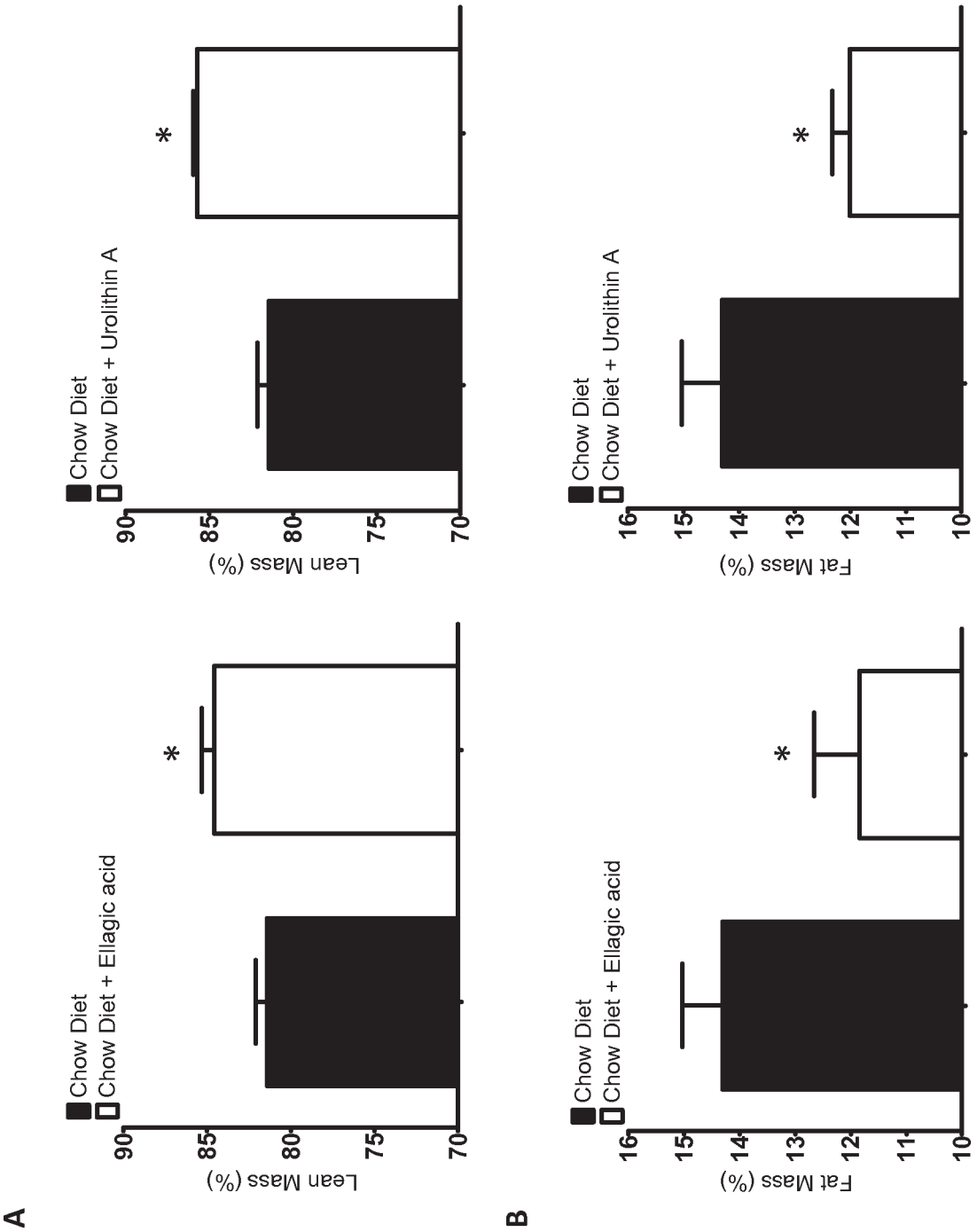

A
Chow Diet
Chow Diet + Ellagic acid
Lean Mass (%)
90
85
80
75
70
*
Chow Diet
Chow Diet + Urolithin A
Lean Mass (%)
90
85
80
75
70
*
B
Chow Diet
Chow Diet + Ellagic acid
Fat Mass (%)
16
15
14
13
12
11
10
*
Chow Diet
Chow Diet + Urolithin A
Fat Mass (%)
16
15
14
13
12
11
10
*

Figure 19

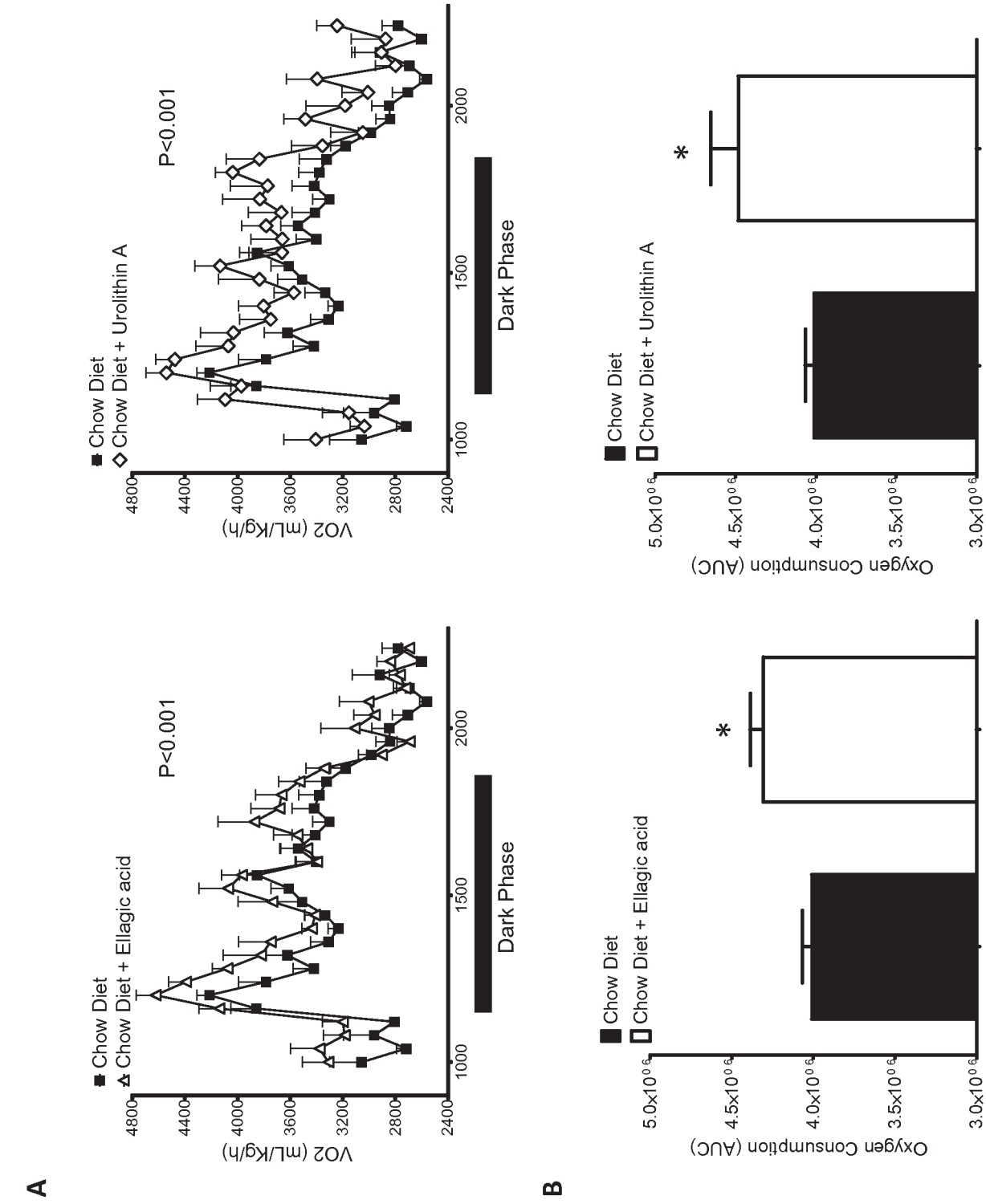

A
Chow Diet
Chow Diet + Ellagic acid
P<0.001
VO2 (mL/Kg/h)
4800
4400
4000
3600
3200
2800
2400
1000
1500
2000
Dark Phase
Chow Diet
Chow Diet + Urolithin A
P<0.001
VO2 (mL/Kg/h)
4800
4400
4000
3600
3200
2800
2400
1000
1500
2000
Dark Phase
B
Chow Diet
Chow Diet + Ellagic acid
*
Oxygen Consumption (AUC)
5.0x10^6
4.5x10^6
4.0x10^6
3.5x10^6
3.0x10^6
Chow Diet
Chow Diet + Urolithin A
*
Oxygen Consumption (AUC)
5.0x10^6
4.5x10^6
4.0x10^6
3.5x10^6
3.0x10^6

Figure 20

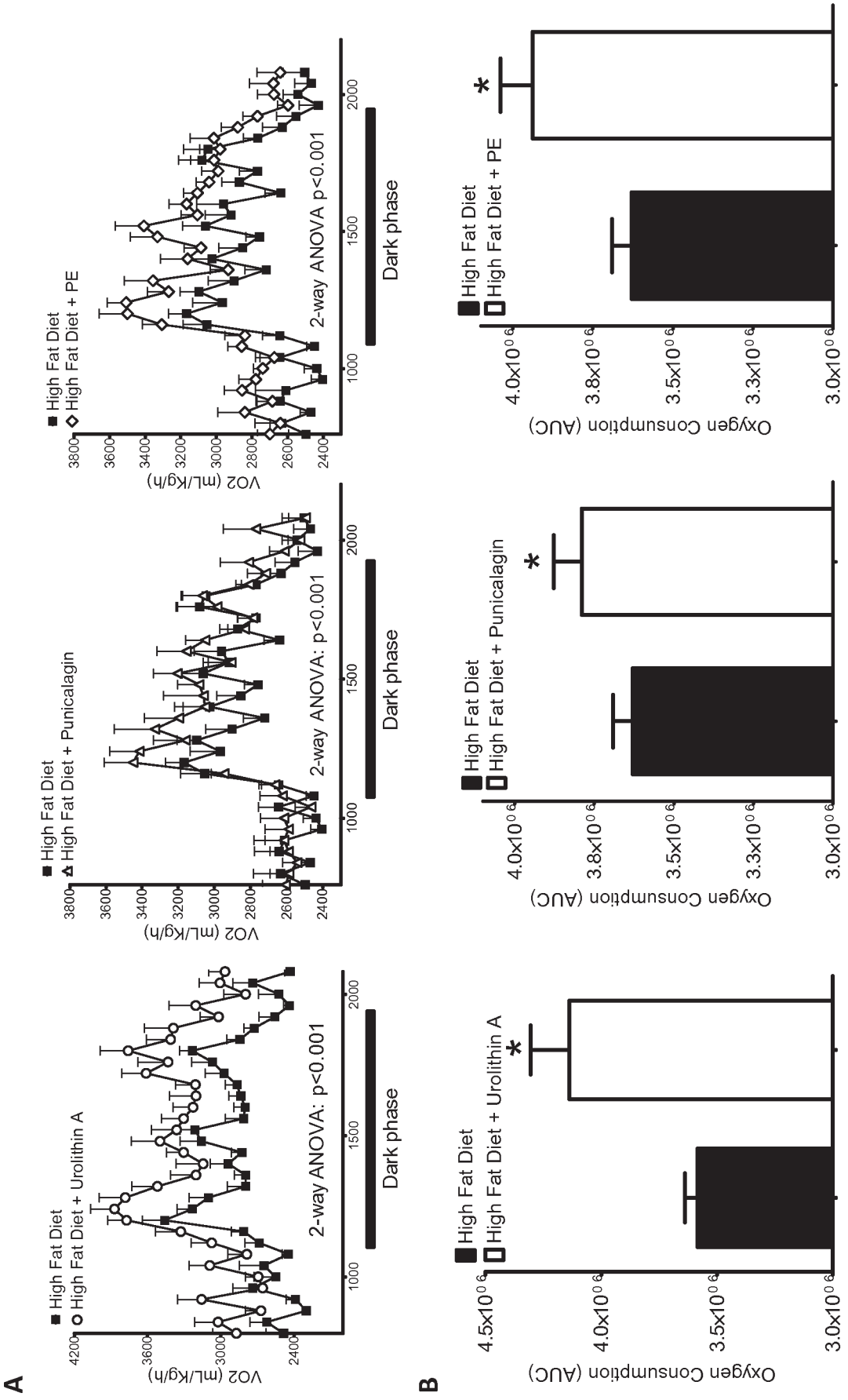

A
B
High Fat Diet
High Fat Diet + Urolithin A
High Fat Diet + Punicalagin
High Fat Diet + PE
VO2 (mL/Kg/h)
2-way ANOVA: p<0.001
Dark phase
Oxygen Consumption (AUC)
*

