FIG. 1

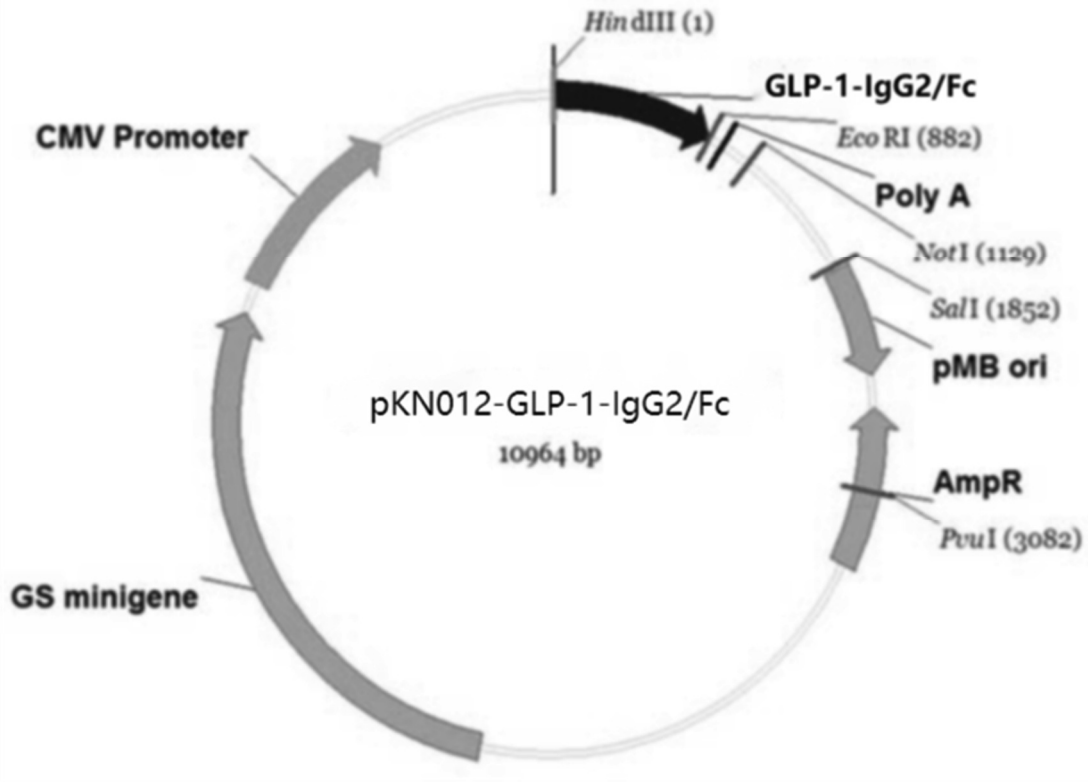

HindIII (1)
GLP-1-IgG2/Fc
EcoRI (882)
Poly A
NotI (1129)
SalI (1852)
pMB ori
AmpR
PvuI (3082)
CMV Promoter
GS minigene
pKN012-GLP-1-IgG2/Fc
10964 bp

FIG. 2

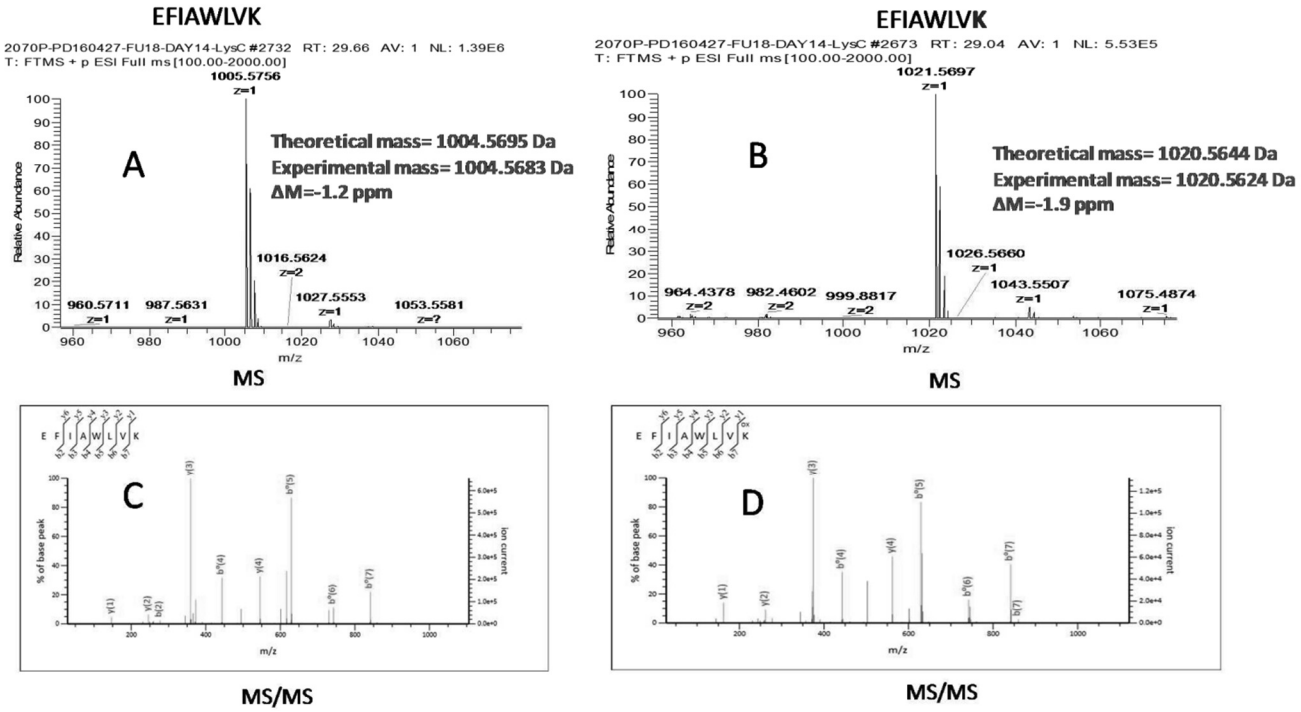
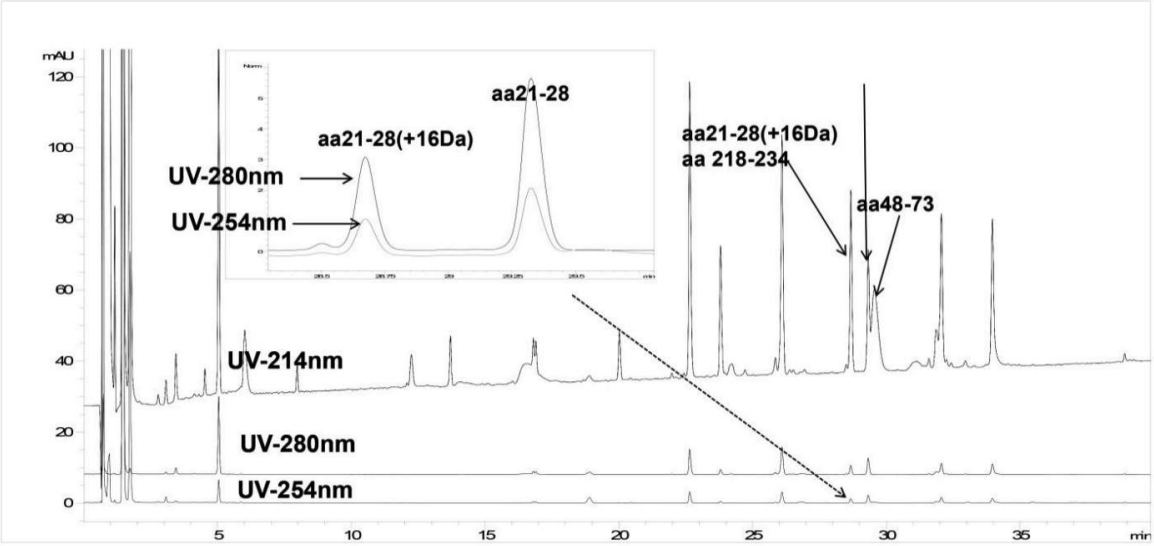

EFIAWLVK
2070P-PD160427-FU18-DAY14-LysC #2732 RT: 29.66 AV: 1 NL: 1.39E6
T: FTMS + p ESI Full ms [100.00-2000.00]
A
Theoretical mass= 1004.5695 Da
Experimental mass= 1004.5683 Da
ΔM=-1.2 ppm
1005.5756 z=1
1016.5624 z=2
960.5711 z=1
987.5631 z=1
1027.5553 z=1
1053.5581 z=?
Relative Abundance
m/z
MS
EFIAWLVK
2070P-PD160427-FU18-DAY14-LysC #2673 RT: 29.04 AV: 1 NL: 5.53E5
T: FTMS + p ESI Full ms [100.00-2000.00]
B
Theoretical mass= 1020.5644 Da
Experimental mass= 1020.5624 Da
ΔM=-1.9 ppm
1021.5697 z=1
1026.5660 z=1
964.4378 z=2
982.4602 z=2
999.8817 z=2
1043.5507 z=1
1075.4874 z=1
Relative Abundance
m/z
MS
C
% of base peak
Ion current
m/z
MS/MS
D
% of base peak
Ion current
m/z
MS/MS

