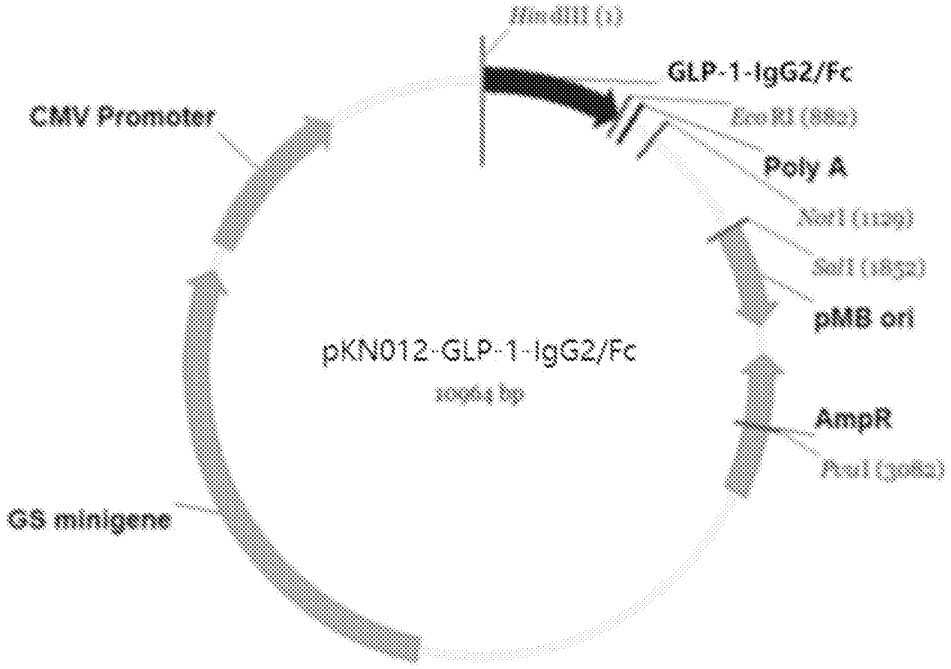
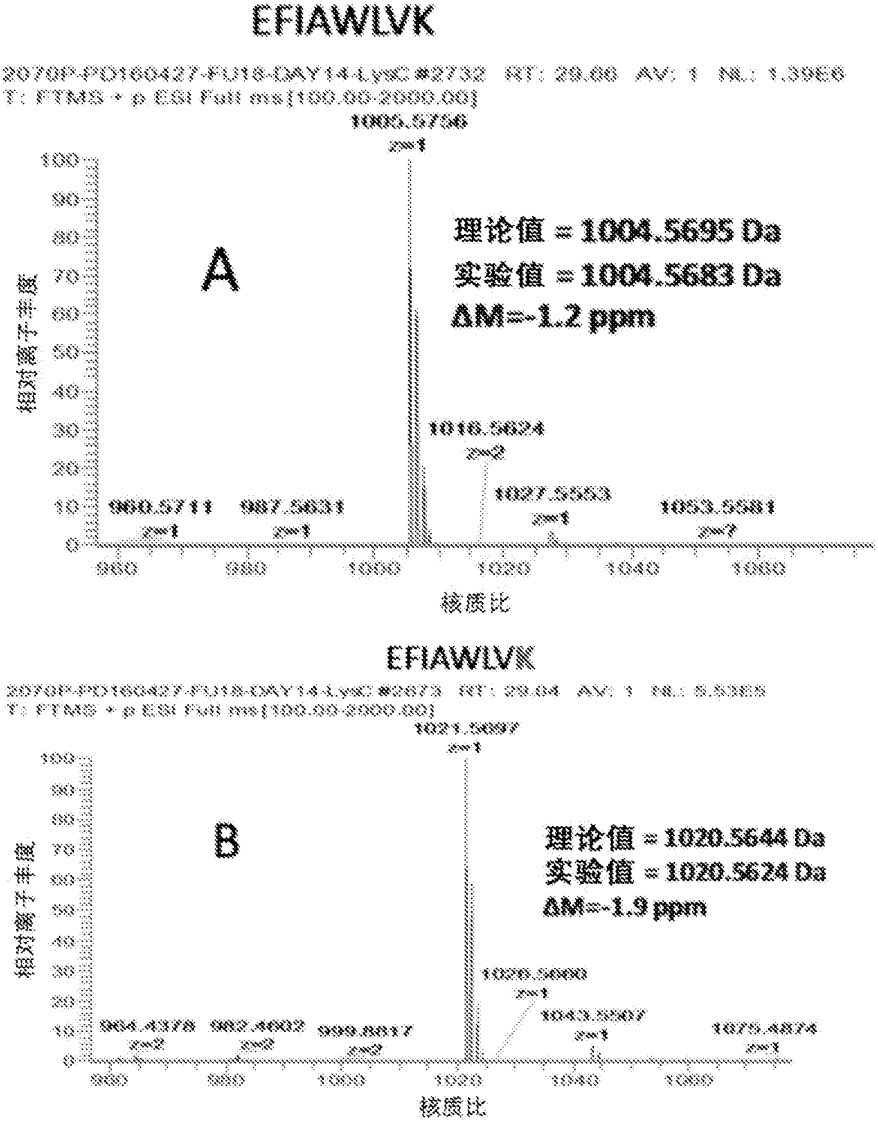
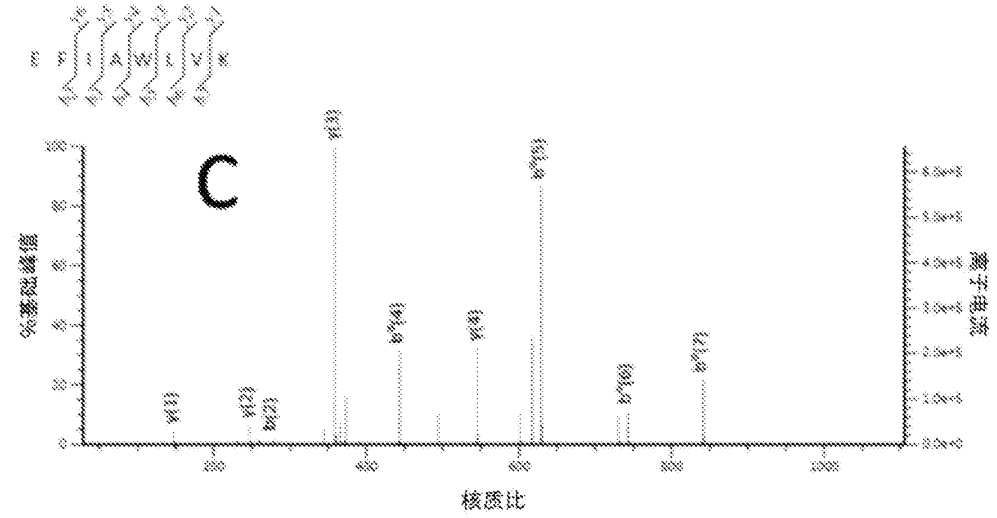
[图 1]