Figure 21

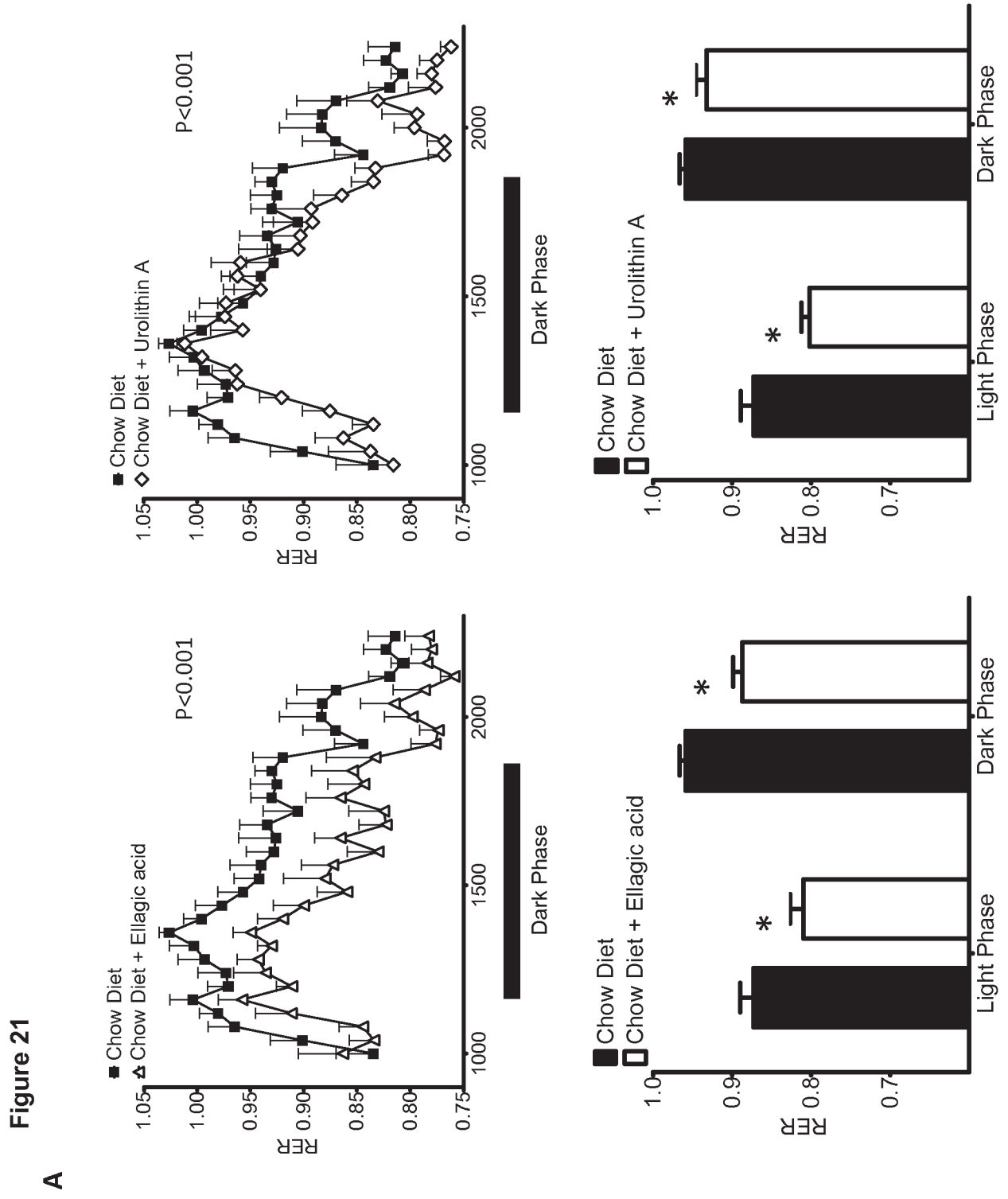

A
Chow Diet
Chow Diet + Ellagic acid
P<0.001
RER
1.05
1.00
0.95
0.90
0.85
0.80
0.75
1000
1500
2000
Dark Phase
Chow Diet
Chow Diet + Urolithin A
P<0.001
RER
Dark Phase
B
Chow Diet
Chow Diet + Ellagic acid
RER
1.0
0.9
0.8
0.7
*
Light Phase
Dark Phase
Chow Diet
Chow Diet + Urolithin A
RER
Light Phase
Dark Phase

Figure 22

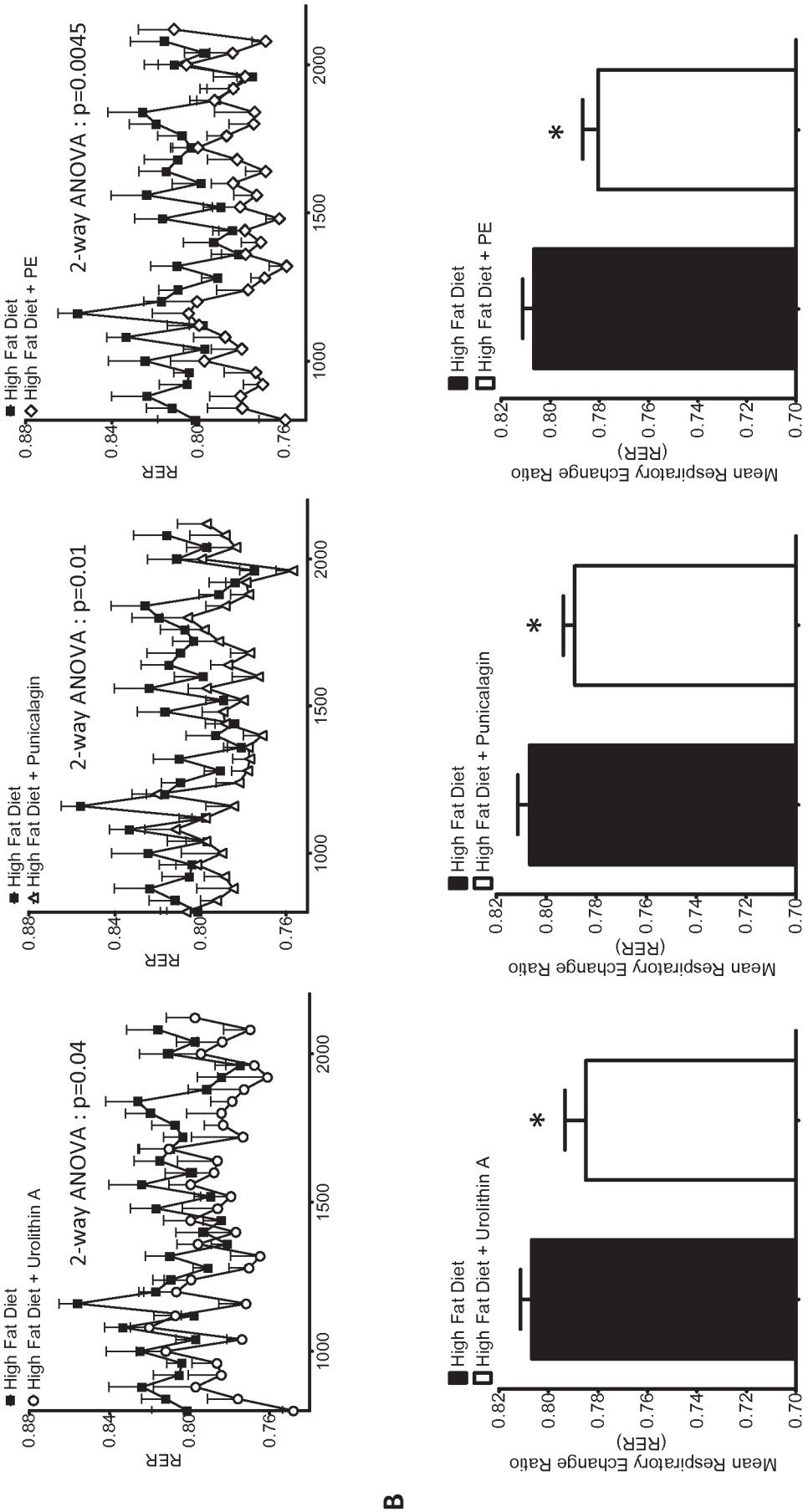

A
High Fat Diet
High Fat Diet + Urolithin A
2-way ANOVA : p=0.04
High Fat Diet
High Fat Diet + Punicalagin
2-way ANOVA : p=0.01
High Fat Diet
High Fat Diet + PE
2-way ANOVA : p=0.0045
RER
0.88
0.84
0.80
0.76
1000
1500
2000
B
Mean Respiratory Echange Ratio (RER)
0.82
0.80
0.78
0.76
0.74
0.72
0.70
*