FIG. 3A



ε_W= 5500

ε_Y= 1490

21-28	EFIA**W**LVK
218-234	TTPPMLDSDGSFFL**Y**SK
48-73	SCVECPPCPAPPVAGPSVFLFPPKPK

FIG. 3B

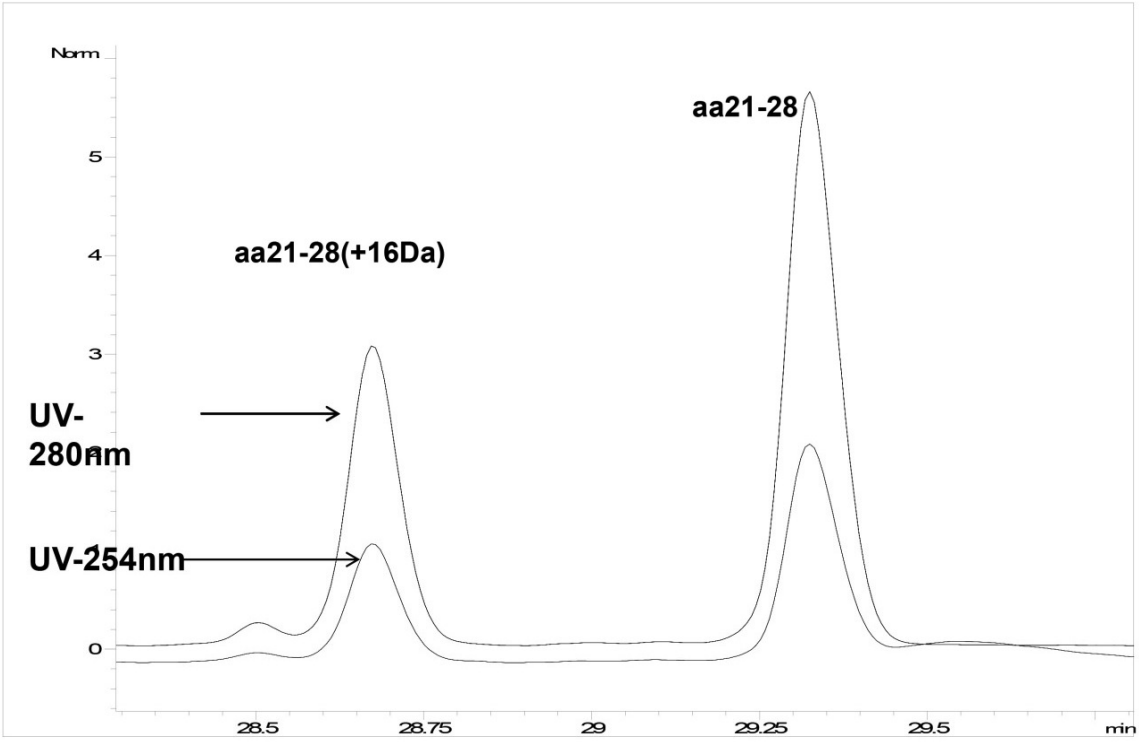

Norm
5
4
3
0
aa21-28
aa21-28(+16Da)
UV-280nm
UV-254nm
28.5
28.75
29
29.25
29.5
min

FIG. 4

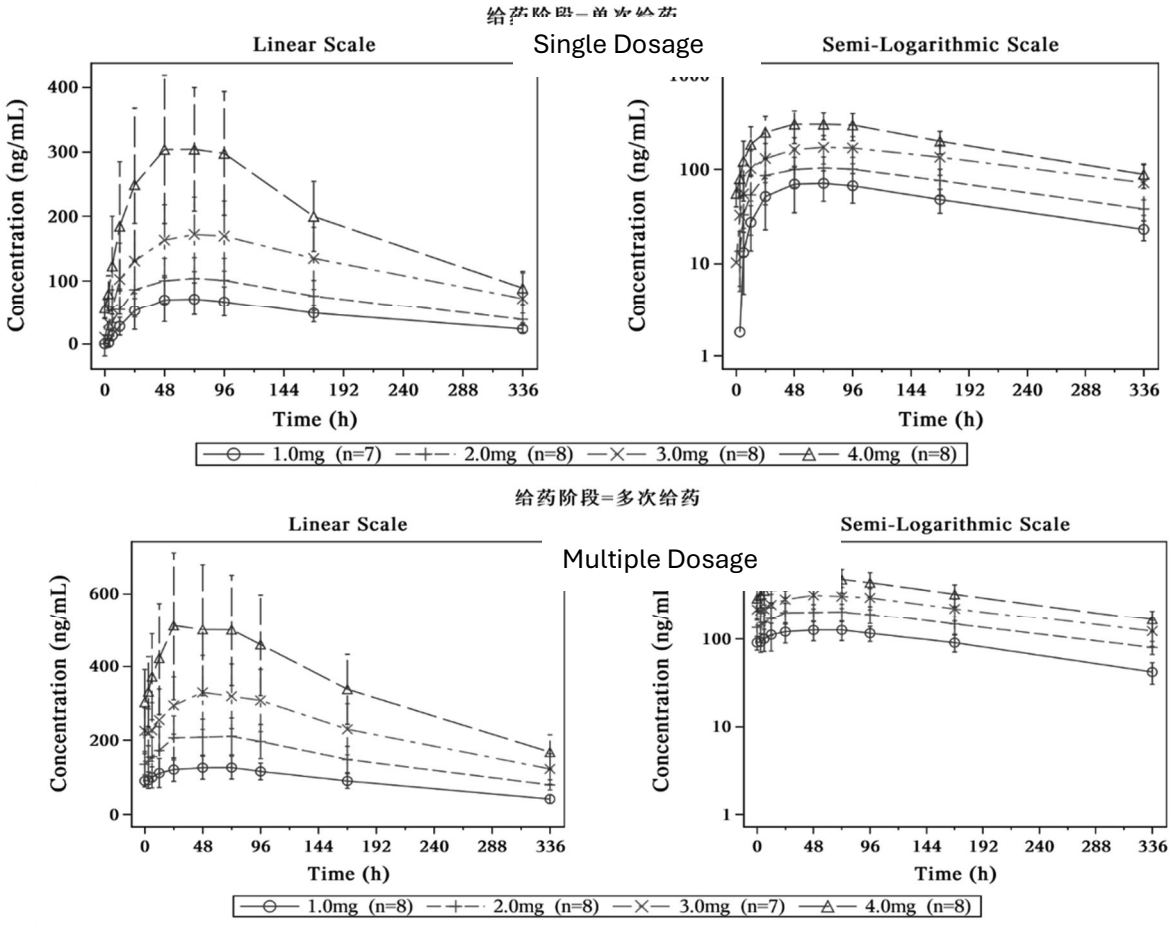

给药阶段=单次给药
Single Dosage
Linear Scale
Semi-Logarithmic Scale
Concentration (ng/mL)
Time (h)
1.0mg (n=7)
2.0mg (n=8)
3.0mg (n=8)
4.0mg (n=8)
给药阶段=多次给药
Multiple Dosage
Linear Scale
Semi-Logarithmic Scale
Concentration (ng/mL)
Concentration (ng/ml
Time (h)
1.0mg (n=8)
2.0mg (n=8)
3.0mg (n=7)
4.0mg (n=8)

FIG. 5

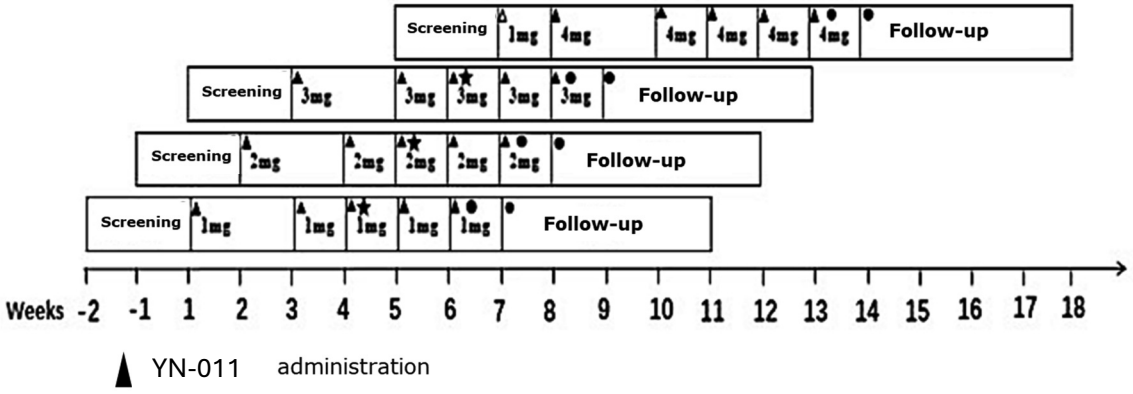

Screening
1mg
4mg
4mg
4mg
4mg
4mg
Follow-up
Screening
3mg
3mg
3mg
3mg
3mg
3mg
Follow-up
Screening
2mg
2mg
2mg
2mg
2mg
2mg
Follow-up
Screening
1mg
1mg
1mg
1mg
1mg
1mg
Follow-up
Weeks -2 -1 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
YN-011 administration

FIG. 6

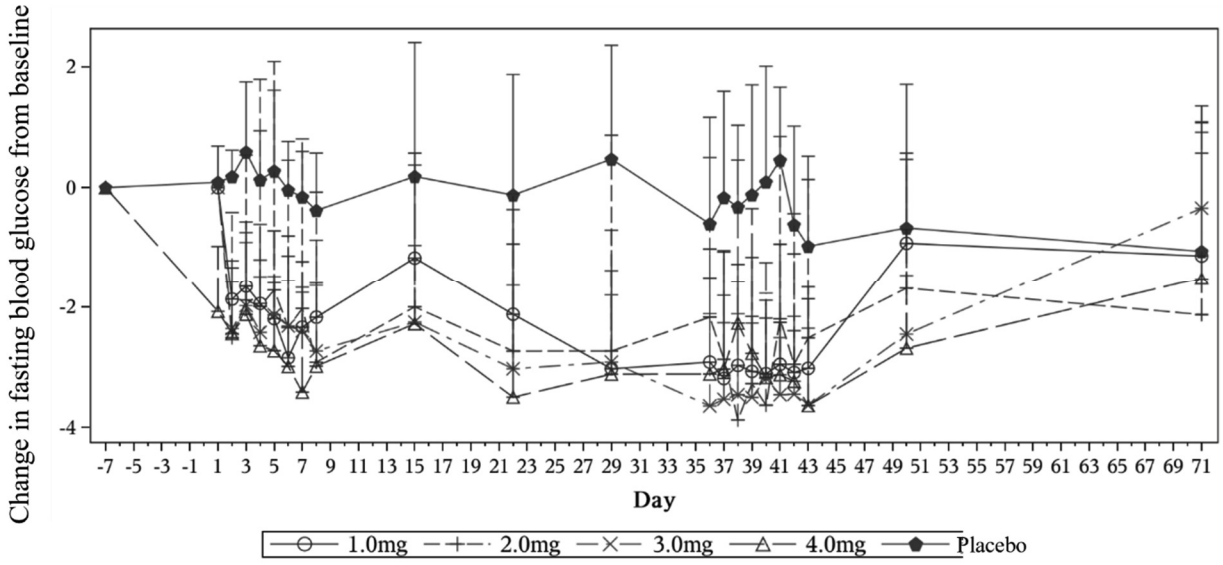

Change in fasting blood glucose from baseline
2
0
-2
-4
-7 -5 -3 -1 1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35 37 39 41 43 45 47 49 51 53 55 57 59 61 63 65 67 69 71
Day
1.0mg
2.0mg
3.0mg
4.0mg
Placebo