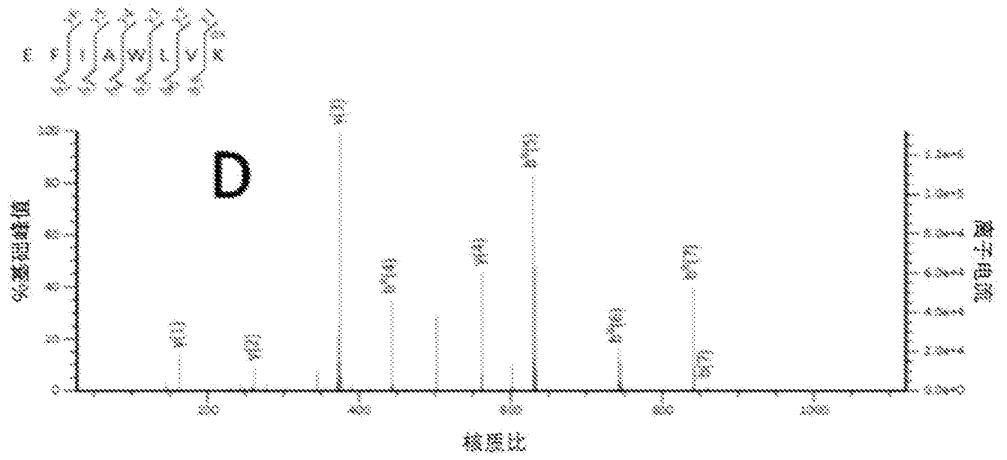

GLP-1-IgG2/Fc
CMV Promoter
Poly A
pMB ori
pKN012-GLP-1-IgG2/Fc
AmpR
GS minigene

[图 2]

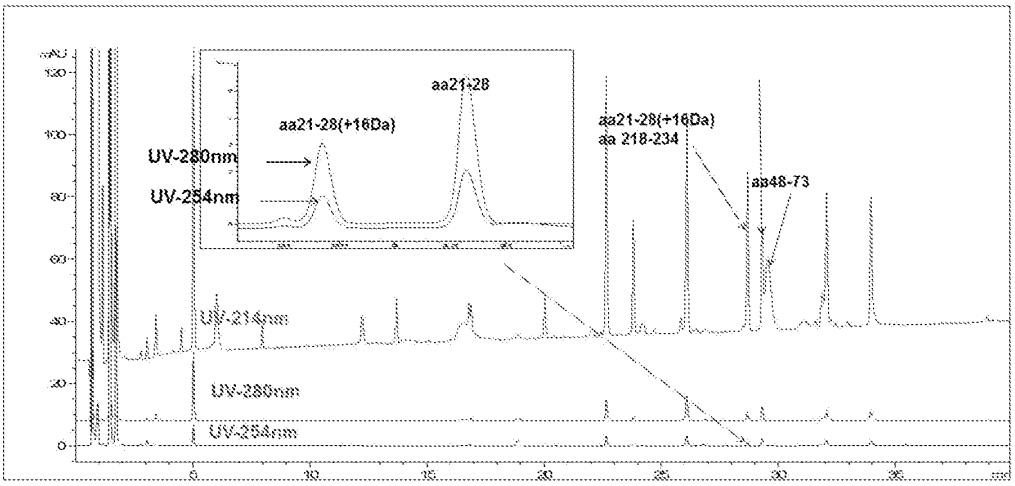

EFIAWLVK
2070P-PD160427-FU18-DAY14-LysC #2732 RT: 29.68 AV: 1 NL: 1.39E6
T: FTMS + p ESI Full ms [100.00-2000.00]
1005.5756
z=1
A
理论值 = 1004.5695 Da
实验值 = 1004.5683 Da
ΔM=-1.2 ppm
1016.5624
z=2
1027.5553
z=1
960.5711
z=1
987.5631
z=1
1053.5581
z=2
相对离子丰度
核质比
EFIAWLVK
2070P-PD160427-FU18-DAY14-LysC #2673 RT: 29.04 AV: 1 NL: 5.53E5
T: FTMS + p ESI Full ms [100.00-2000.00]
1021.5697
z=1
B
理论值 = 1020.5644 Da
实验值 = 1020.5624 Da
ΔM=-1.9 ppm
1020.5660
z=1
964.4378
z=2
982.4602
z=2
999.8817
z=2
1043.5507
z=1
1079.4874
z=1
相对离子丰度
核质比

[图 2(续)]





[图 3A]