Figure 23

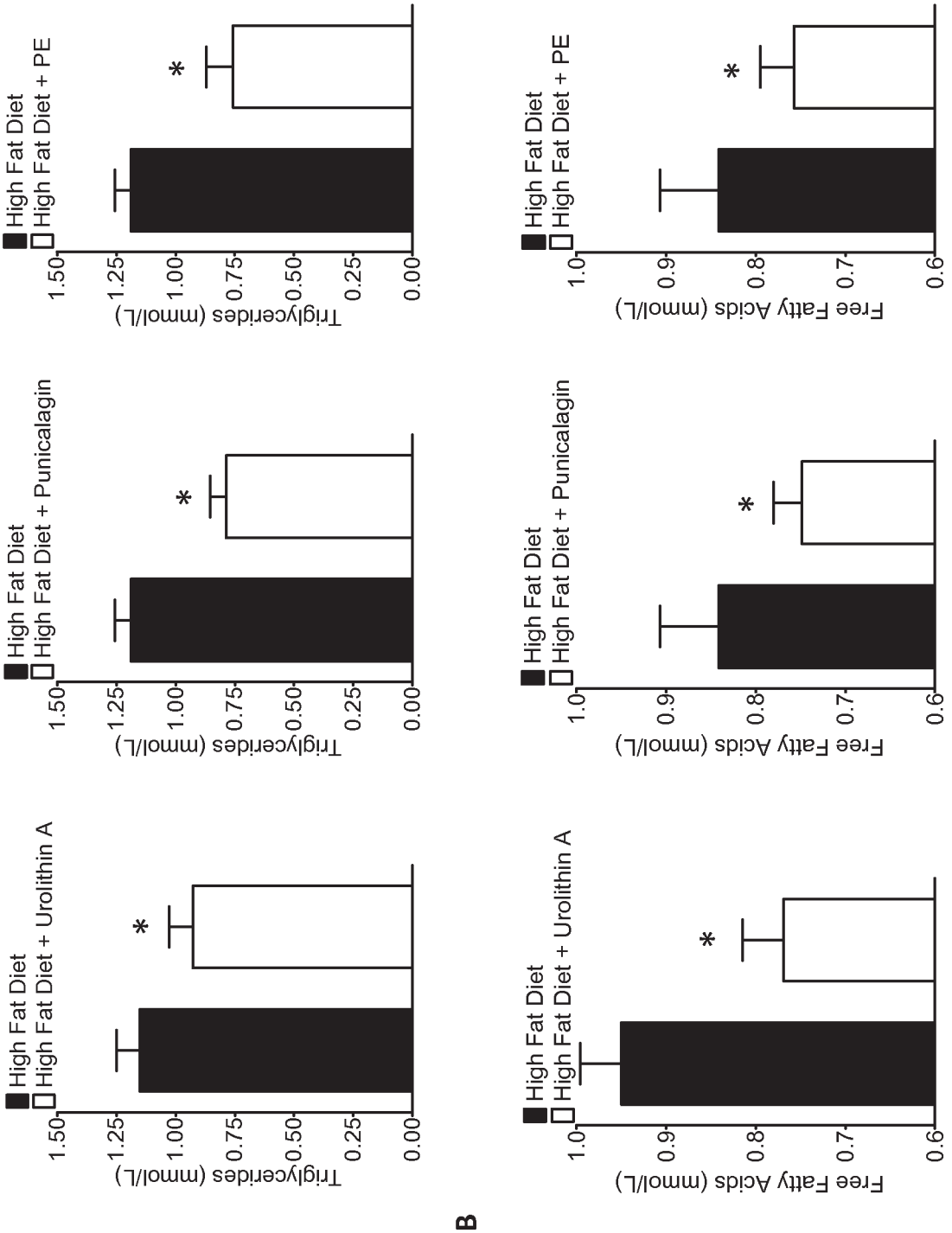
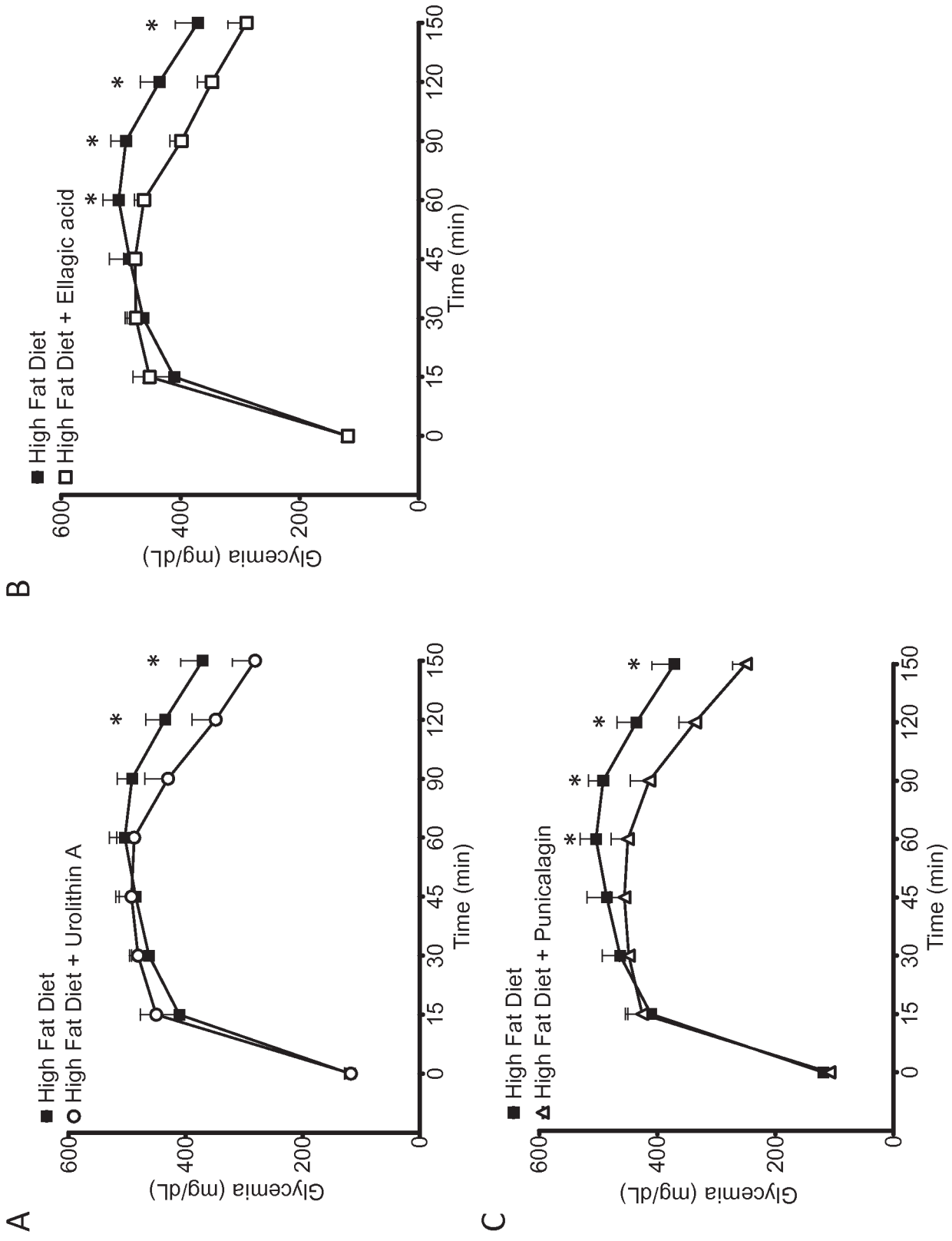

A
B
High Fat Diet
High Fat Diet + Urolithin A
High Fat Diet + Punicalagin
High Fat Diet + PE
Triglycerides (mmol/L)
Free Fatty Acids (mmol/L)
1.50
1.25
1.00
0.75
0.50
0.25
0.00
1.0
0.9
0.8
0.7
0.6
*

Figure 24


A
High Fat Diet
High Fat Diet + Urolithin A
Glycemia (mg/dL)
Time (min)
B
High Fat Diet
High Fat Diet + Ellagic acid
Glycemia (mg/dL)
Time (min)
C
High Fat Diet
High Fat Diet + Punicalagin
Glycemia (mg/dL)
Time (min)

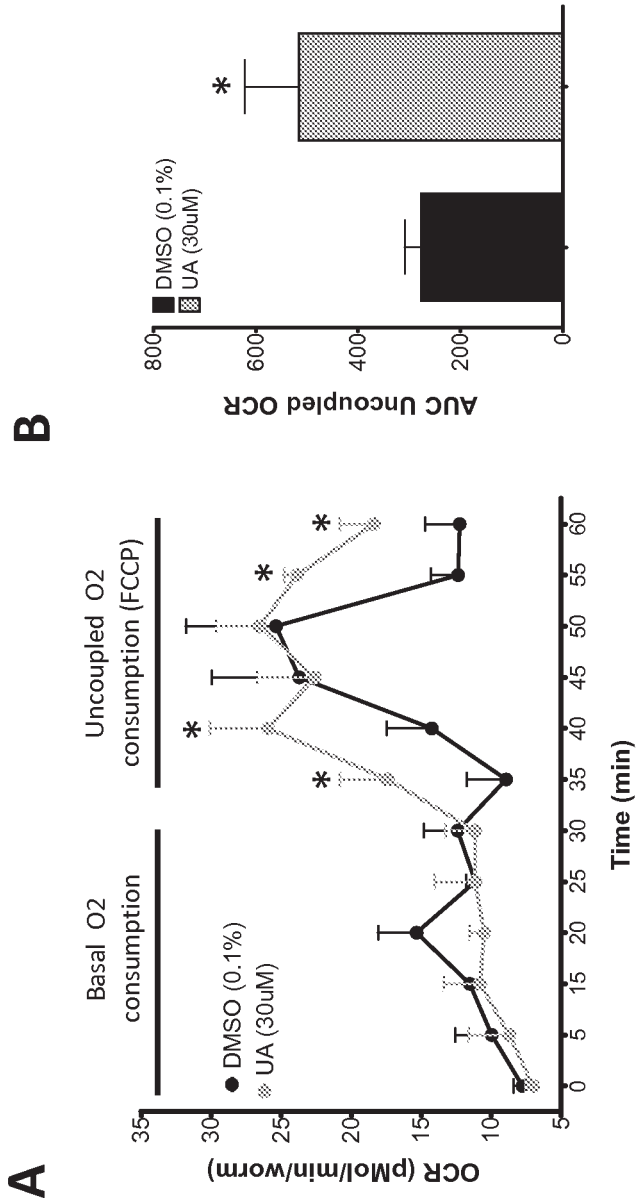

A
B
Basal O2 consumption
Uncoupled O2 consumption (FCCP)
DMSO (0.1%)
UA (30uM)
OCR (pMol/min/worm)
Time (min)
AUC Uncoupled OCR
*

Figure 25

**Figure 26**

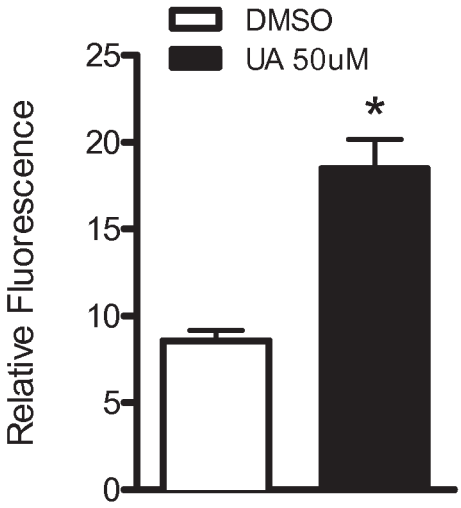
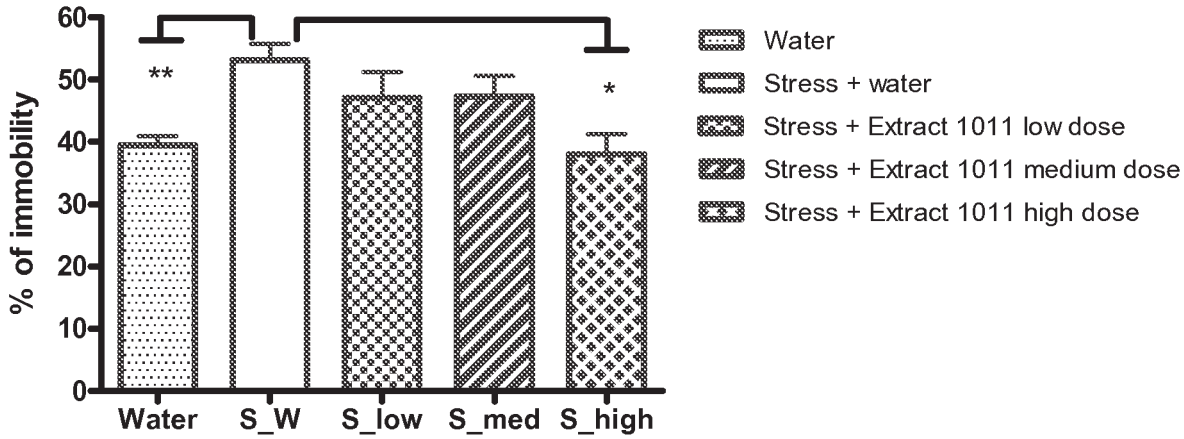
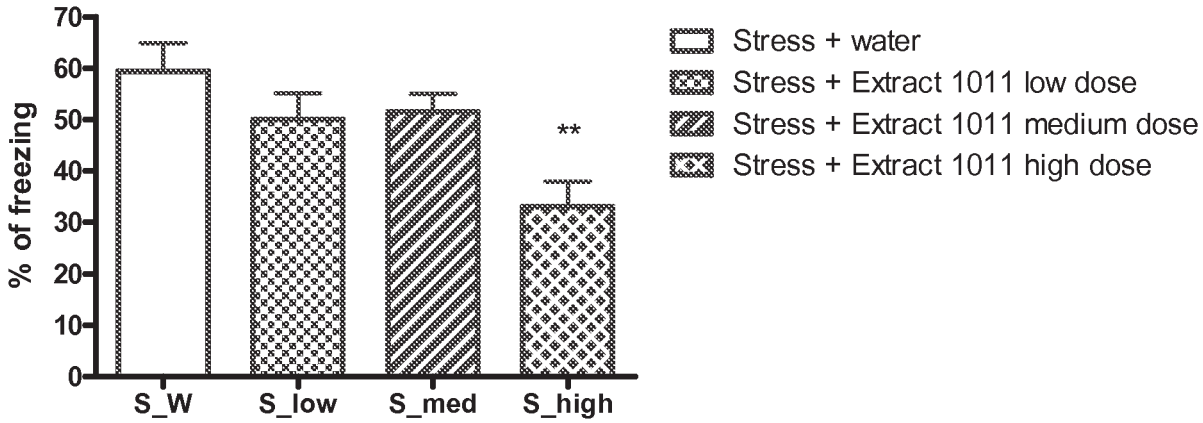


**Figure 27**




One way ANOVA followed by Dunnett's test
**p<0.01 vs water -non-stressed
*p<0.05 vs water -chronic stress