FIG. 7

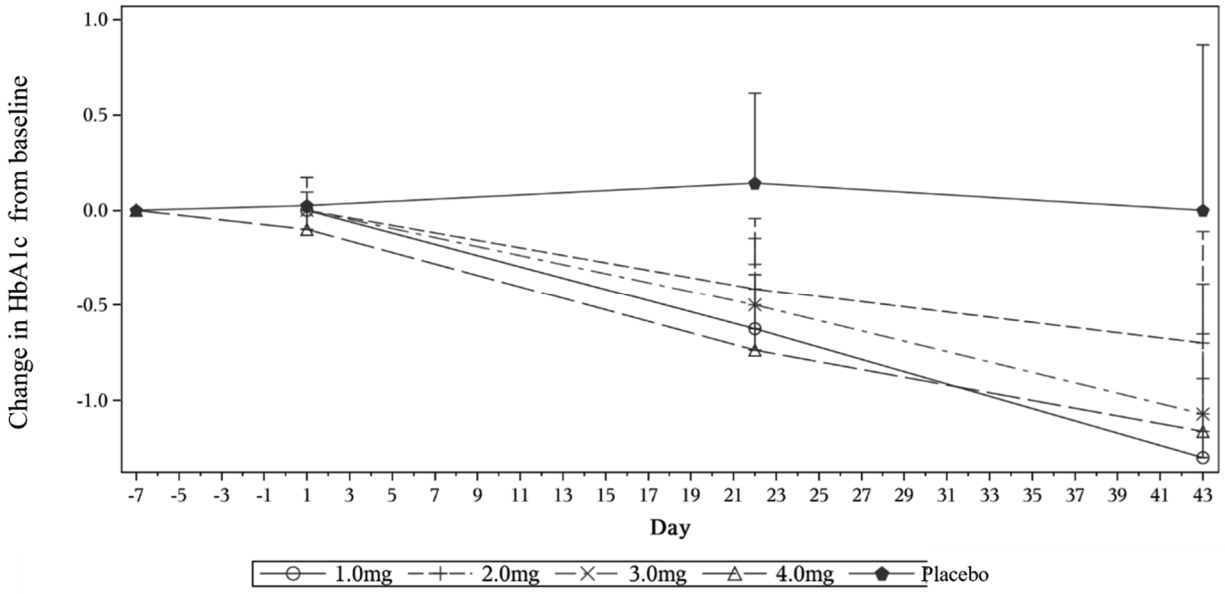

Change in HbA1c from baseline
1.0
0.5
0.0
-0.5
-1.0
-7 -5 -3 -1 1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35 37 39 41 43
Day
1.0mg
2.0mg
3.0mg
4.0mg
Placebo

FIG. 8

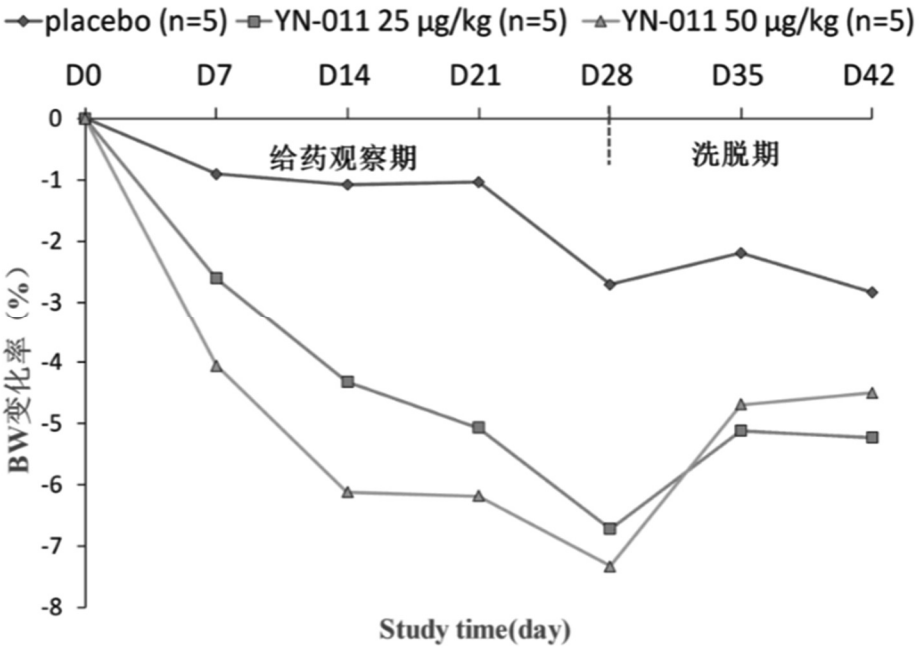

placebo (n=5)
YN-011 25 μg/kg (n=5)
YN-011 50 μg/kg (n=5)
D0
D7
D14
D21
D28
D35
D42
0
-1
-2
-3
-4
-5
-6
-7
-8
给药观察期
洗脱期
BW变化率（%）
Study time(day)

FIG. 9

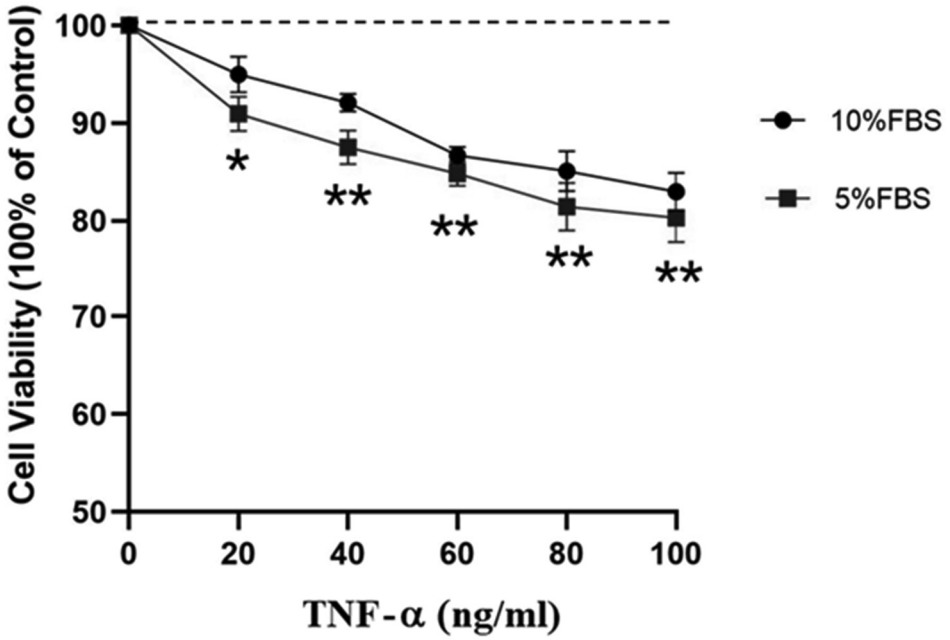

Cell Viability (100% of Control)
100
90
80
70
60
50
0
20
40
60
80
100
TNF-α (ng/ml)
*
**
**
**
**
10%FBS
5%FBS

FIG. 10

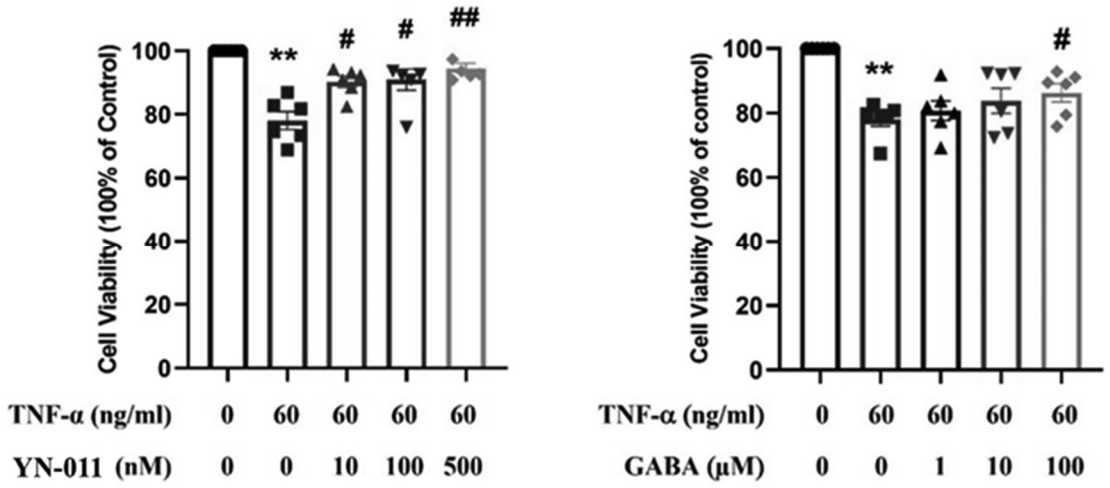

Cell Viability (100% of Control)
100
80
60
40
20
0
**
#
#
##
TNF-α (ng/ml) 0 60 60 60 60
YN-011 (nM) 0 0 10 100 500
Cell Viability (100% of control)
100
80
60
40
20
0
**
#
TNF-α (ng/ml) 0 60 60 60 60
GABA (μM) 0 0 1 10 100

FIG. 11

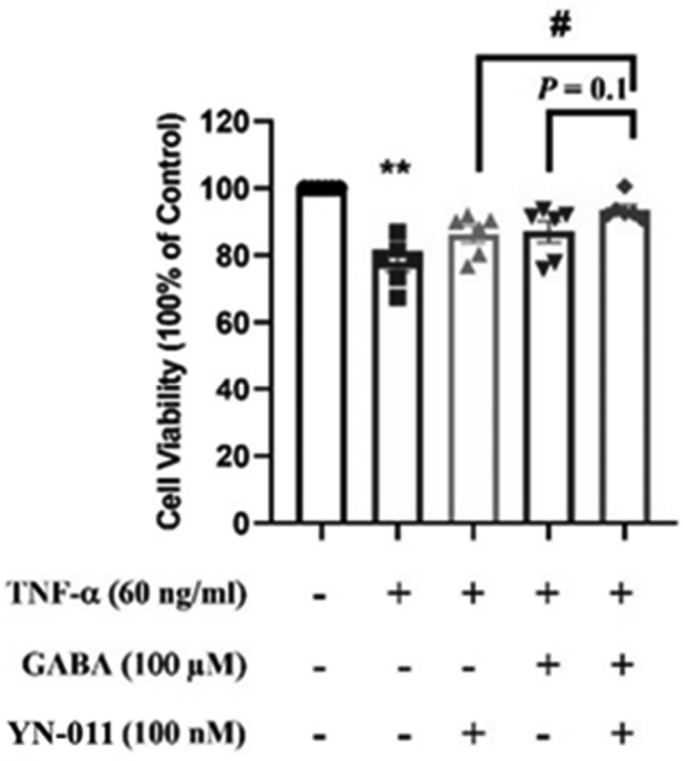

#
P = 0.1
**
Cell Viability (100% of Control)
120
100
80
60
40
20
0
TNF-α (60 ng/ml) - + + + +
GABA (100 μM) - - - + +
YN-011 (100 nM) - - + - +