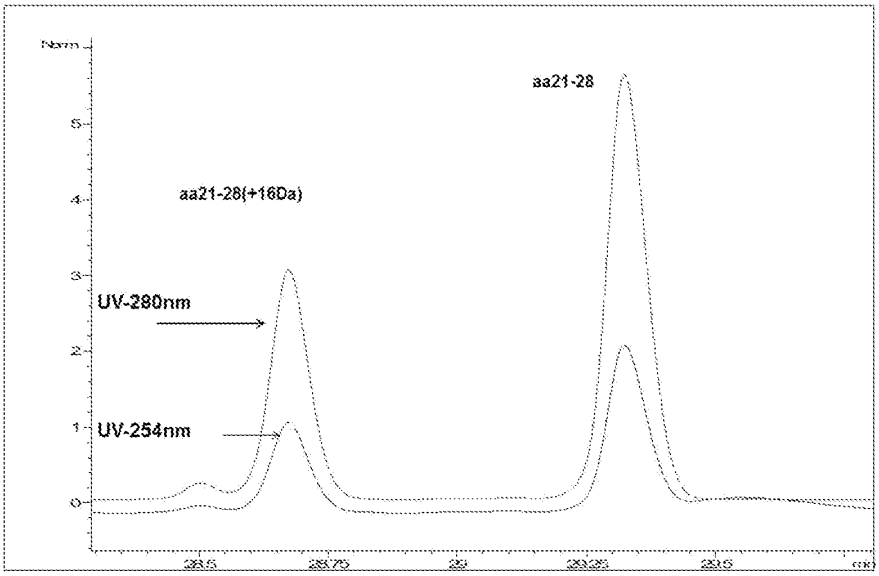


ε_w= 5500

ε_y= 1490

21-28	EFIAWLVK
218-234	TTPPMLDSDGSFFLYSK
48-73	SCVECPPCPAPPVAGPSVFLFPPKPK

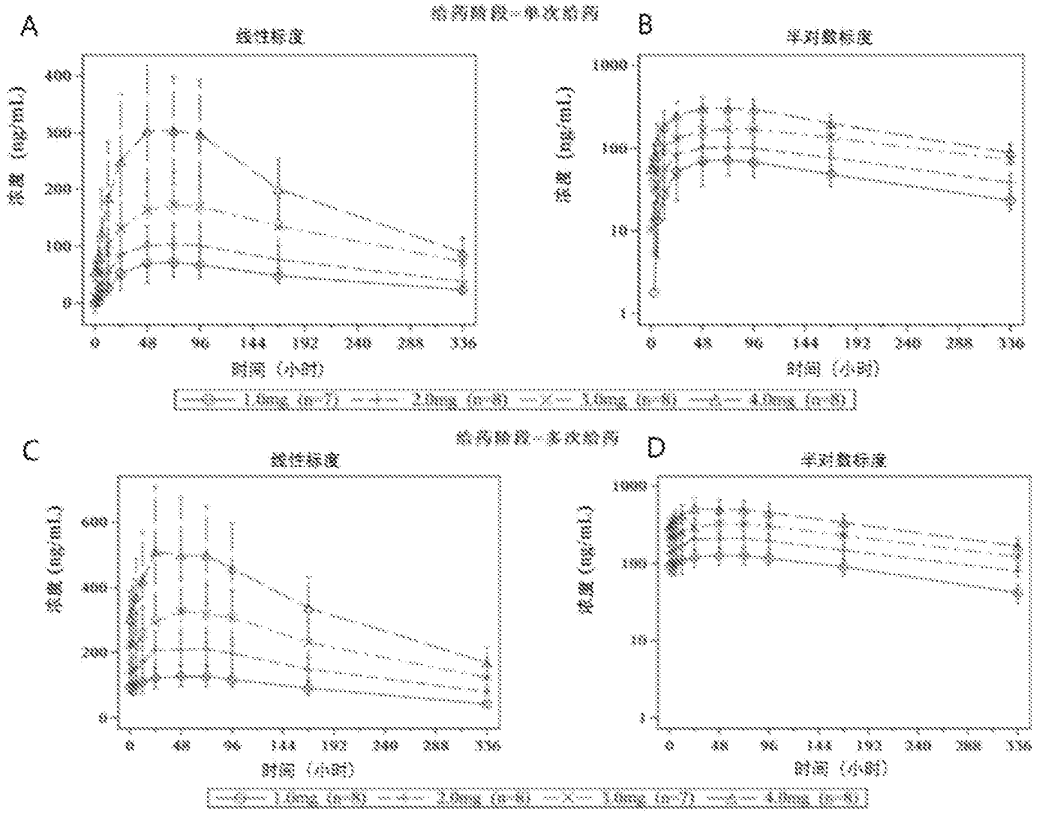
[图 3B]



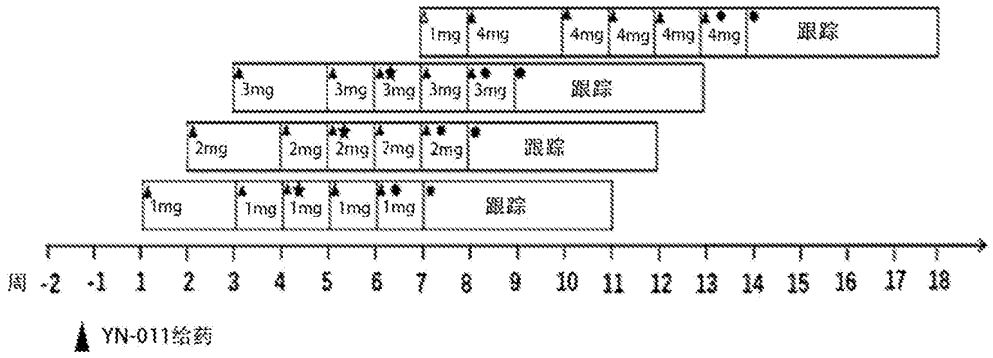
细则 26.
21.07.2023

细则 26.
21.07.2023

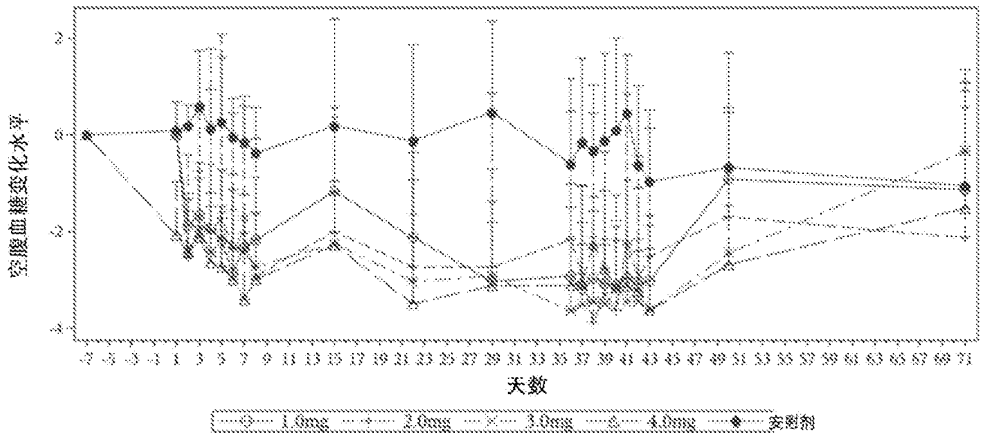
[图 4]


给药阶段-单次给药
A
线性标度
浓度 (ng/mL)
时间 (小时)
B
半对数标度
浓度 (ng/mL)
时间 (小时)
1.0mg (n=7)
2.0mg (n=8)
3.0mg (n=8)
4.0mg (n=8)
给药阶段-多次给药
C
线性标度
浓度 (ng/mL)
时间 (小时)
D
半对数标度
浓度 (ng/mL)
时间 (小时)
1.0mg (n=8)
2.0mg (n=8)
3.0mg (n=7)
4.0mg (n=8)