**Figure 28**




One way ANOVA followed by Dunnett's test:
** p<0.01 vs S_W

**Figure 29**

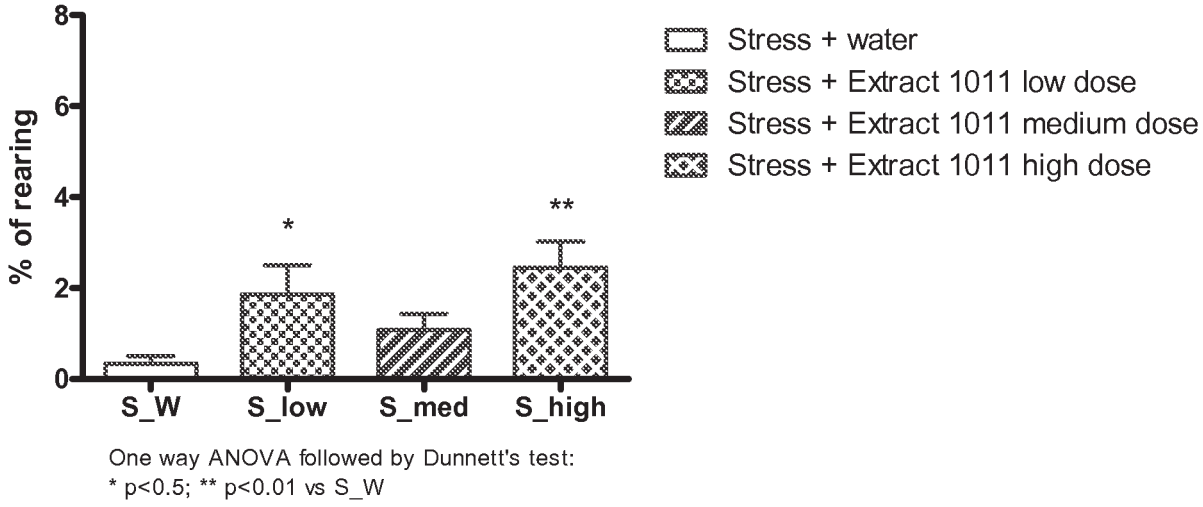



**Figure 30**

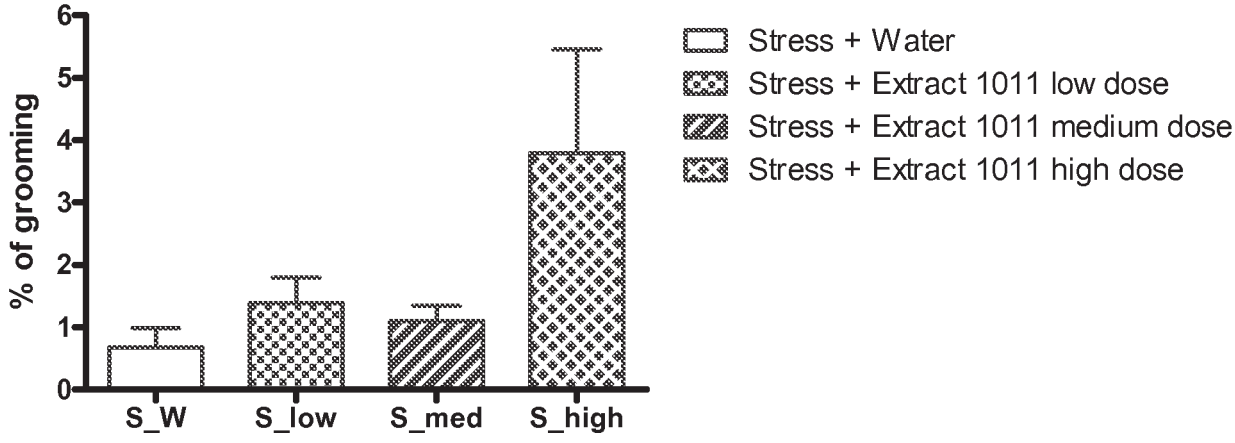


**Figure 31**

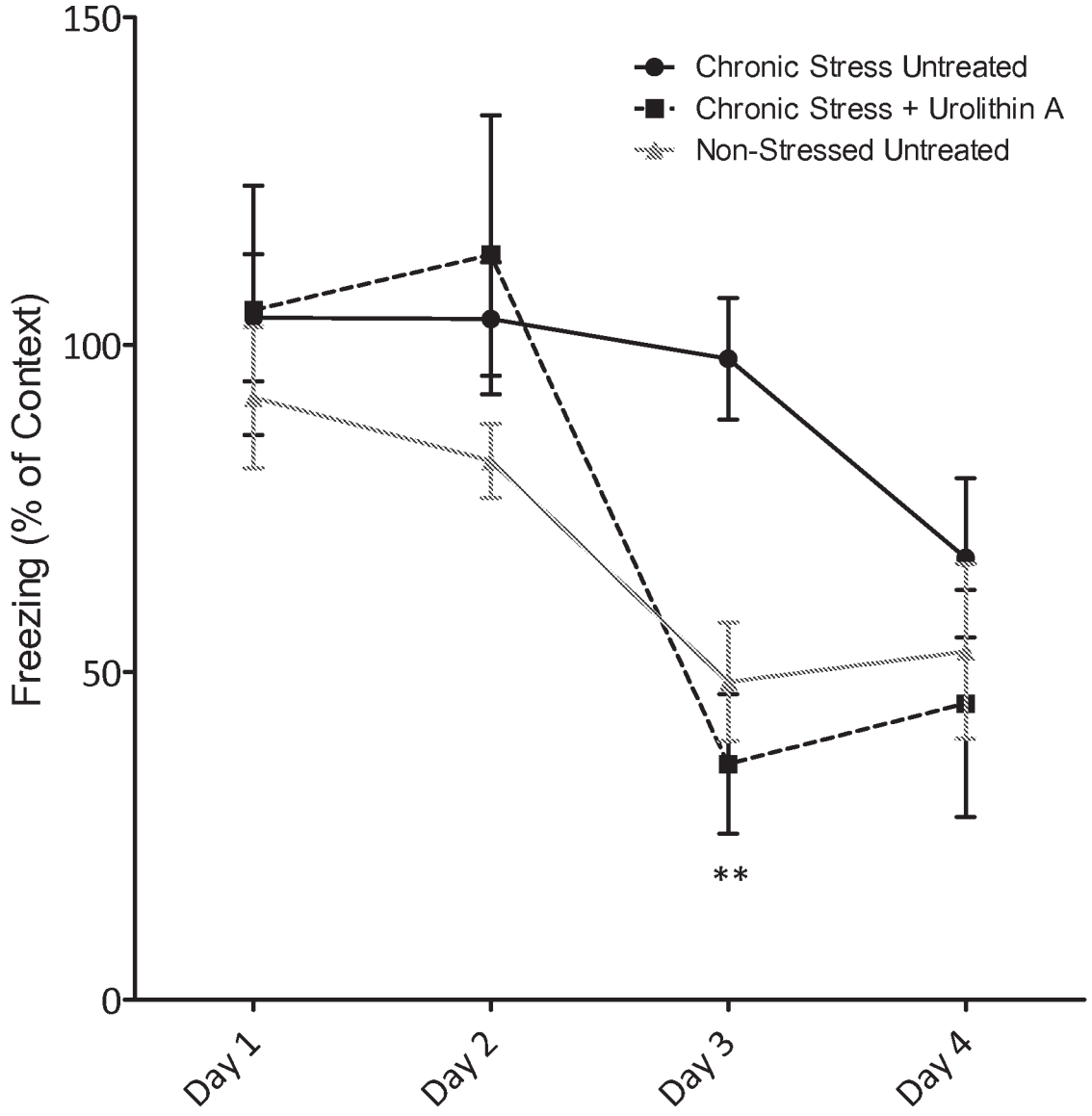
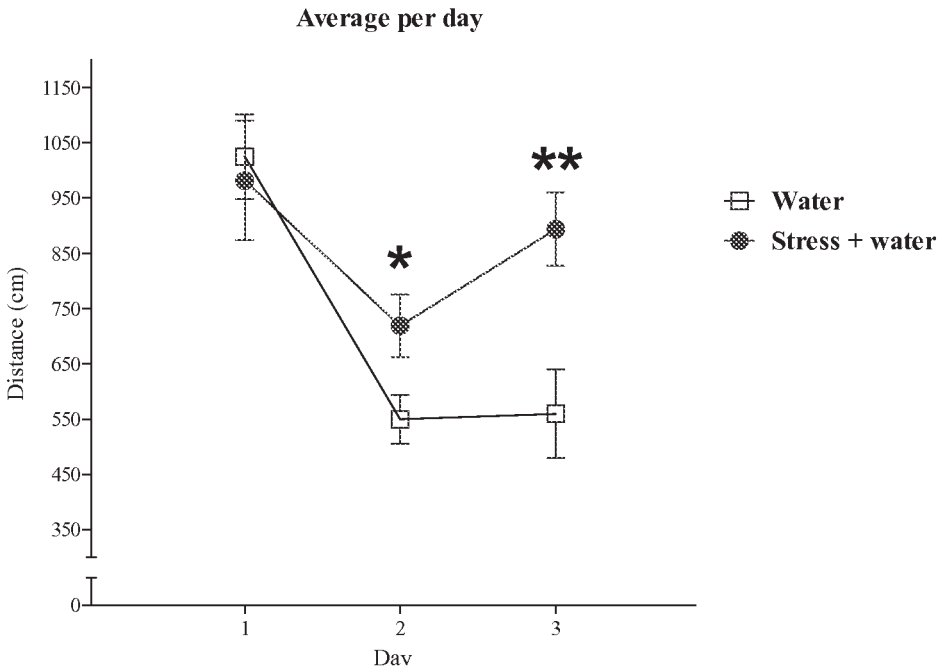
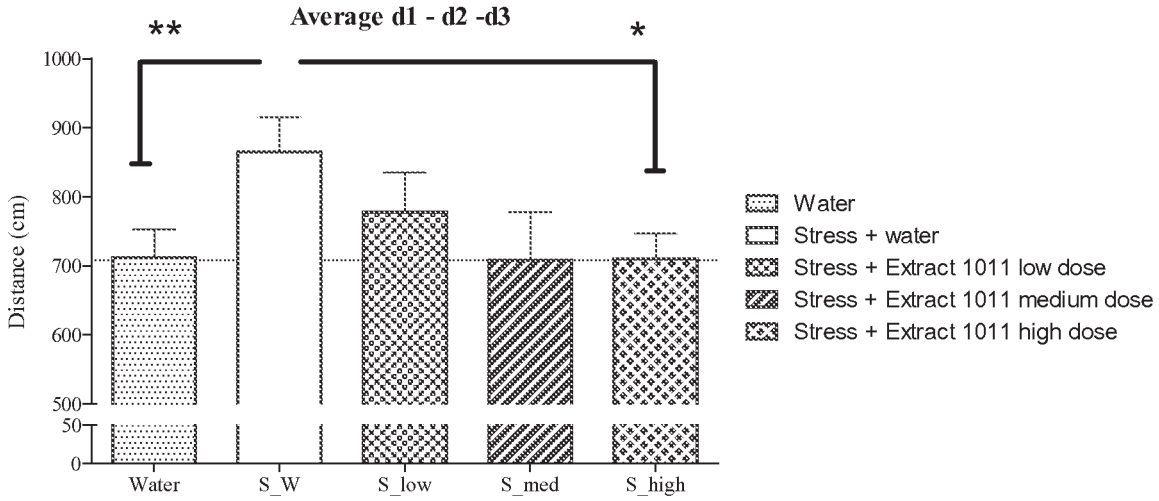

150
100
50
0
Freezing (% of Context)
Chronic Stress Untreated
Chronic Stress + Urolithin A
Non-Stressed Untreated
**
Day 1
Day 2
Day 3
Day 4