FIG. 12

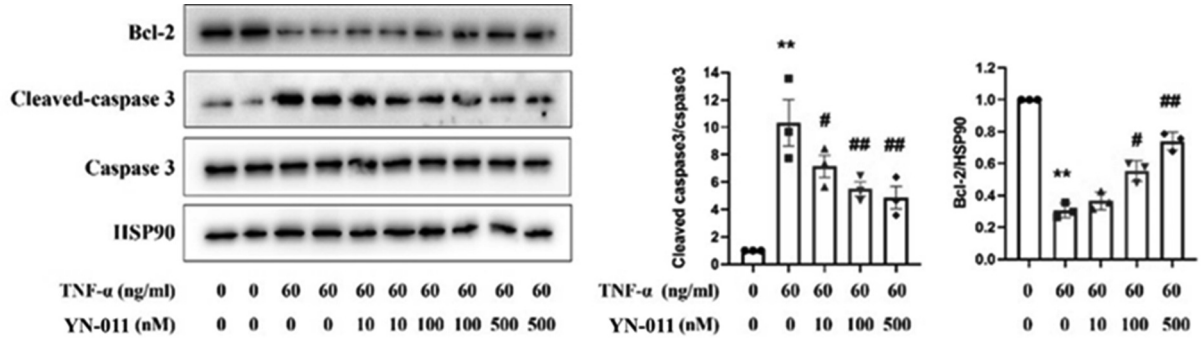

Bcl-2
Cleaved-caspase 3
Caspase 3
HSP90
TNF-α (ng/ml) 0 0 60 60 60 60 60 60 60 60
YN-011 (nM) 0 0 0 0 10 10 100 100 500 500
Cleaved caspase3/cspase3
TNF-α (ng/ml) 0 60 60 60 60
YN-011 (nM) 0 0 10 100 500
Bcl-2/HSP90
0 60 60 60 60
0 0 10 100 500

FIG. 13

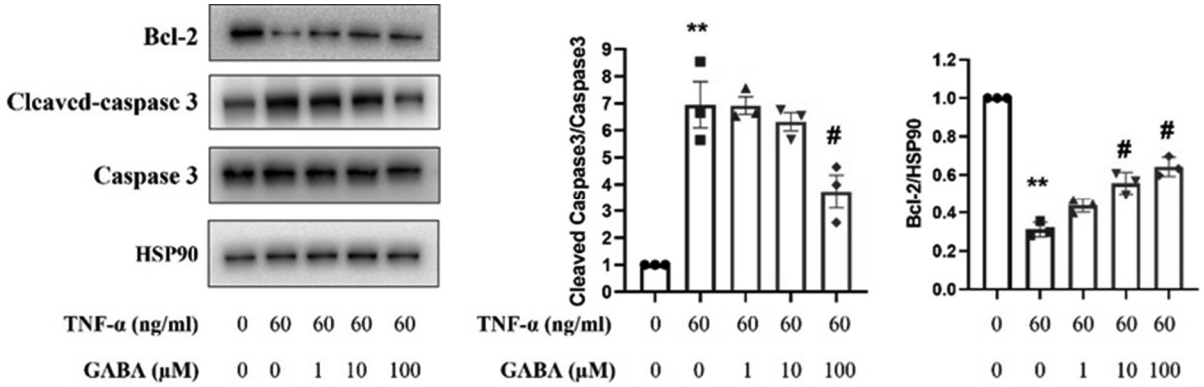

Bcl-2
Cleaved-caspase 3
Caspase 3
HSP90
TNF-α (ng/ml) 0 60 60 60 60
GABA (μM) 0 0 1 10 100
Cleaved Caspase3/Caspase3
**
#
TNF-α (ng/ml) 0 60 60 60 60
GABA (μM) 0 0 1 10 100
Bcl-2/HSP90
**
#
#
0 60 60 60 60
0 0 1 10 100

FIG. 14

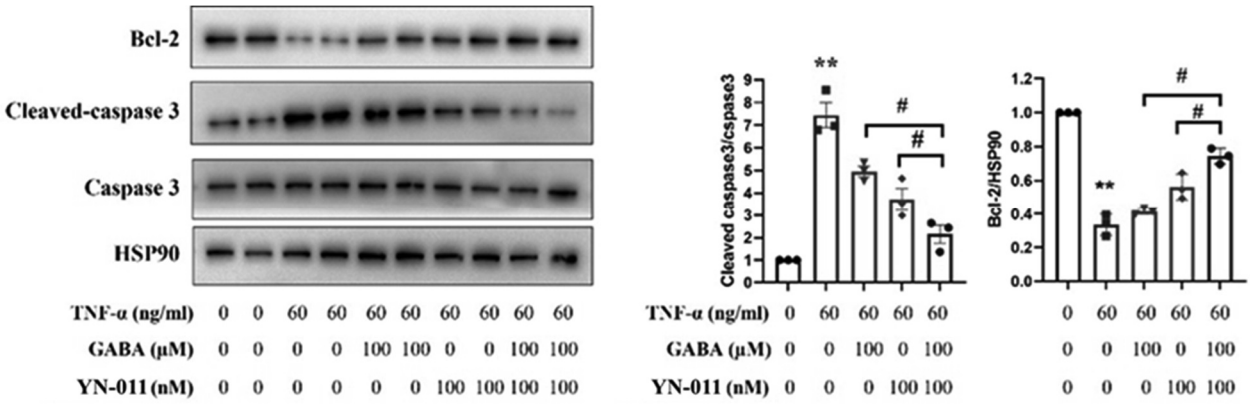

Bcl-2
Cleaved-caspase 3
Caspase 3
HSP90
TNF-α (ng/ml) 0 0 60 60 60 60 60 60 60 60
GABA (μM) 0 0 0 0 100 100 0 0 100 100
YN-011 (nM) 0 0 0 0 0 0 100 100 100 100
Cleaved caspase3/cspase3
**
#
#
TNF-α (ng/ml) 0 60 60 60 60
GABA (μM) 0 0 100 0 100
YN-011 (nM) 0 0 0 100 100
Bcl-2/HSP90
**
#
#
0 60 60 60 60
0 0 100 0 100
0 0 0 100 100

FIG. 15

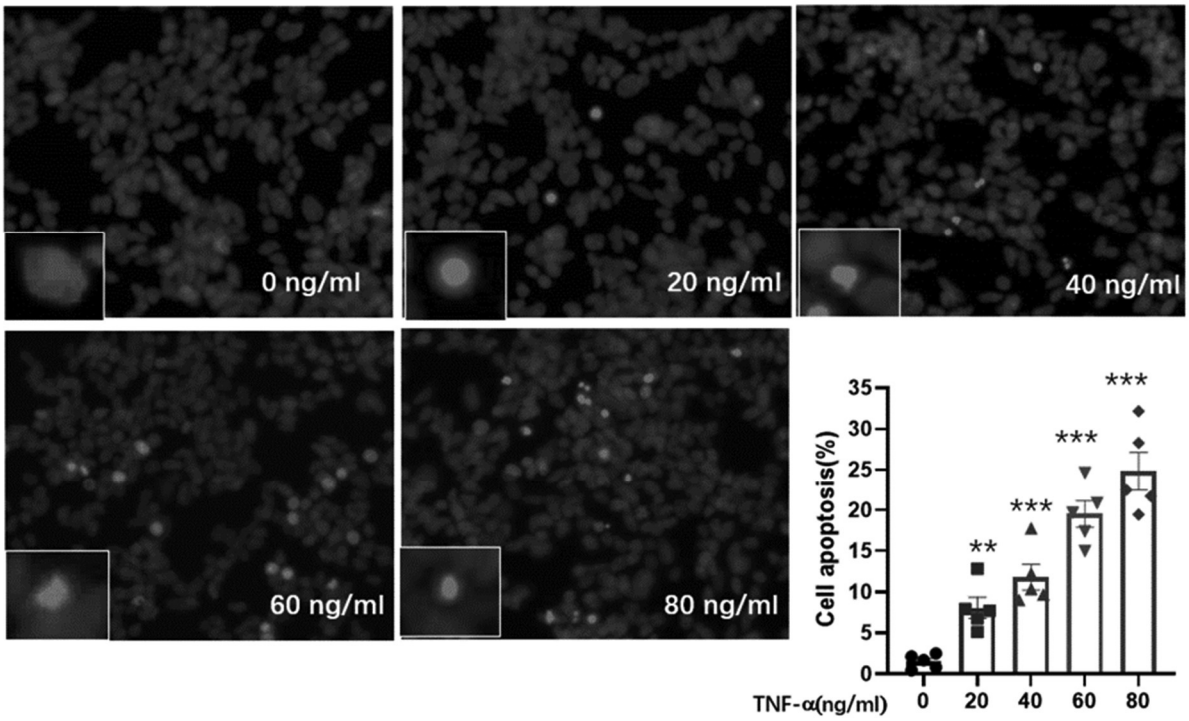

0 ng/ml
20 ng/ml
40 ng/ml
60 ng/ml
80 ng/ml
Cell apoptosis(%)
35
30
25
20
15
10
5
0
**
***
***
***
TNF-α(ng/ml)
0
20
40
60
80