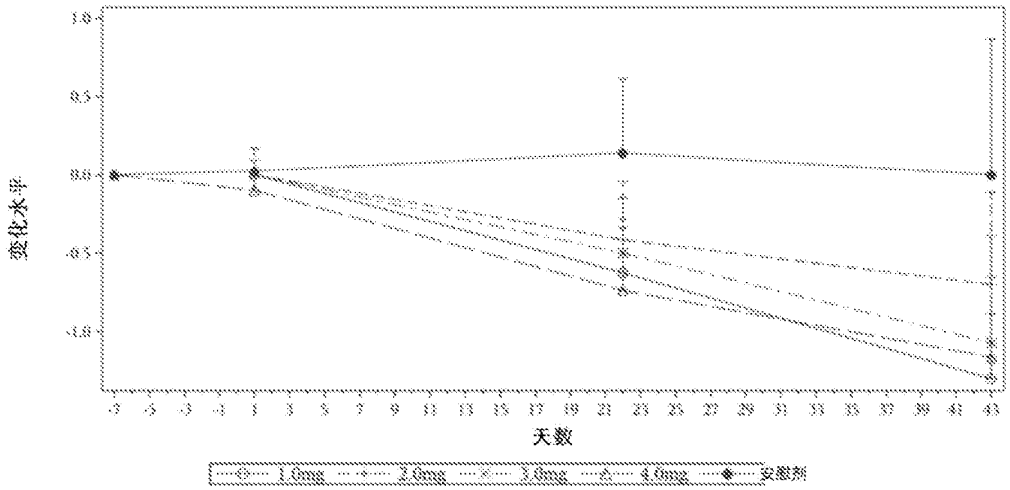
[图 5]


1mg
4mg
4mg
4mg
4mg
4mg
跟踪
3mg
3mg
3mg
3mg
3mg
跟踪
2mg
2mg
2mg
2mg
2mg
跟踪
1mg
1mg
1mg
1mg
1mg
跟踪
周 -2 -1 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
YN-011给药

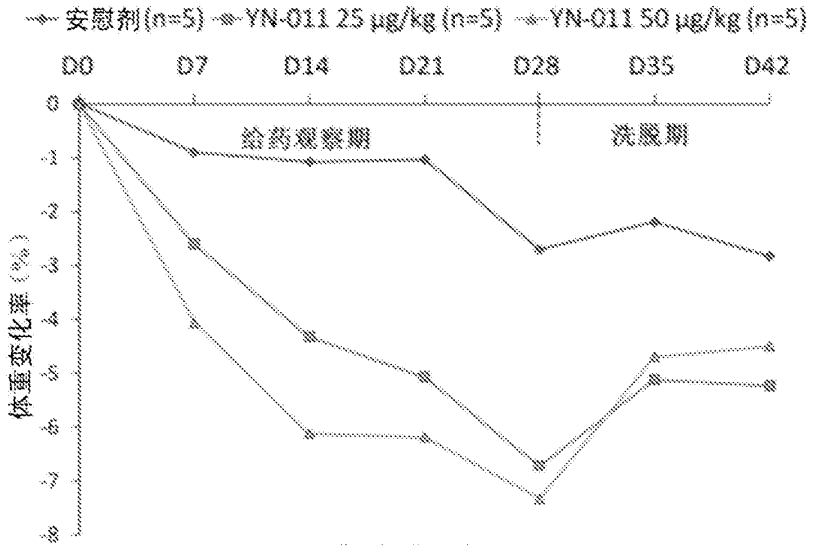
[图 6]


空腹血糖变化水平
天数
1.0mg
2.0mg
3.0mg
4.0mg
安慰剂

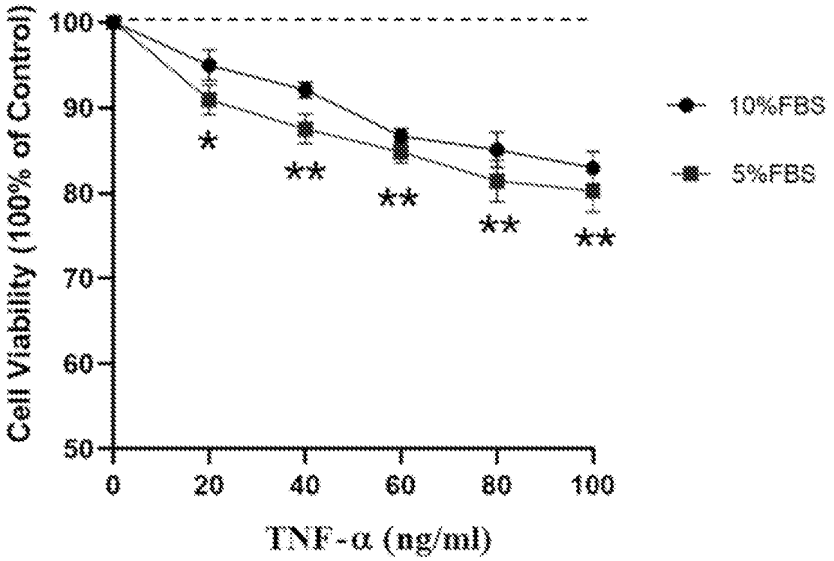
[图 7]


变化水平
天数
1.0mg
2.0mg
3.0mg
4.0mg
安慰剂

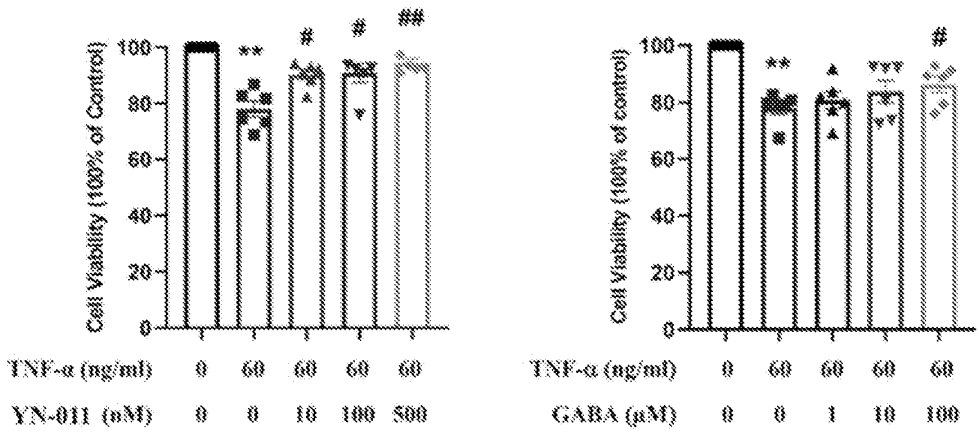
[图 8]