**Figure 32**




* p<0.05, **p<0.001 versus water

**Figure 33**




* p<0.05, **p<0.001 versus Stress + water, student's T-test

**Figure 34**

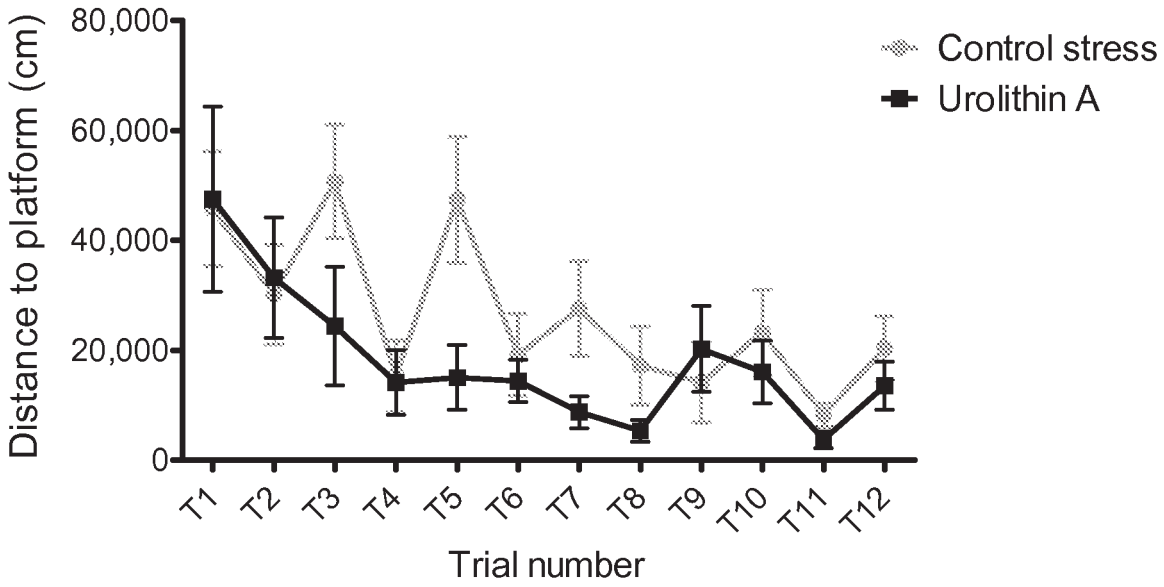

Distance to platform (cm)
80,000
60,000
40,000
20,000
0
T1
T2
T3
T4
T5
T6
T7
T8
T9
T10
T11
T12
Trial number
Control stress
Urolithin A

**Figure 35**

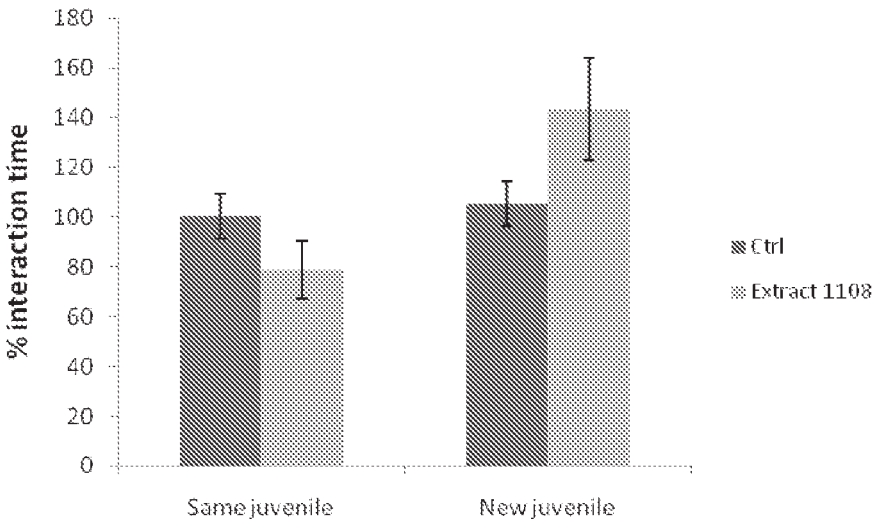



**Figure 36**

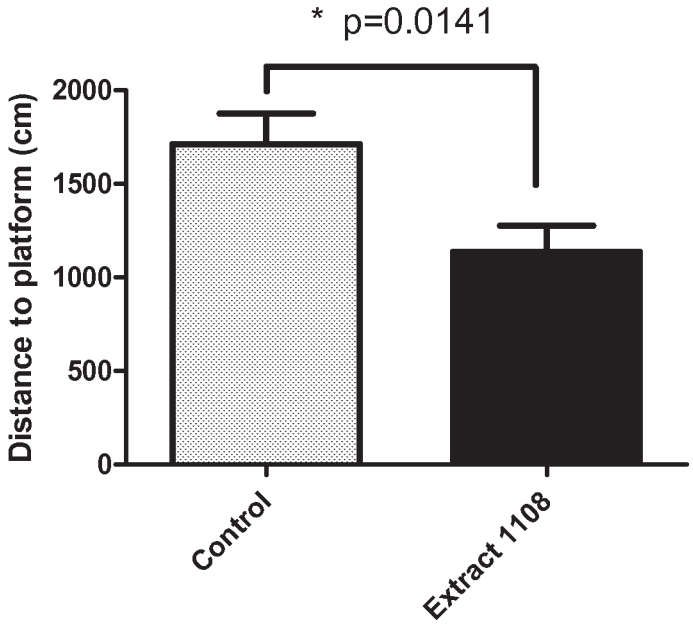


**Figure 37**

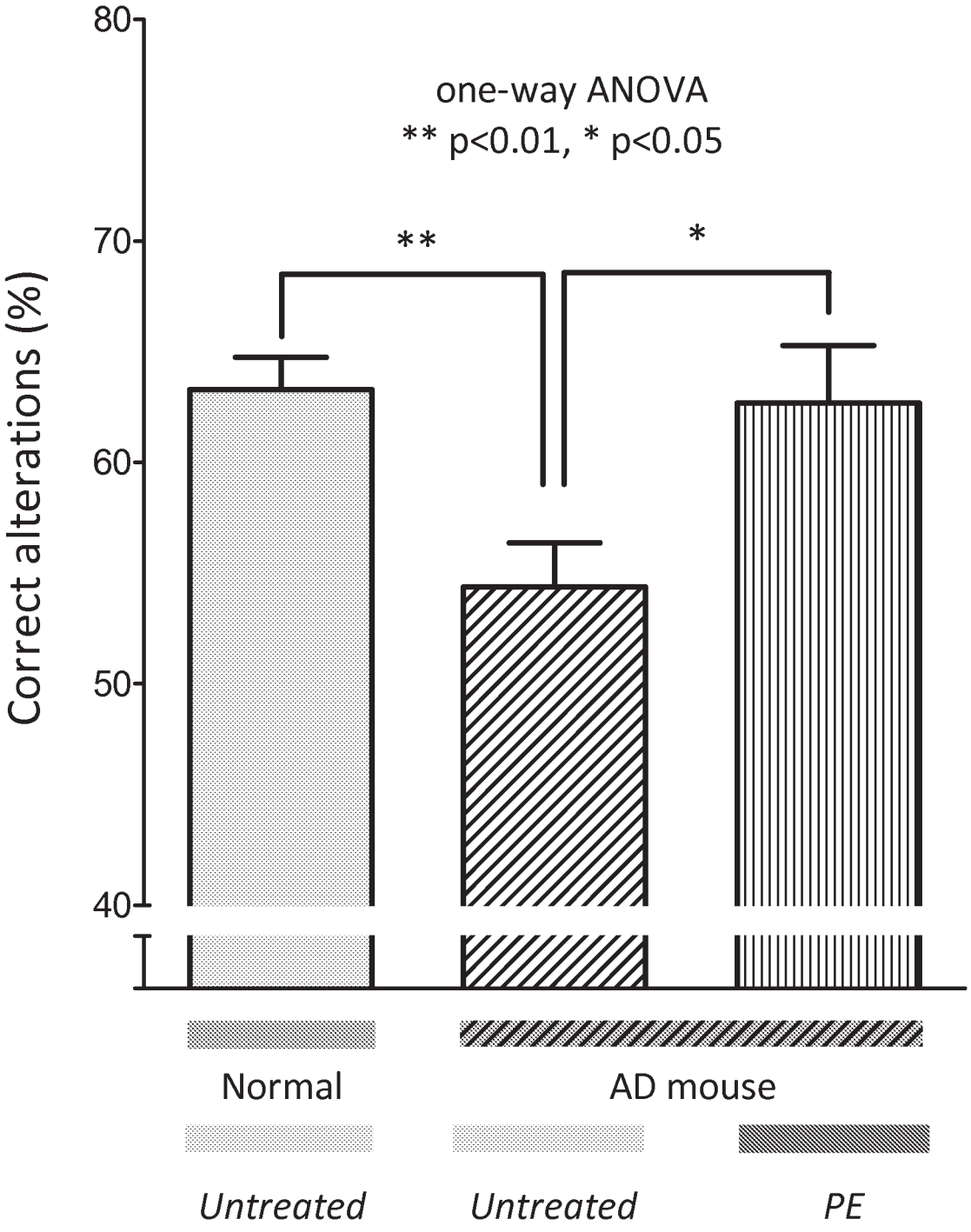

80
70
60
50
40
Correct alterations (%)
one-way ANOVA
** p<0.01, * p<0.05
**
*
Normal
AD mouse
Untreated
Untreated
PE

Figure 38

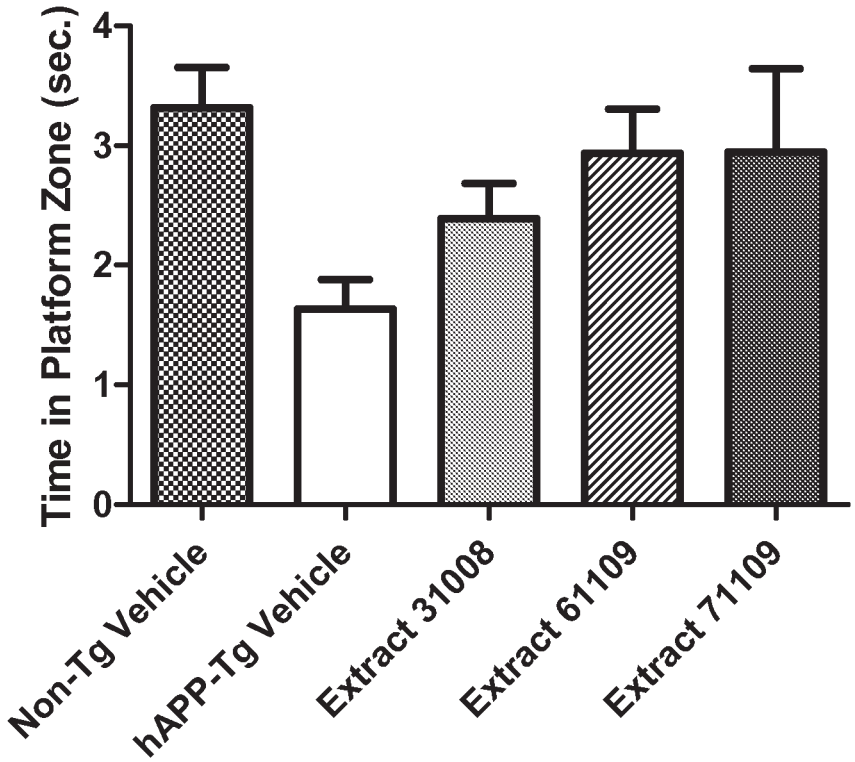

Time in Platform Zone (sec.)
0
1
2
3
4
Non-Tg Vehicle
hAPP-Tg Vehicle
Extract 31008
Extract 61109
Extract 71109