FIG. 16

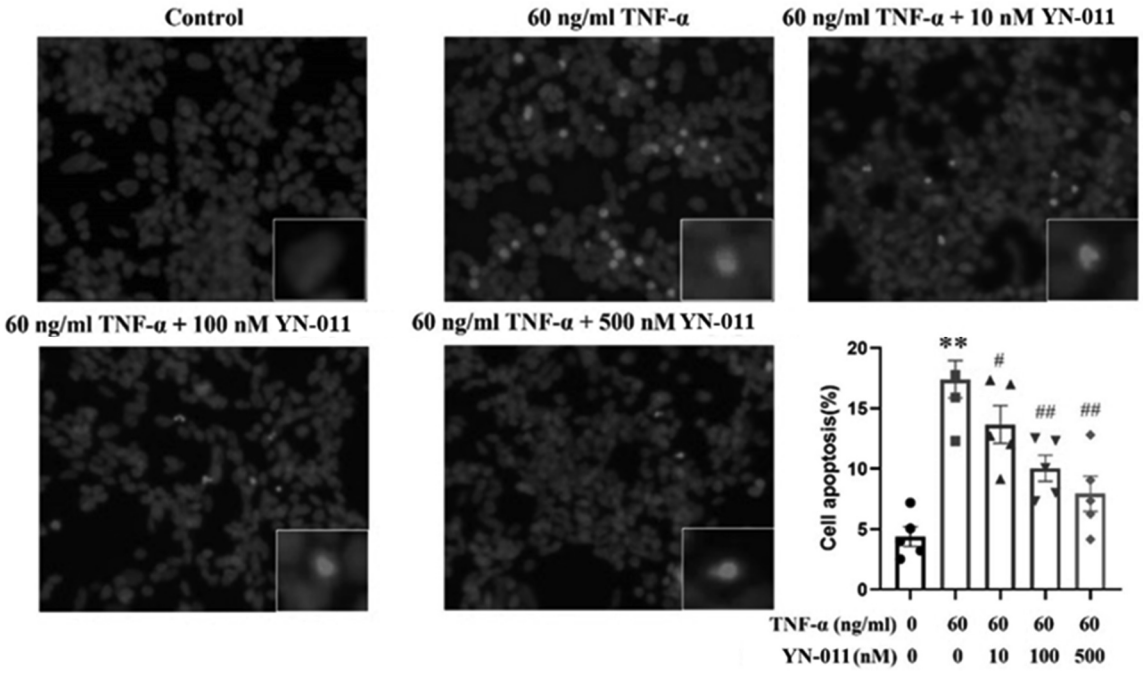

Control
60 ng/ml TNF-α
60 ng/ml TNF-α + 10 nM YN-011
60 ng/ml TNF-α + 100 nM YN-011
60 ng/ml TNF-α + 500 nM YN-011
Cell apoptosis(%)
20
15
10
5
0
**
#
##
##
TNF-α (ng/ml) 0 60 60 60 60
YN-011(nM) 0 0 10 100 500

FIG. 17

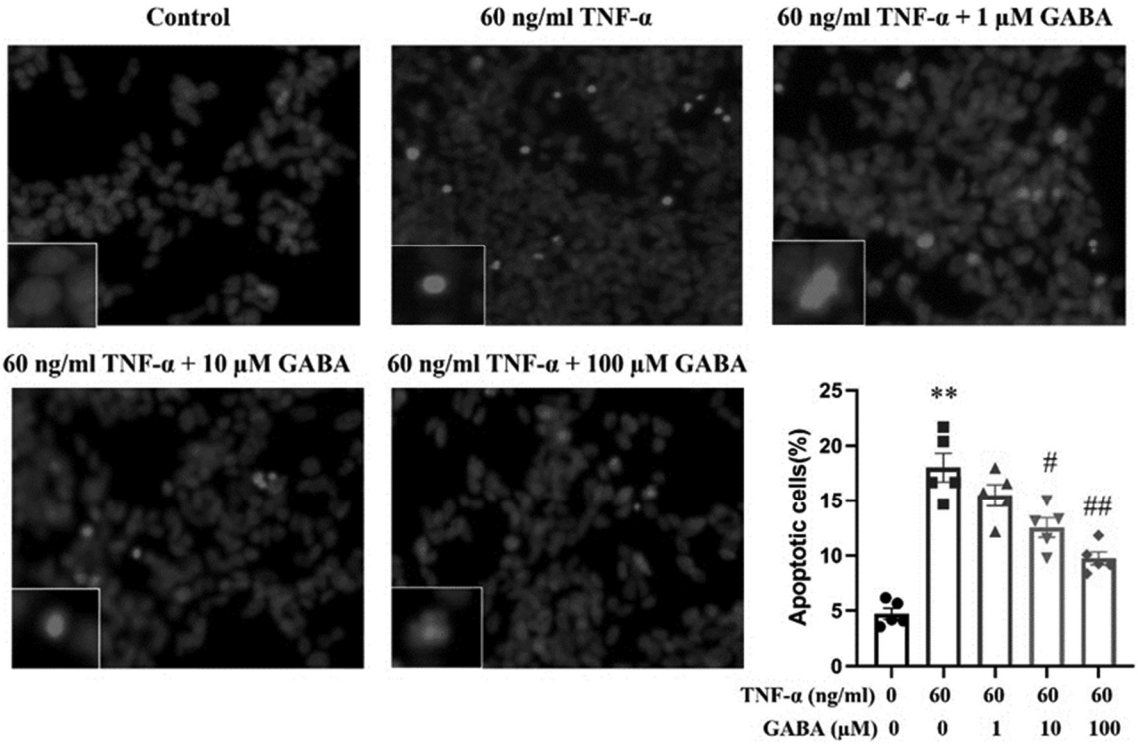

Control
60 ng/ml TNF-α
60 ng/ml TNF-α + 1 μM GABA
60 ng/ml TNF-α + 10 μM GABA
60 ng/ml TNF-α + 100 μM GABA
Apoptotic cells(%)
25
20
15
10
5
0
**
#
##
TNF-α (ng/ml) 0 60 60 60 60
GABA (μM) 0 0 1 10 100

FIG. 18

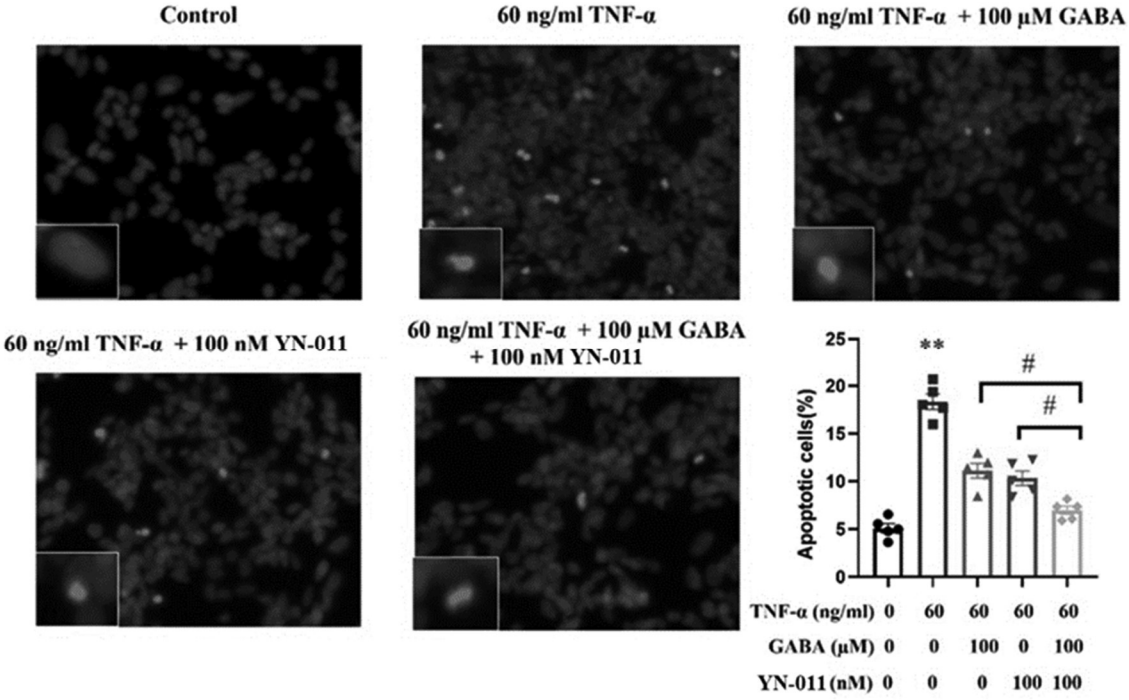

Control
60 ng/ml TNF-α
60 ng/ml TNF-α + 100 μM GABA
60 ng/ml TNF-α + 100 nM YN-011
60 ng/ml TNF-α + 100 μM GABA + 100 nM YN-011
Apoptotic cells(%)
25
20
15
10
5
0
**
#
#
TNF-α (ng/ml) 0 60 60 60 60
GABA (μM) 0 0 100 0 100
YN-011 (nM) 0 0 0 100 100

FIG. 19

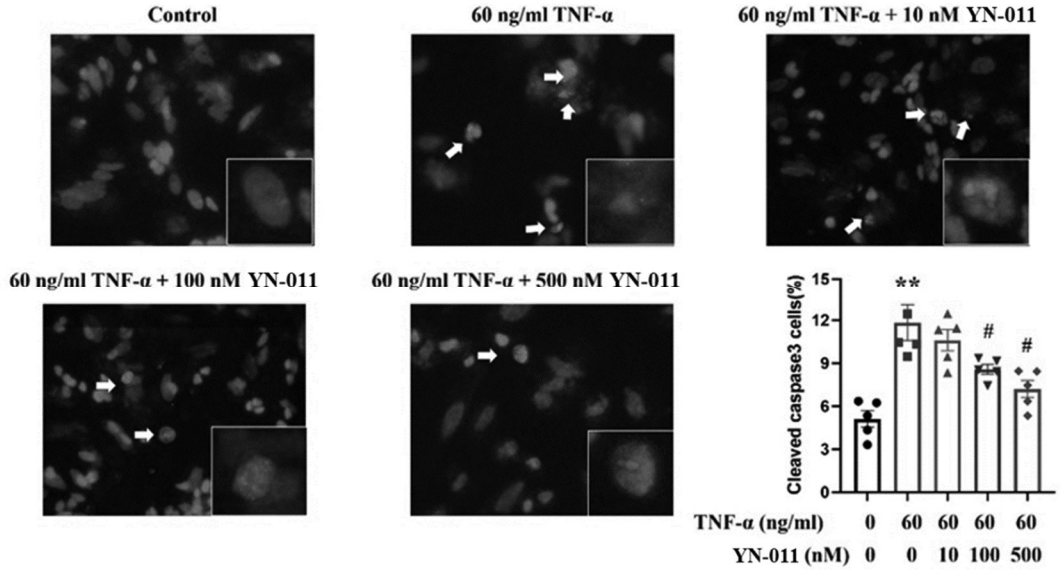

Control
60 ng/ml TNF-α
60 ng/ml TNF-α + 10 nM YN-011
60 ng/ml TNF-α + 100 nM YN-011
60 ng/ml TNF-α + 500 nM YN-011
Cleaved caspase3 cells(%)
15
12
9
6
3
0
**
#
#
TNF-α (ng/ml) 0 60 60 60 60
YN-011 (nM) 0 0 10 100 500