安慰剂(n=5)
YN-011 25 μg/kg (n=5)
YN-011 50 μg/kg (n=5)
D0
D7
D14
D21
D28
D35
D42
给药观察期
洗脱期
体重变化率(%)

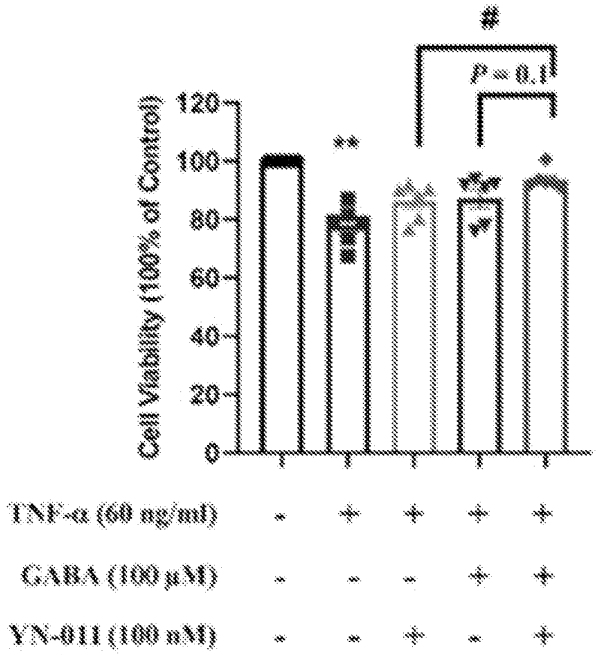
[图 9]


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
*
**
**
**
**

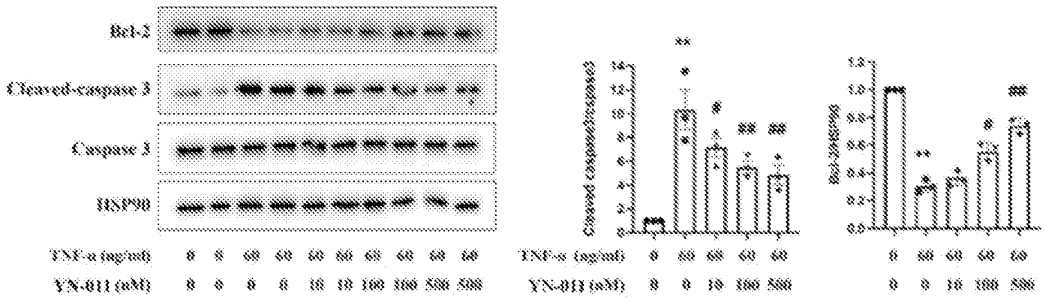
[图 10]


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

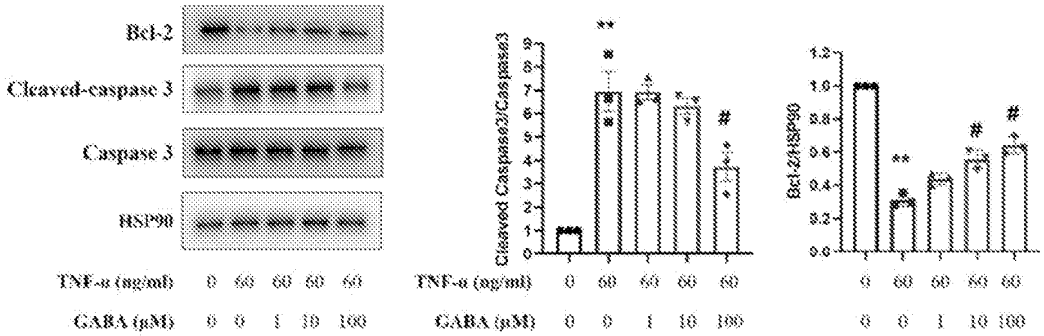
[图 11]


#
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) - - + - +

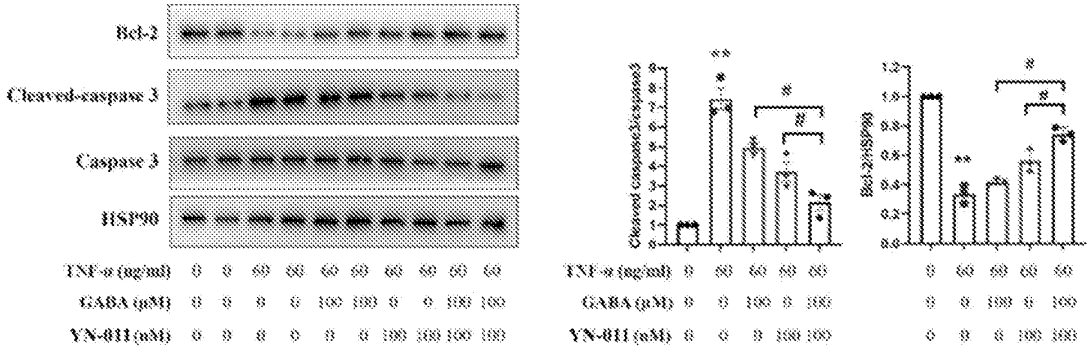
[图 12]


Bcl-2
Cleaved-caspase 3
Caspase 3
HSP90
TNF-α (ng/ml) 0 5 60 60 60 60 60 60 60 60
YN-011 (nM) 0 0 0 0 10 10 100 100 500 500
Cleaved caspase3/caspase3
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