**Figure 39**

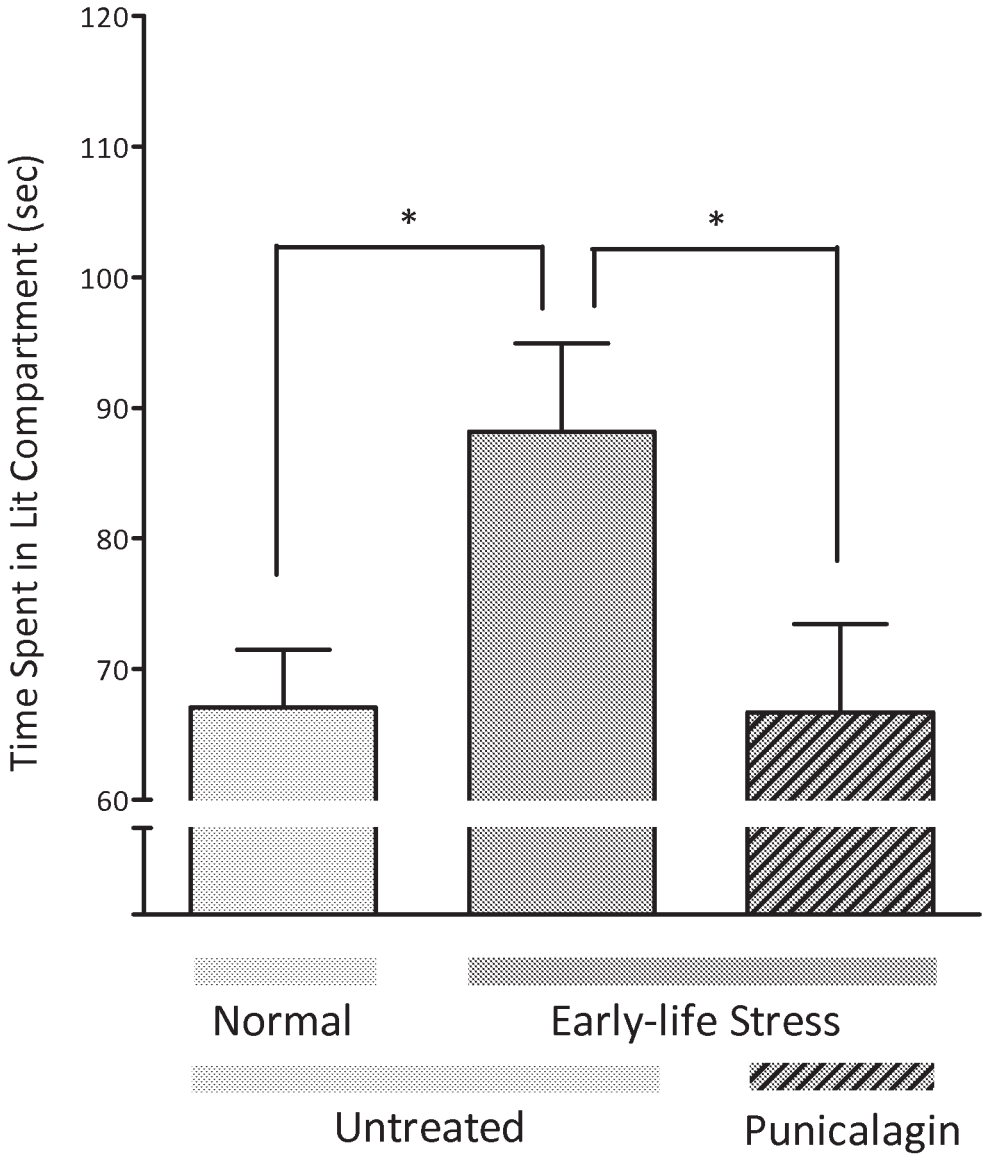

120
110
100
90
80
70
60
Time Spent in Lit Compartment (sec)
*
*
Normal
Early-life Stress
Untreated
Punicalagin

**Figure 40**

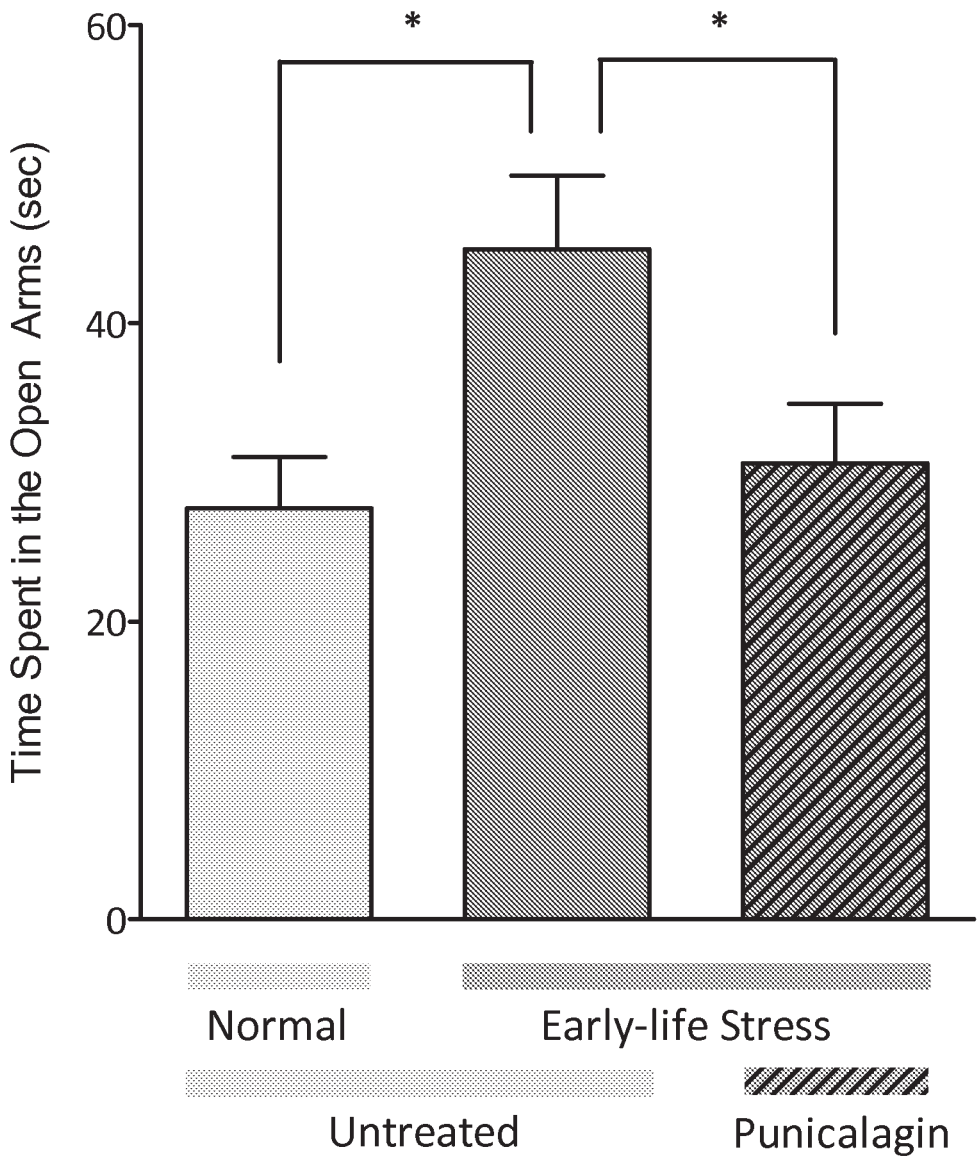

60
40
20
0
Time Spent in the Open Arms (sec)
*
*
Normal
Early-life Stress
Untreated
Punicalagin

**Figure 41**

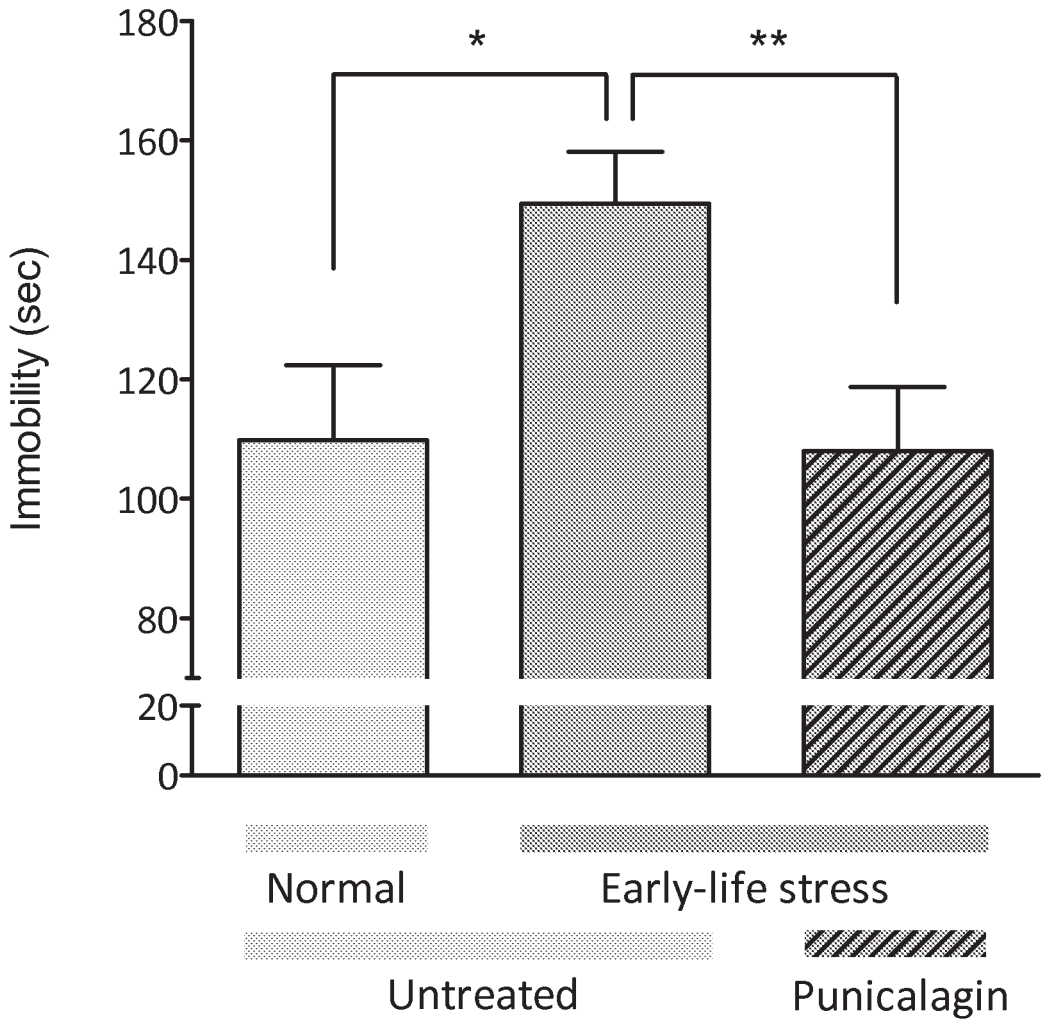

180
160
140
120
100
80
20
0
Immobility (sec)
*
**
Normal
Early-life stress
Untreated
Punicalagin