FIG. 20

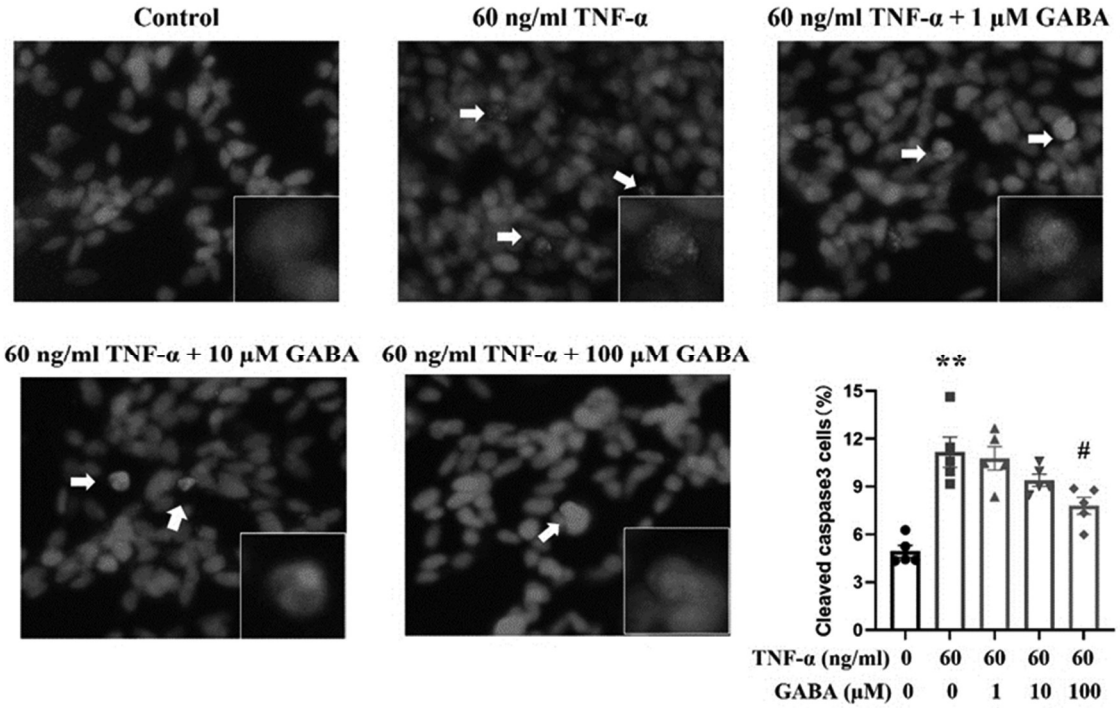

Control
60 ng/ml TNF-α
60 ng/ml TNF-α + 1 μM GABA
60 ng/ml TNF-α + 10 μM GABA
60 ng/ml TNF-α + 100 μM GABA
**
#
Cleaved caspase3 cells (%)
15
12
9
6
3
0
TNF-α (ng/ml) 0 60 60 60 60
GABA (μM) 0 0 1 10 100

FIG. 21

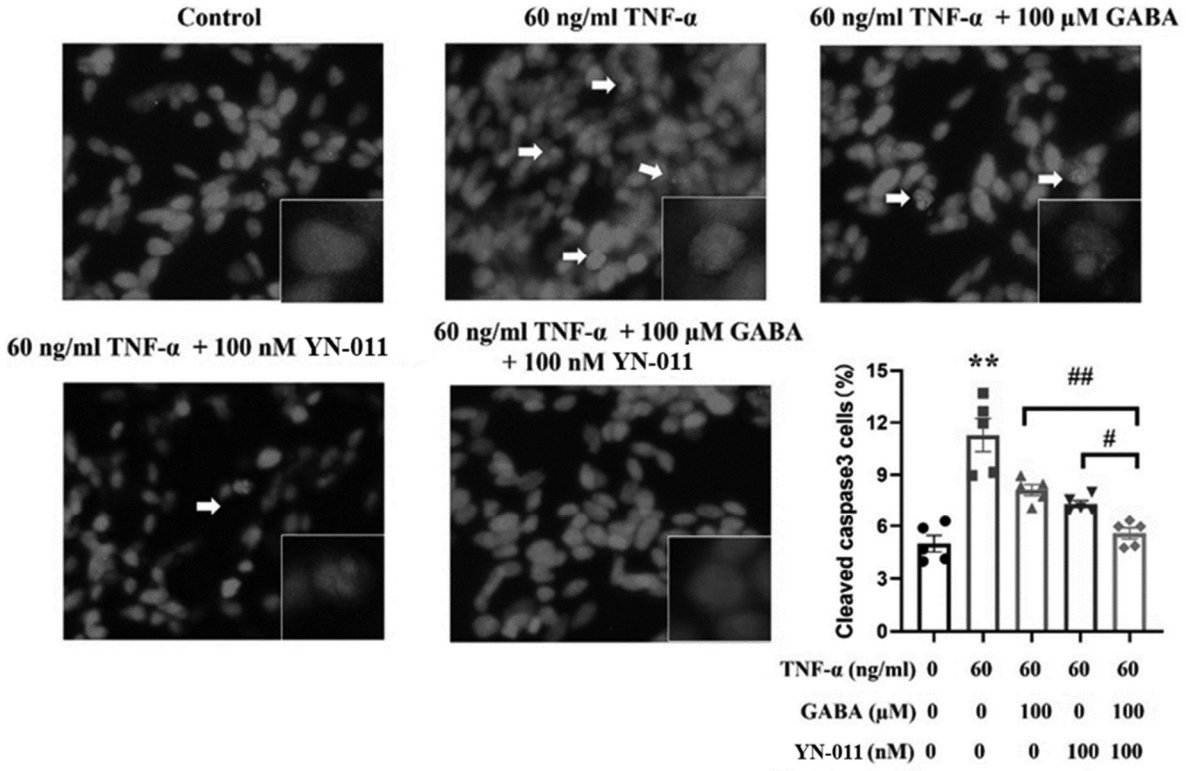

Control
60 ng/ml TNF-α
60 ng/ml TNF-α + 100 μM GABA
60 ng/ml TNF-α + 100 nM YN-011
60 ng/ml TNF-α + 100 μM GABA + 100 nM YN-011
Cleaved caspase3 cells (%)
15
12
9
6
3
0
**
##
#
TNF-α (ng/ml) 0 60 60 60 60
GABA (μM) 0 0 100 0 100
YN-011 (nM) 0 0 0 100 100

FIG. 22

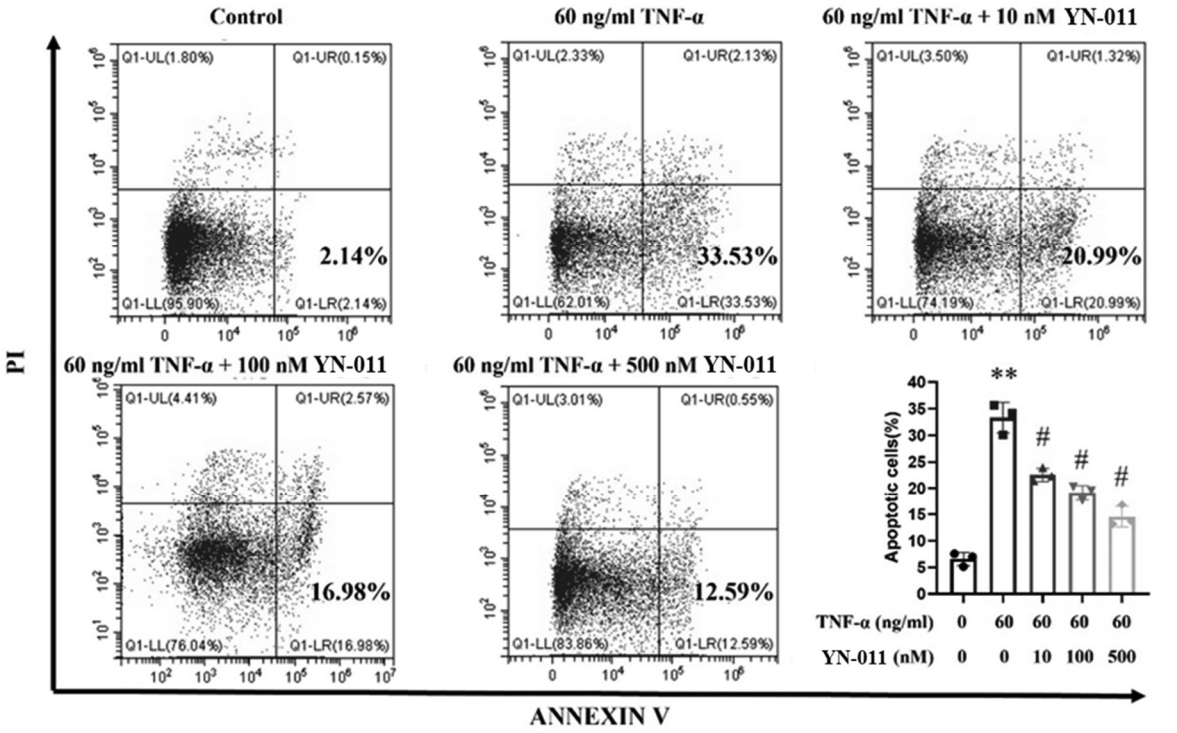

Control
60 ng/ml TNF-α
60 ng/ml TNF-α + 10 nM YN-011
60 ng/ml TNF-α + 100 nM YN-011
60 ng/ml TNF-α + 500 nM YN-011
Q1-UL(1.80%)
Q1-UR(0.15%)
2.14%
Q1-LL(95.90%)
Q1-LR(2.14%)
Q1-UL(2.33%)
Q1-UR(2.13%)
33.53%
Q1-LL(62.01%)
Q1-LR(33.53%)
Q1-UL(3.50%)
Q1-UR(1.32%)
20.99%
Q1-LL(74.19%)
Q1-LR(20.99%)
Q1-UL(4.41%)
Q1-UR(2.57%)
16.98%
Q1-LL(76.04%)
Q1-LR(16.98%)
Q1-UL(3.01%)
Q1-UR(0.55%)
12.59%
Q1-LL(83.86%)
Q1-LR(12.59%)
PI
ANNEXIN V
Apoptotic cells(%)
**
#
#
#
TNF-α (ng/ml) 0 60 60 60 60
YN-011 (nM) 0 0 10 100 500