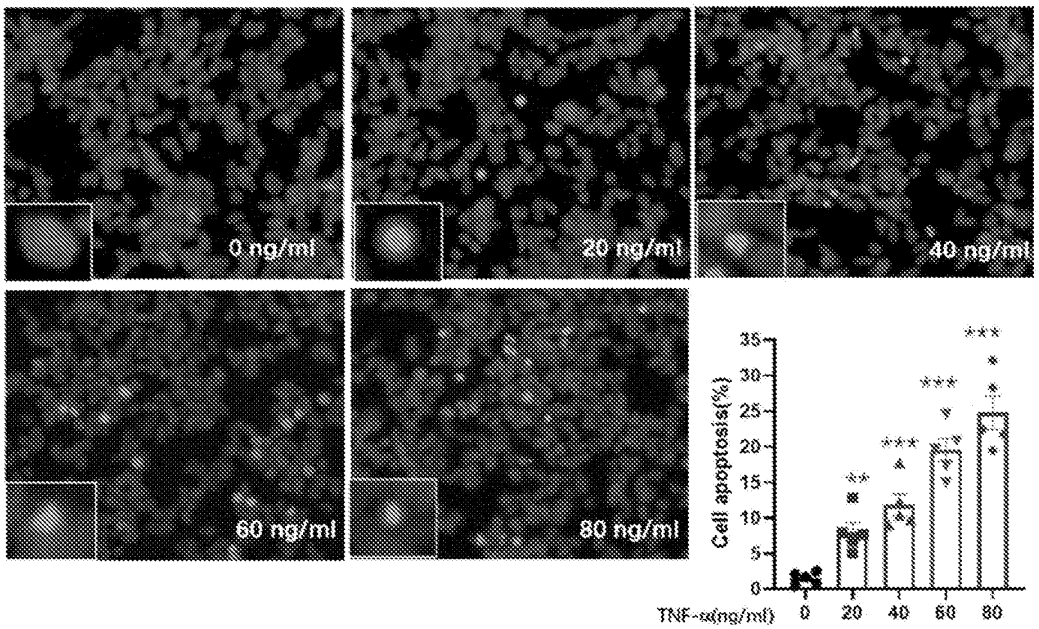
[图 13]


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

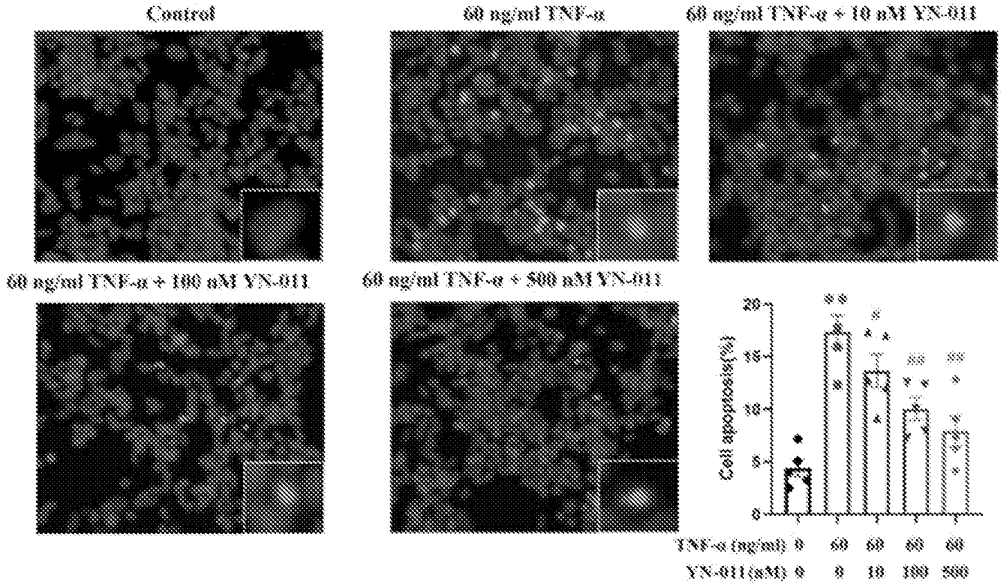
[图 14]


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/caspase3
Bcl-2/HSP90
TNF-α (ng/ml) 0 60 60 60 60
GABA (μM) 0 0 100 0 100
YN-011 (nM) 0 0 0 100 100

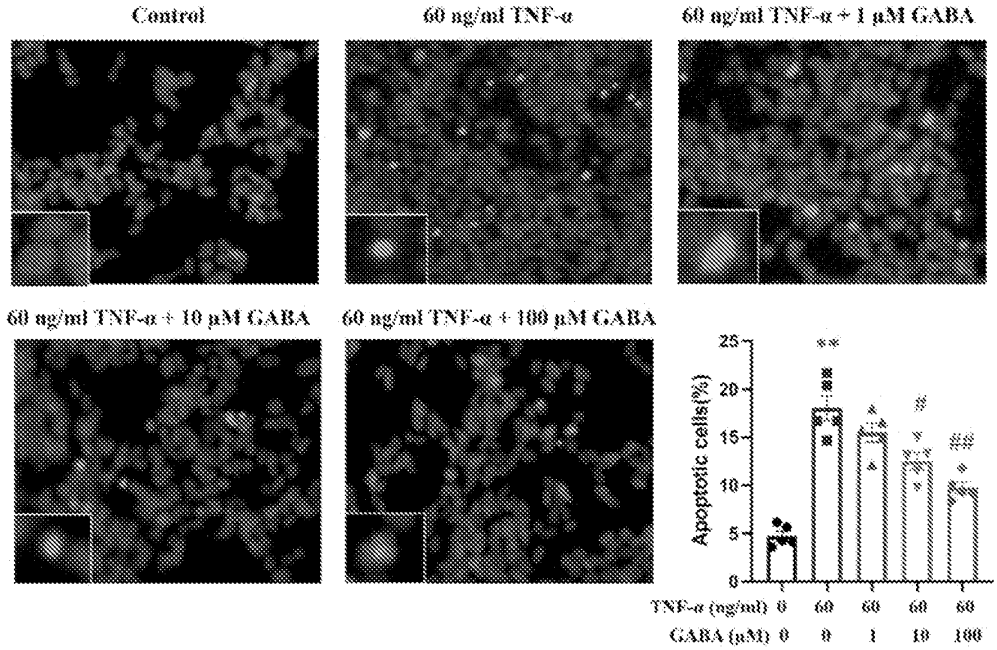
[图 15]


0 ng/ml
20 ng/ml
40 ng/ml
60 ng/ml
80 ng/ml
Cell apoptosis(%)
TNF-α(ng/ml) 0 20 40 60 80