**Figure 42**

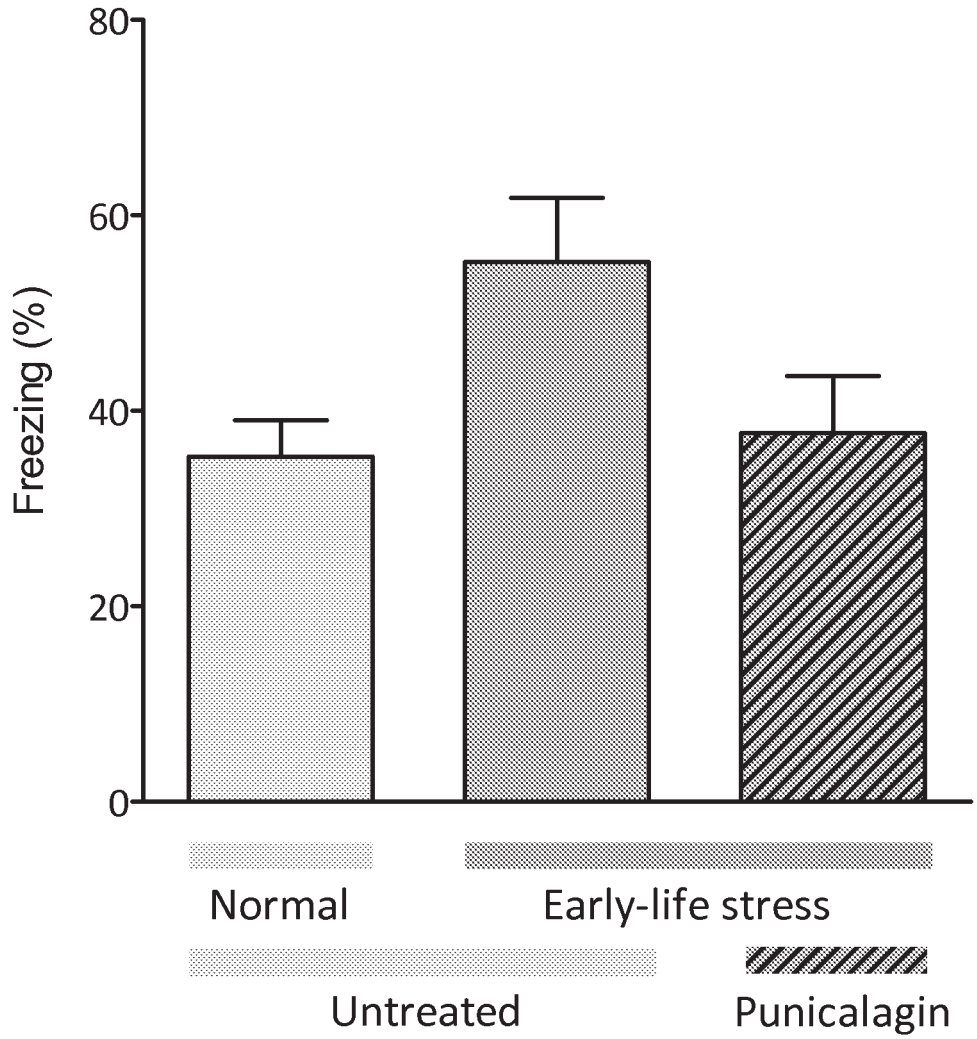

80
60
40
20
0
Freezing (%)
Normal
Early-life stress
Untreated
Punicalagin

**Figure 43**

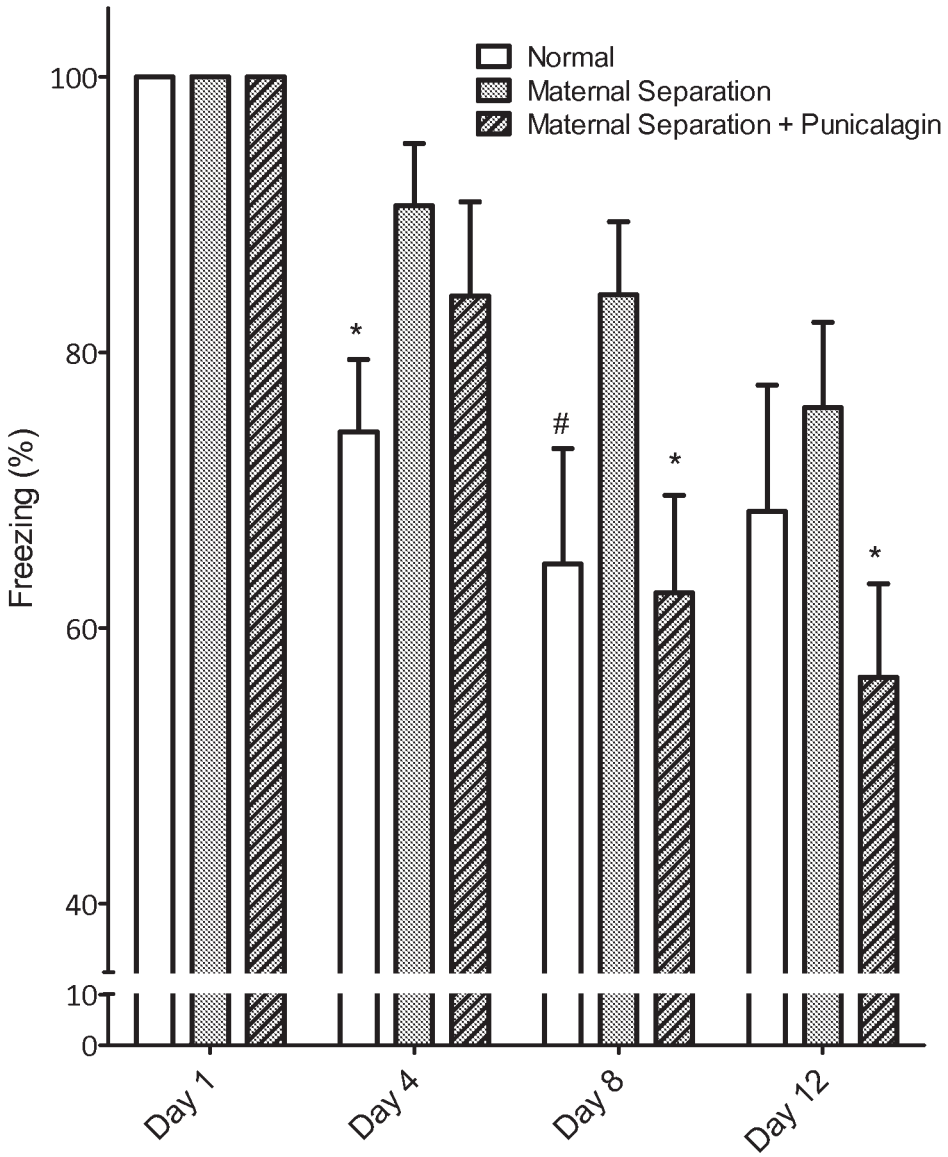

Normal
Maternal Separation
Maternal Separation + Punicalagin
Freezing (%)
100
80
60
40
10
0
*
#
*
*
Day 1
Day 4
Day 8
Day 12

**Figure 44**

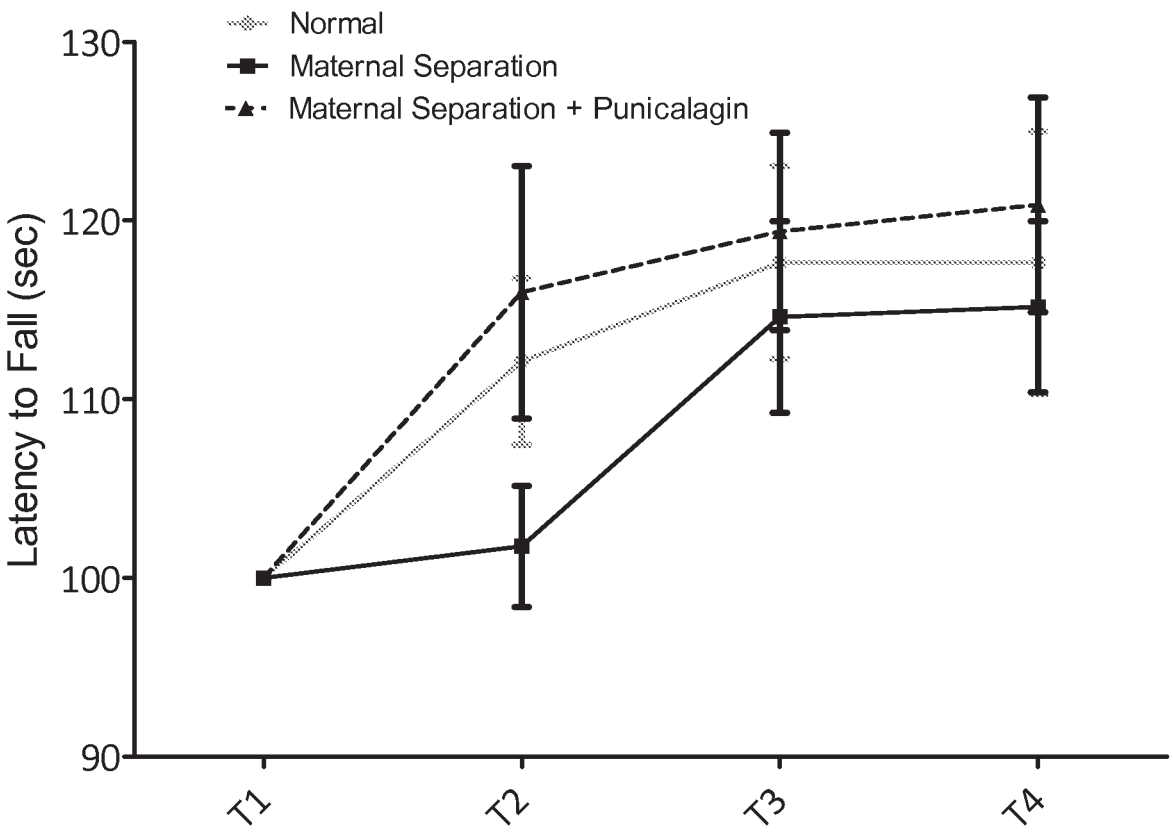

Normal
Maternal Separation
Maternal Separation + Punicalagin
Latency to Fall (sec)
130
120
110
100
90
T1
T2
T3
T4

**Figure 45**

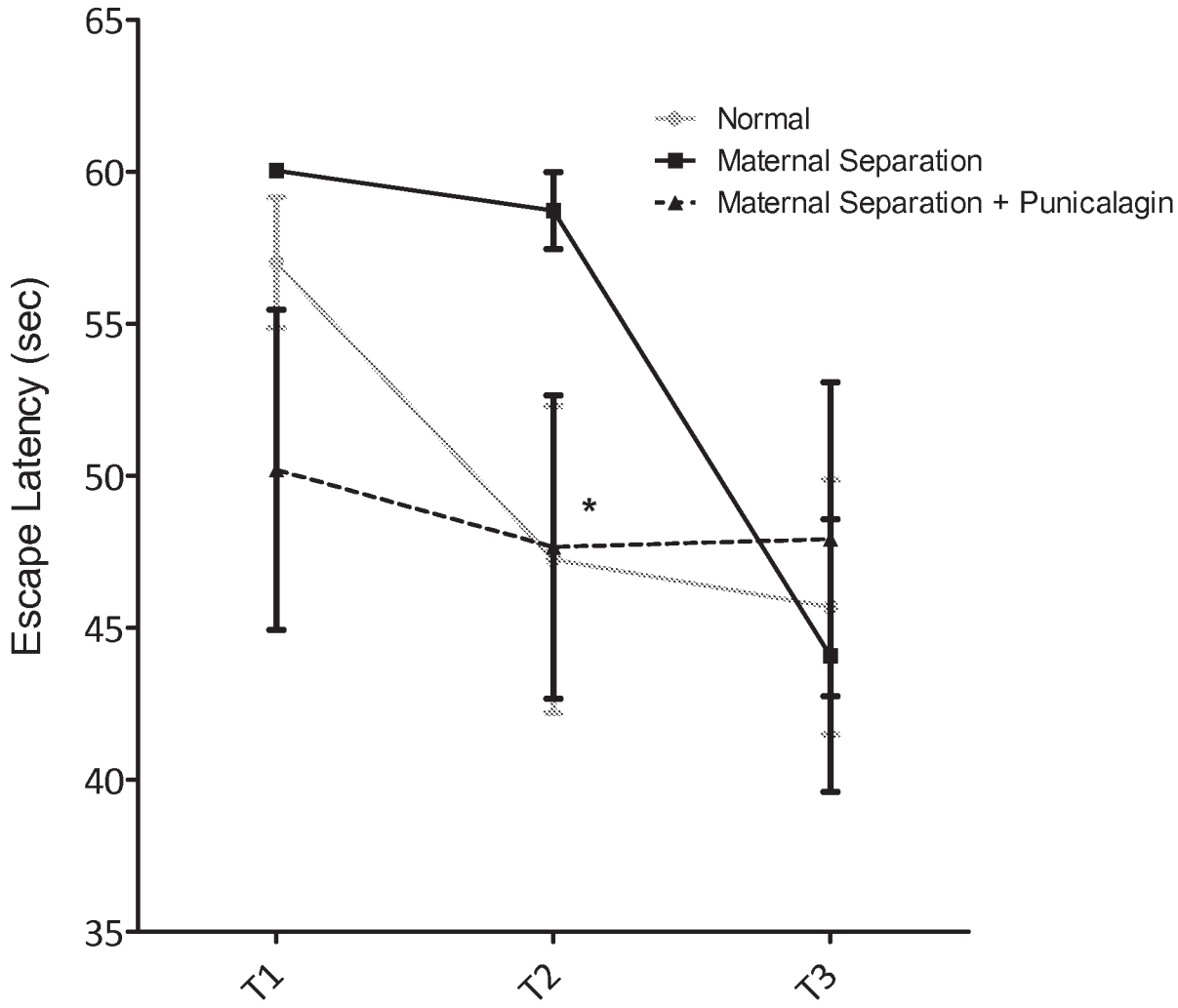

65
60
55
50
45
40
35
Escape Latency (sec)
T1
T2
T3
*
Normal
Maternal Separation
Maternal Separation + Punicalagin