FIG. 23

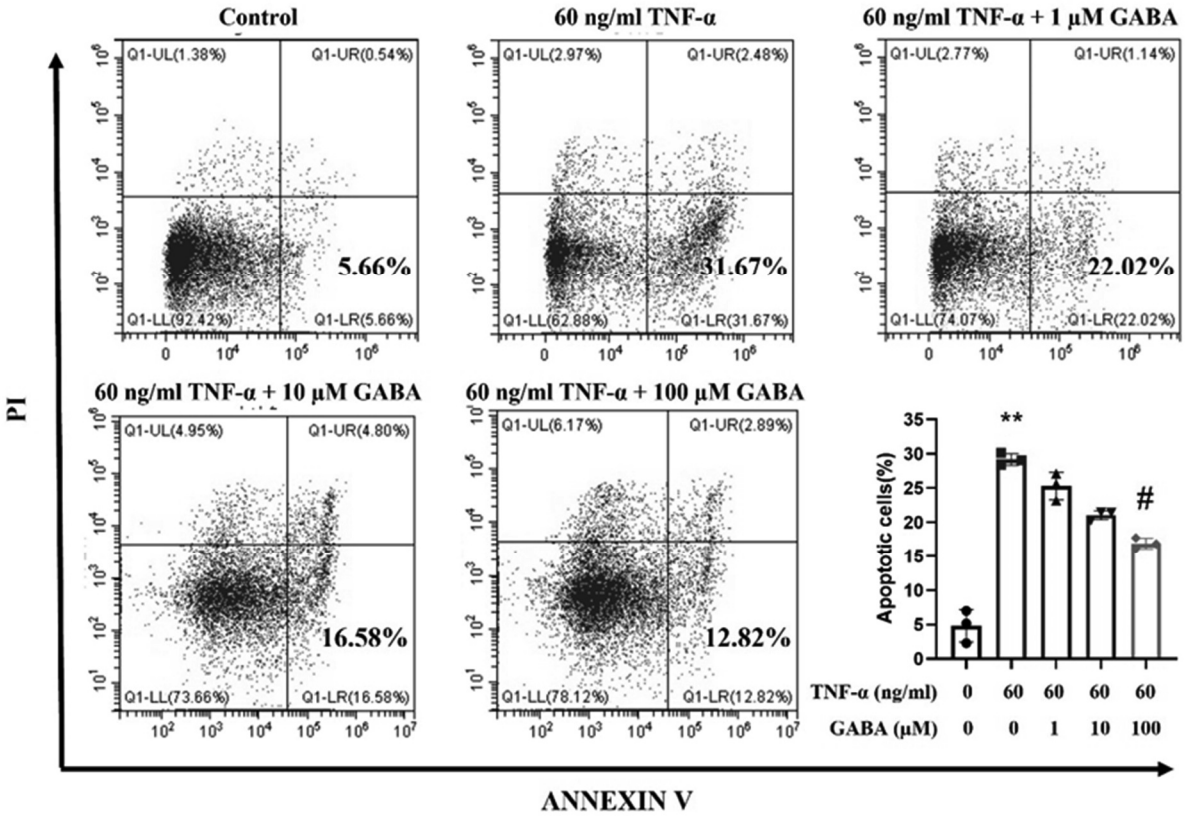

Control
Q1-UL(1.38%)
Q1-UR(0.54%)
5.66%
Q1-LL(92.42%)
Q1-LR(5.66%)
60 ng/ml TNF-α
Q1-UL(2.97%)
Q1-UR(2.48%)
31.67%
Q1-LL(62.88%)
Q1-LR(31.67%)
60 ng/ml TNF-α + 1 μM GABA
Q1-UL(2.77%)
Q1-UR(1.14%)
22.02%
Q1-LL(74.07%)
Q1-LR(22.02%)
60 ng/ml TNF-α + 10 μM GABA
Q1-UL(4.95%)
Q1-UR(4.80%)
16.58%
Q1-LL(73.66%)
Q1-LR(16.58%)
60 ng/ml TNF-α + 100 μM GABA
Q1-UL(6.17%)
Q1-UR(2.89%)
12.82%
Q1-LL(78.12%)
Q1-LR(12.82%)
PI
ANNEXIN V
Apoptotic cells(%)
**
#
TNF-α (ng/ml) 0 60 60 60 60
GABA (μM) 0 0 1 10 100

FIG. 24

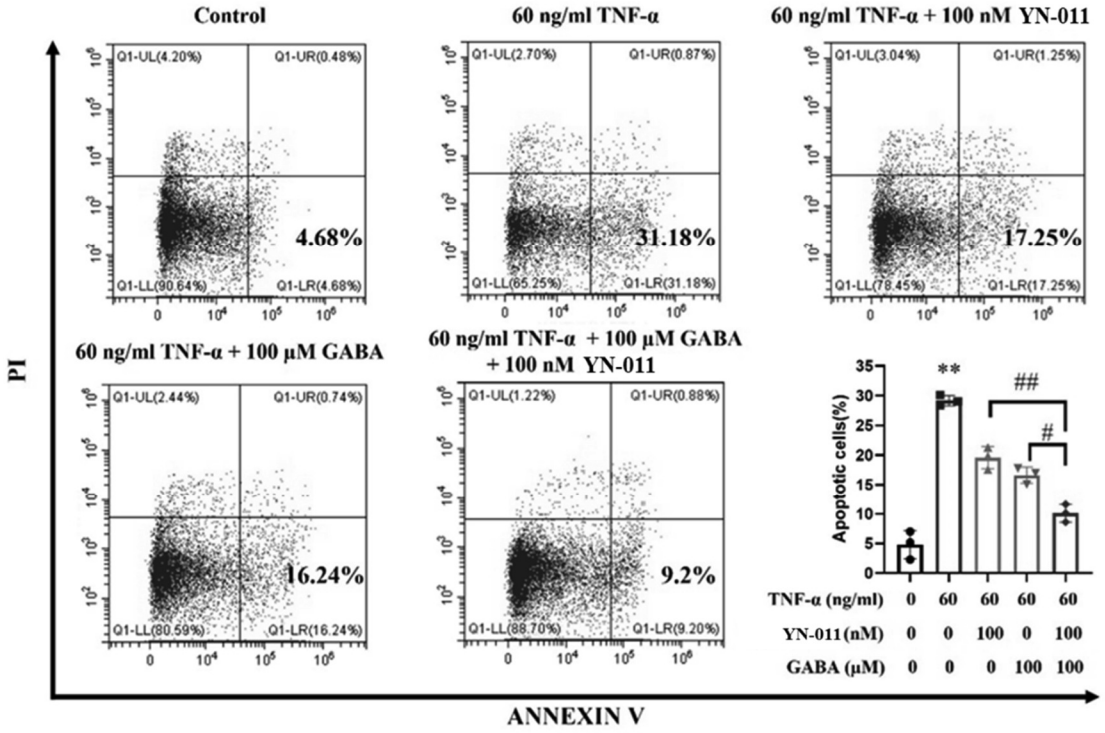

Control
60 ng/ml TNF-α
60 ng/ml TNF-α + 100 nM YN-011
60 ng/ml TNF-α + 100 μM GABA
60 ng/ml TNF-α + 100 μM GABA + 100 nM YN-011
Q1-UL(4.20%)
Q1-UR(0.48%)
4.68%
Q1-LL(90.64%)
Q1-LR(4.68%)
Q1-UL(2.70%)
Q1-UR(0.87%)
31.18%
Q1-LL(65.25%)
Q1-LR(31.18%)
Q1-UL(3.04%)
Q1-UR(1.25%)
17.25%
Q1-LL(78.45%)
Q1-LR(17.25%)
Q1-UL(2.44%)
Q1-UR(0.74%)
16.24%
Q1-LL(80.59%)
Q1-LR(16.24%)
Q1-UL(1.22%)
Q1-UR(0.88%)
9.2%
Q1-LL(88.70%)
Q1-LR(9.20%)
PI
ANNEXIN V
Apoptotic cells(%)
**
##
#
TNF-α (ng/ml) 0 60 60 60 60
YN-011 (nM) 0 0 100 0 100
GABA (μM) 0 0 0 100 100

FIG. 25

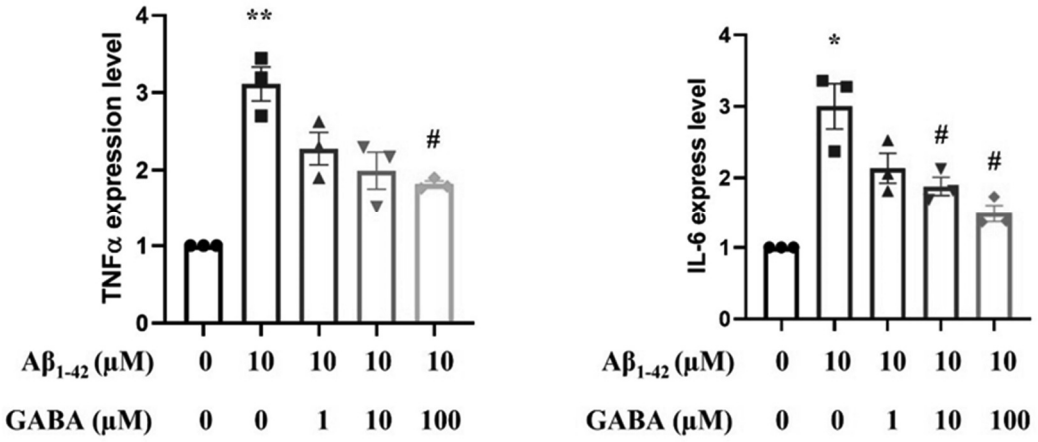

TNFα expression level
IL-6 express level
**
*
#
Aβ1-42 (μM) 0 10 10 10 10
GABA (μM) 0 0 1 10 100

FIG. 26

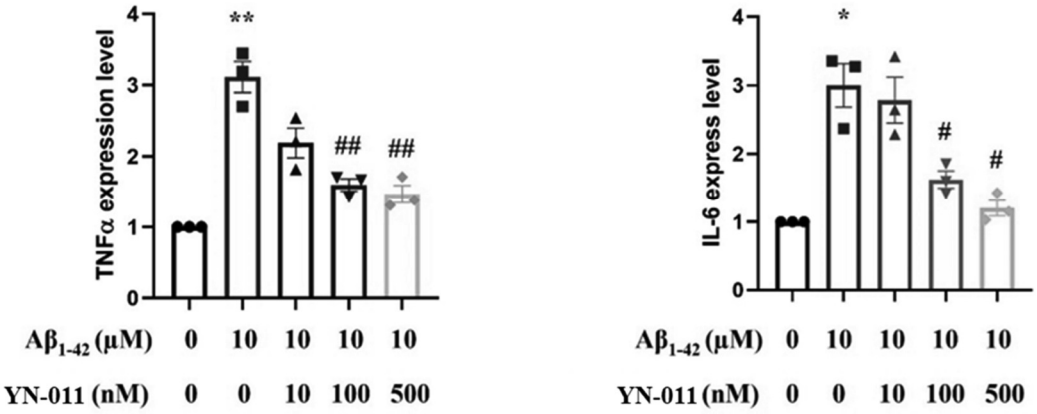

TNFα expression level
IL-6 express level
Aβ1-42 (μM) 0 10 10 10 10
YN-011 (nM) 0 0 10 100 500