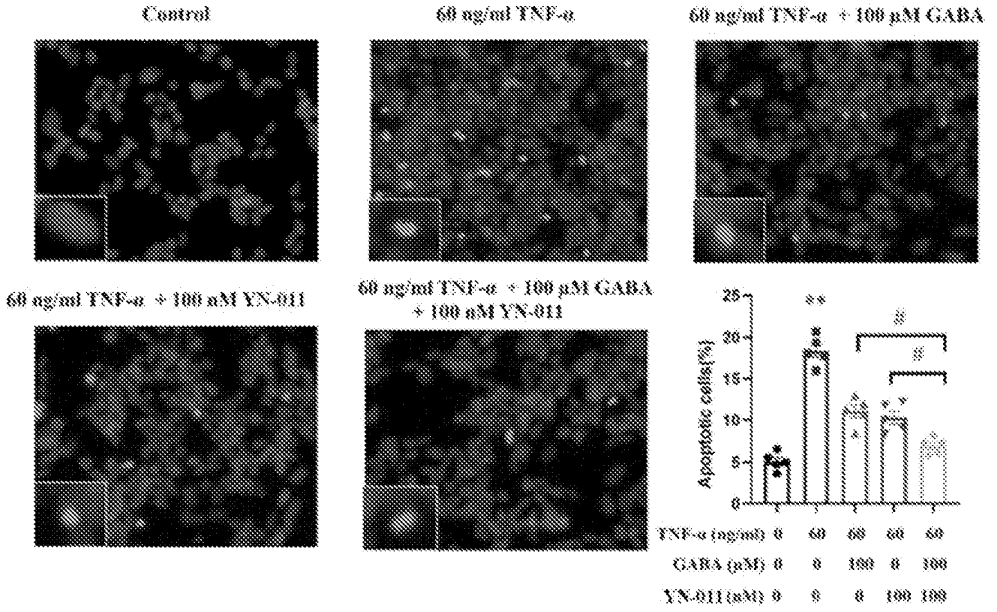
[图 16]


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(%)
TNF-α (ng/ml) 0 60 60 60 60
YN-011 (nM) 0 0 10 100 500

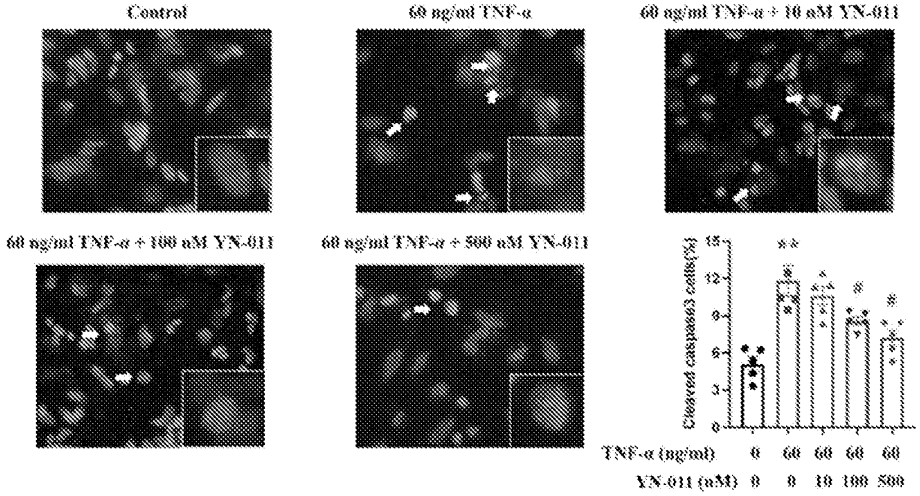
[图 17]


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(%)
TNF-α (ng/ml) 0 60 60 60 60
GABA (μM) 0 0 1 10 100

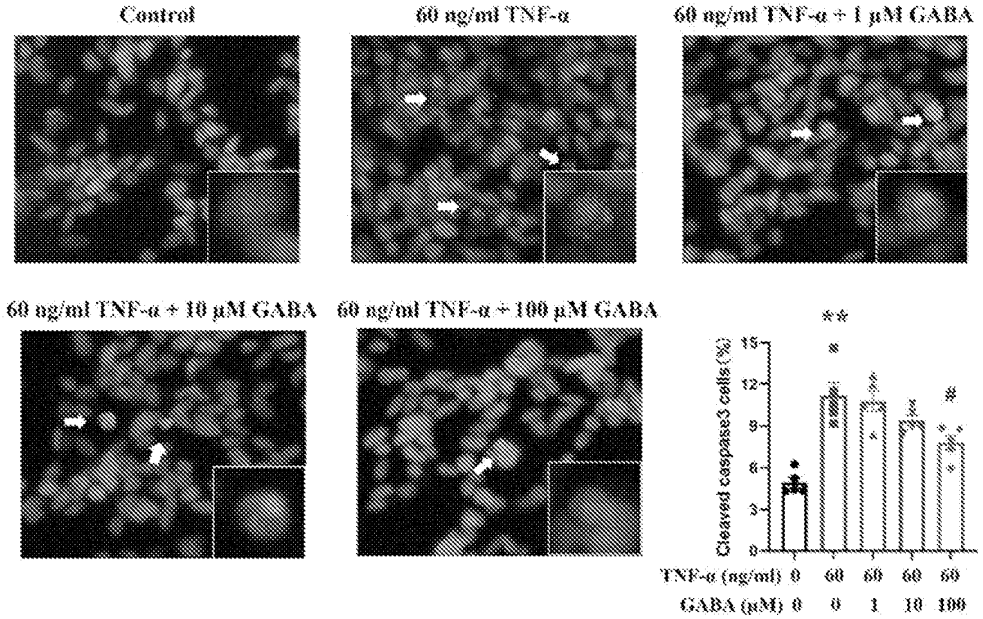
[图 18]


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(%)
TNF-α (ng/ml) 0 60 60 60 60
GABA (μM) 0 0 100 0 100
YN-011 (nM) 0 0 0 100 100