**Figure 46**

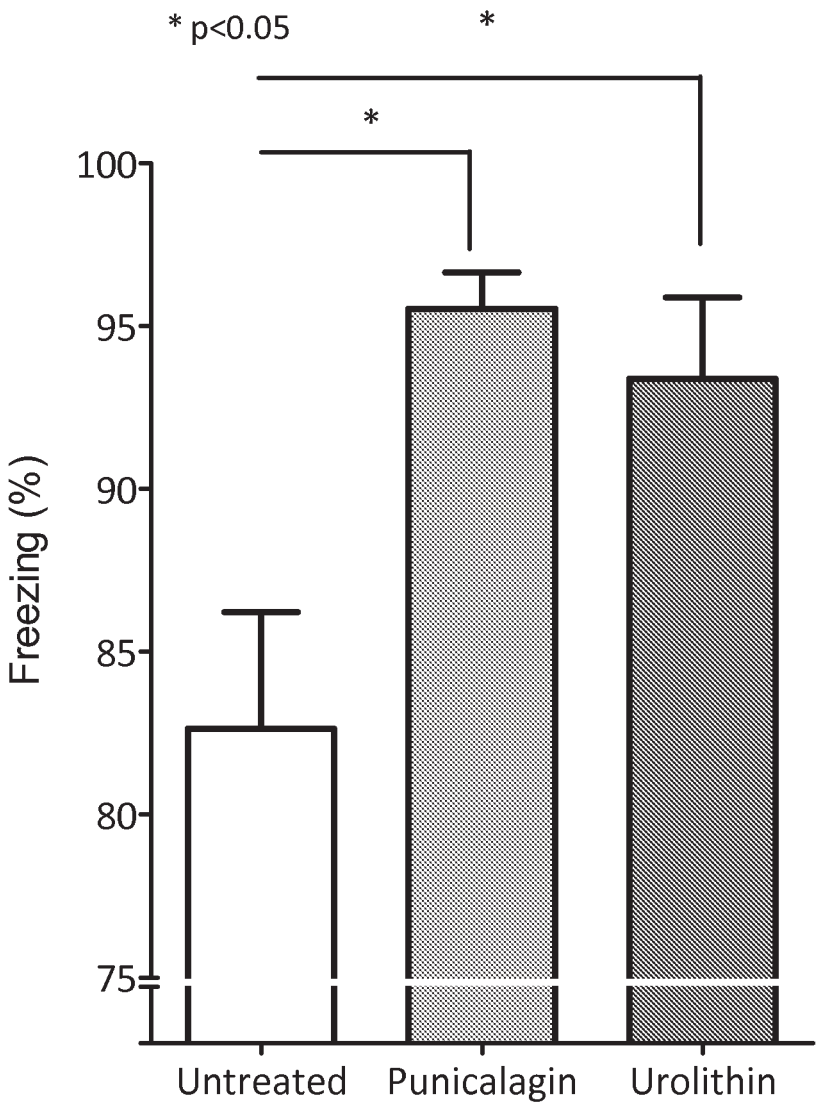

* p<0.05
*
*
100
95
90
85
80
75
Freezing (%)
Untreated
Punicalagin
Urolithin

**Figure 47**

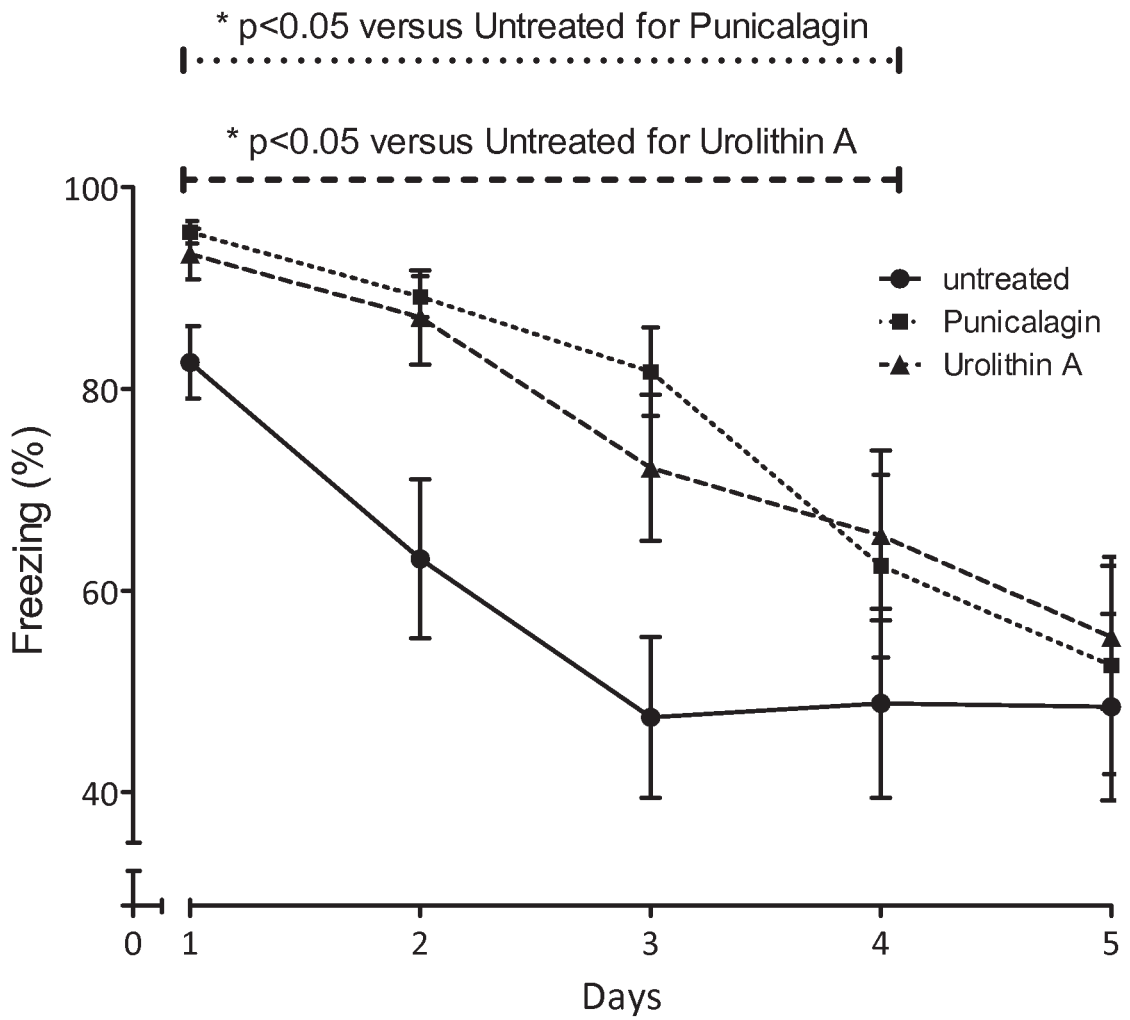

* p<0.05 versus Untreated for Punicalagin
* p<0.05 versus Untreated for Urolithin A
100
80
60
40
Freezing (%)
untreated
Punicalagin
Urolithin A
0
1
2
3
4
5
Days

**Figure 48**

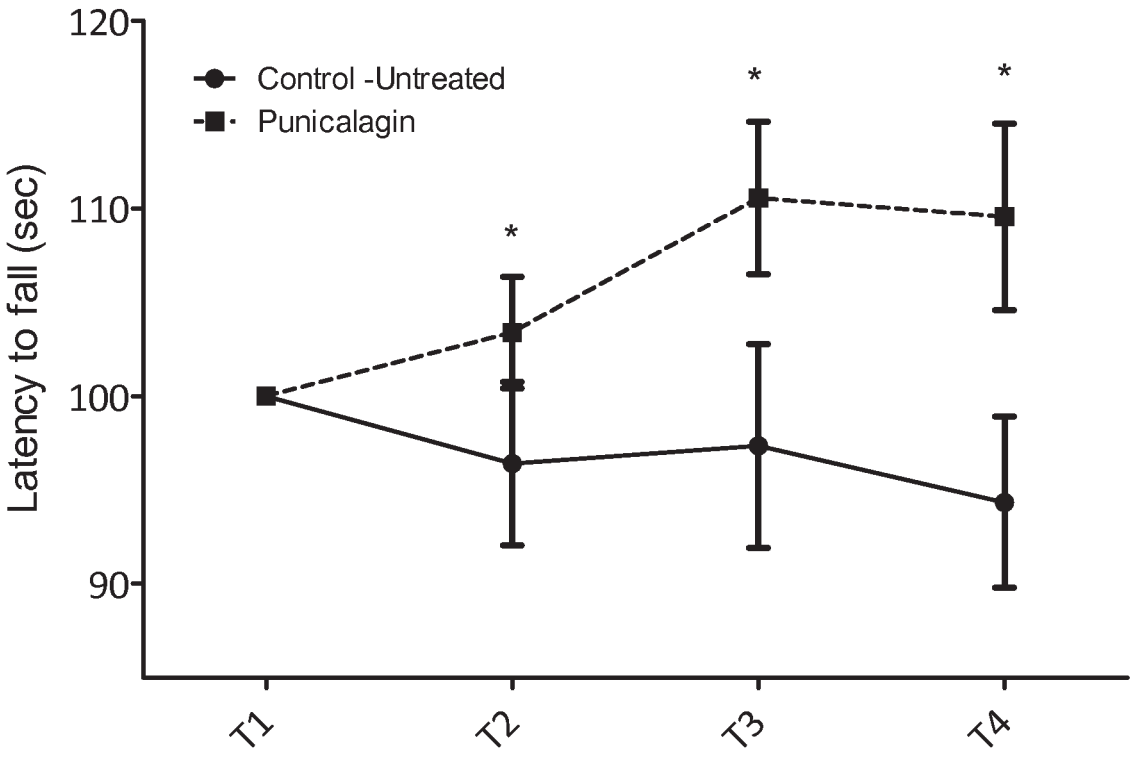
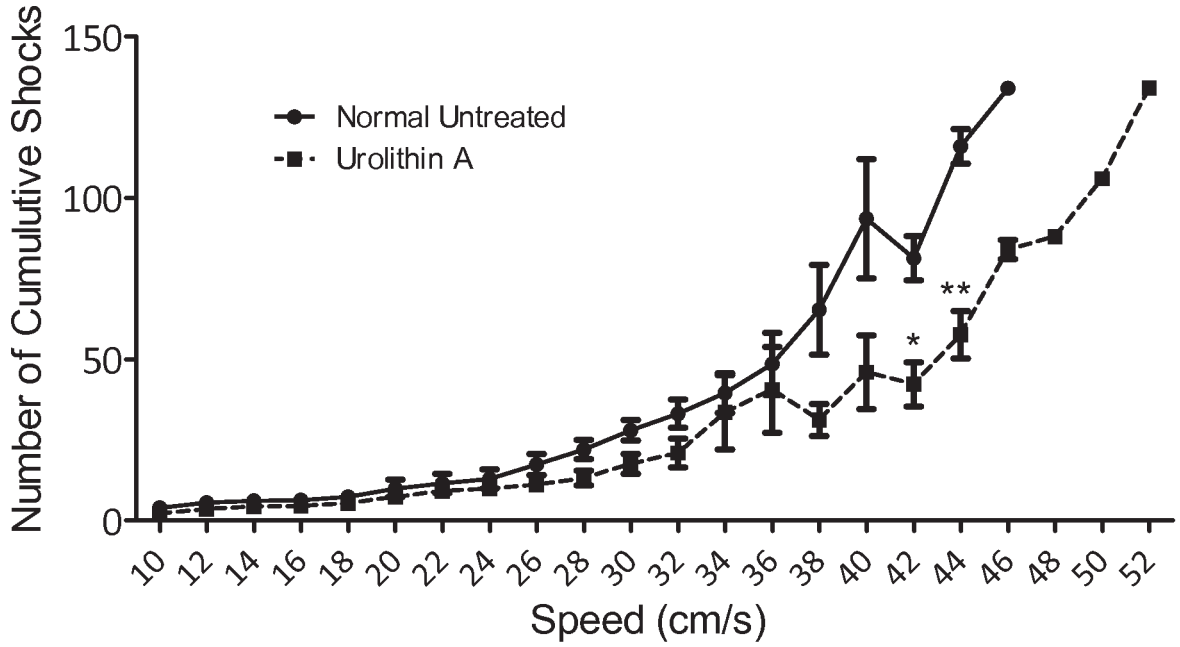

120
110
100
90
Latency to fall (sec)
Control -Untreated
Punicalagin
*
*
*
T1
T2
T3
T4

**Figure 49**


Number of Cumulutive Shocks
150
100
50
0
Normal Untreated
Urolithin A
*
**
10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52
Speed (cm/s)