FIG. 27

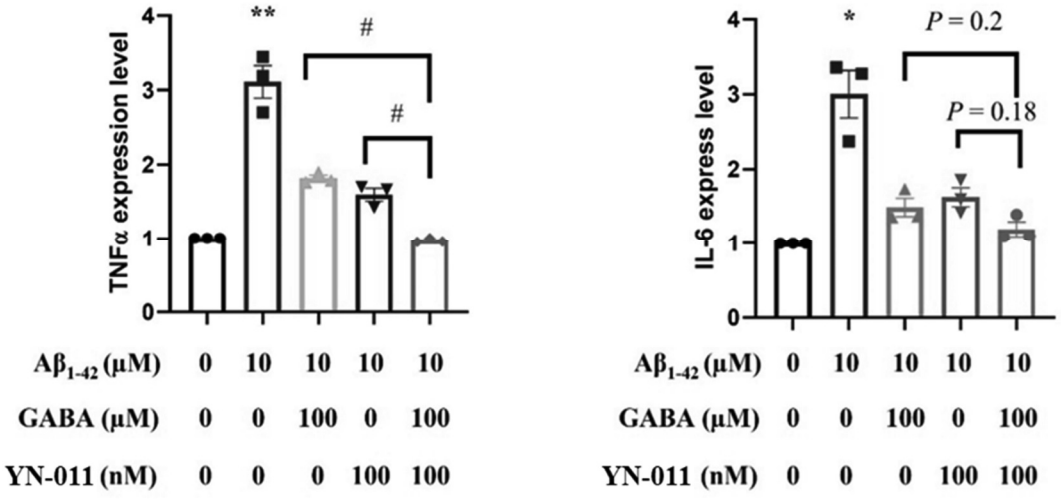

TNFα expression level
**
#
#
4
3
2
1
0
Aβ1-42 (μM) 0 10 10 10 10
GABA (μM) 0 0 100 0 100
YN-011 (nM) 0 0 0 100 100
IL-6 express level
*
P = 0.2
P = 0.18
4
3
2
1
0
Aβ1-42 (μM) 0 10 10 10 10
GABA (μM) 0 0 100 0 100
YN-011 (nM) 0 0 0 100 100

FIG. 28

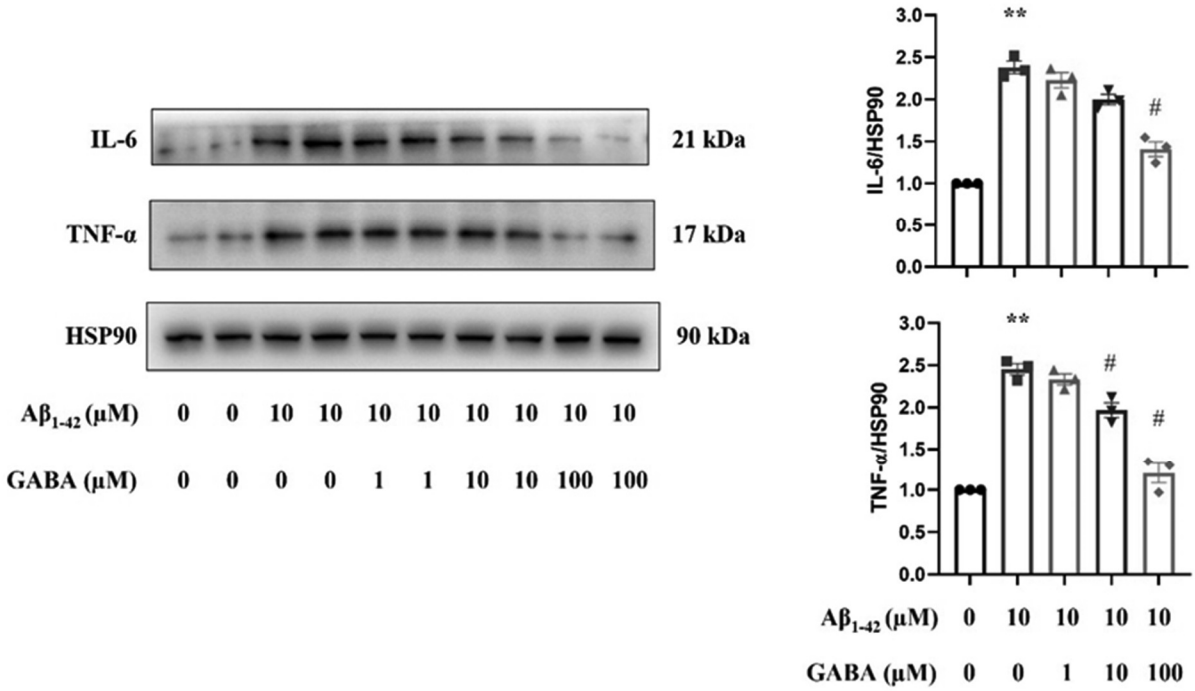

IL-6
21 kDa
TNF-α
17 kDa
HSP90
90 kDa
Aβ1-42 (μM) 0 0 10 10 10 10 10 10 10 10
GABA (μM) 0 0 0 0 1 1 10 10 100 100
IL-6/HSP90
TNF-α/HSP90
3.0
2.5
2.0
1.5
1.0
0.5
0.0
**
#
Aβ1-42 (μM) 0 10 10 10 10
GABA (μM) 0 0 1 10 100

FIG. 29

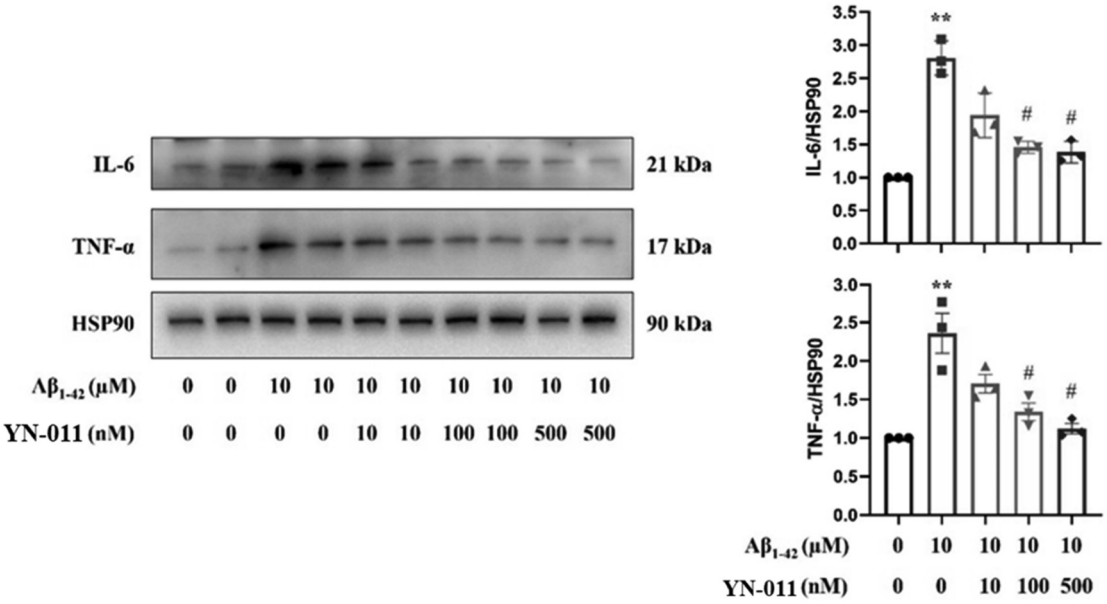
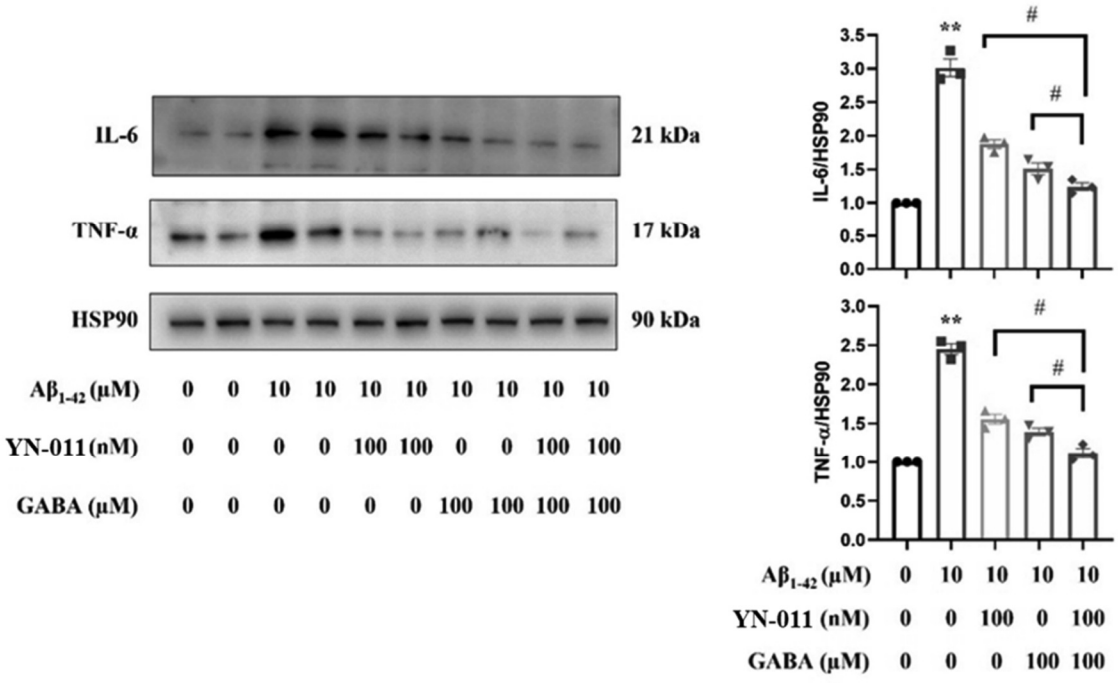

IL-6
TNF-α
HSP90
21 kDa
17 kDa
90 kDa
Aβ1-42 (μM) 0 0 10 10 10 10 10 10 10 10
YN-011 (nM) 0 0 0 0 10 10 100 100 500 500
IL-6/HSP90
TNF-α/HSP90
**
#
Aβ1-42 (μM) 0 10 10 10 10
YN-011 (nM) 0 0 10 100 500

FIG. 30


IL-6
21 kDa
TNF-α
17 kDa
HSP90
90 kDa
Aβ1-42 (μM) 0 0 10 10 10 10 10 10 10 10
YN-011 (nM) 0 0 0 0 100 100 0 0 100 100
GABA (μM) 0 0 0 0 0 0 100 100 100 100
IL-6/HSP90
TNF-α/HSP90
**
#
Aβ1-42 (μM) 0 10 10 10 10
YN-011 (nM) 0 0 100 0 100
GABA (μM) 0 0 0 100 100