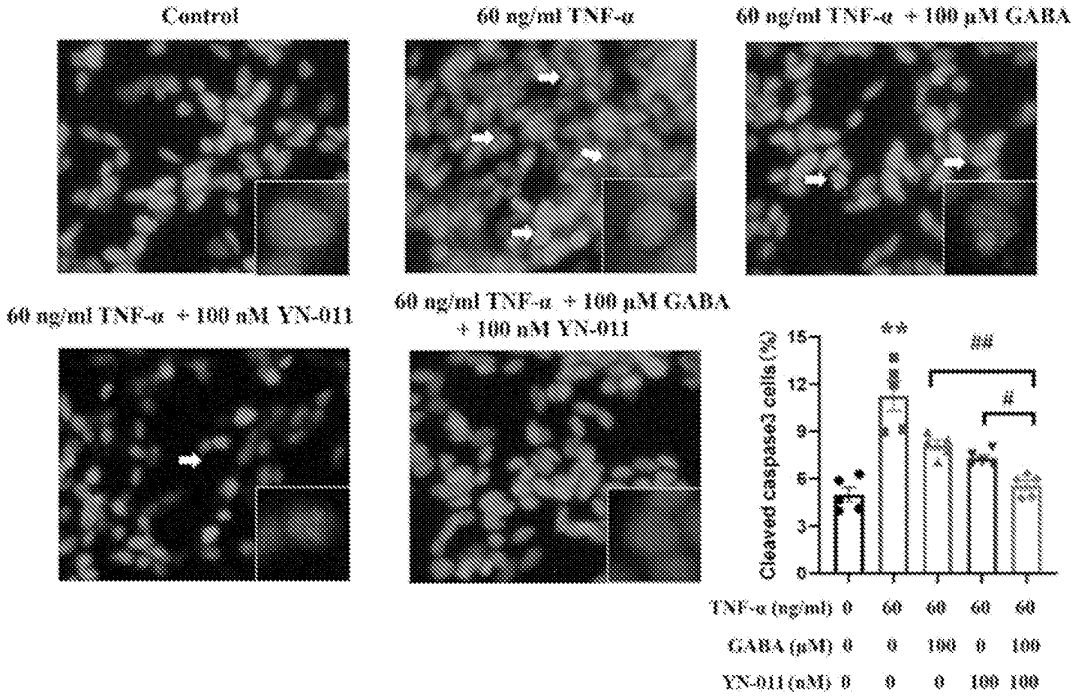
[图 19]


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(%)
TNF-α (ng/ml) 0 60 60 60 60
YN-011 (nM) 0 0 10 100 500

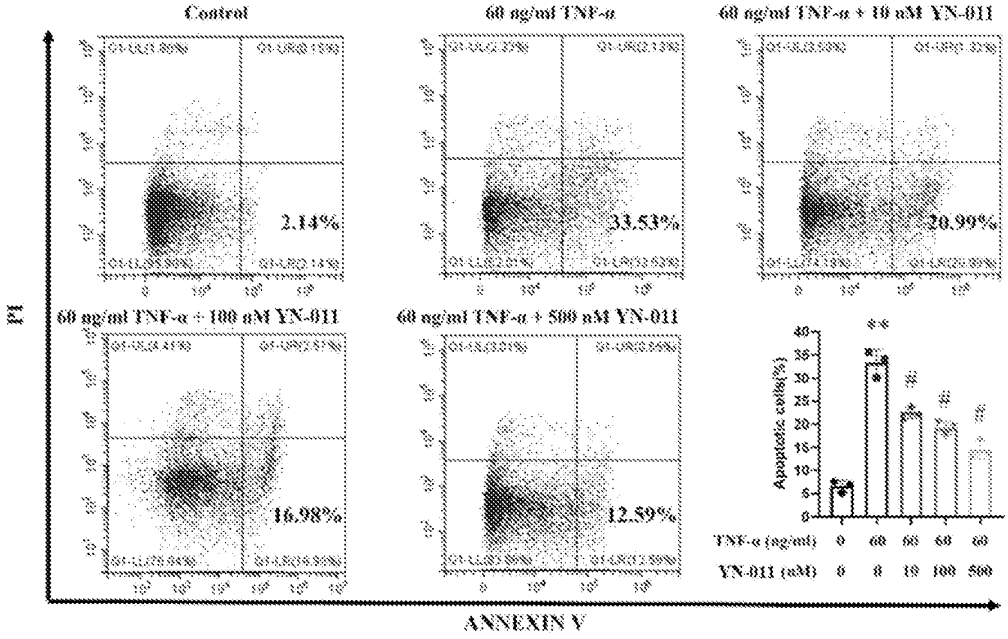
[图 20]


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 (%)
TNF-α (ng/ml) 0 60 60 60 60
GABA (μM) 0 0 1 10 100

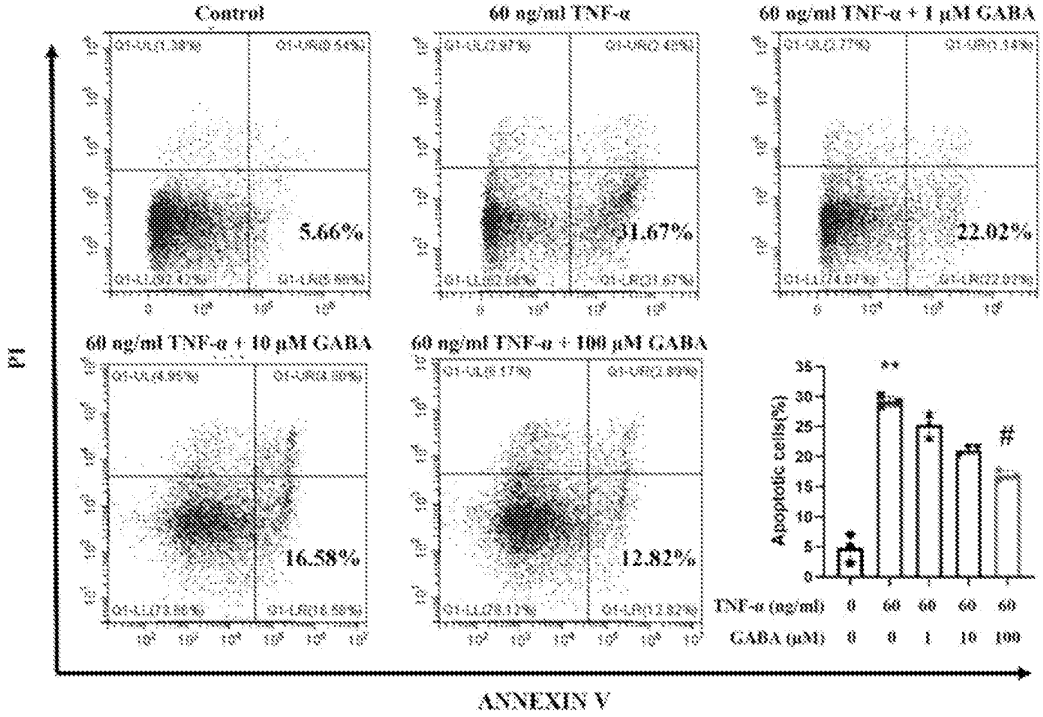
[图 21]


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 (%)
**
##
#
TNF-α (ng/ml) 0 60 60 60 60
GABA (μM) 0 0 100 0 100
YN-011 (nM) 0 0 0 100 100

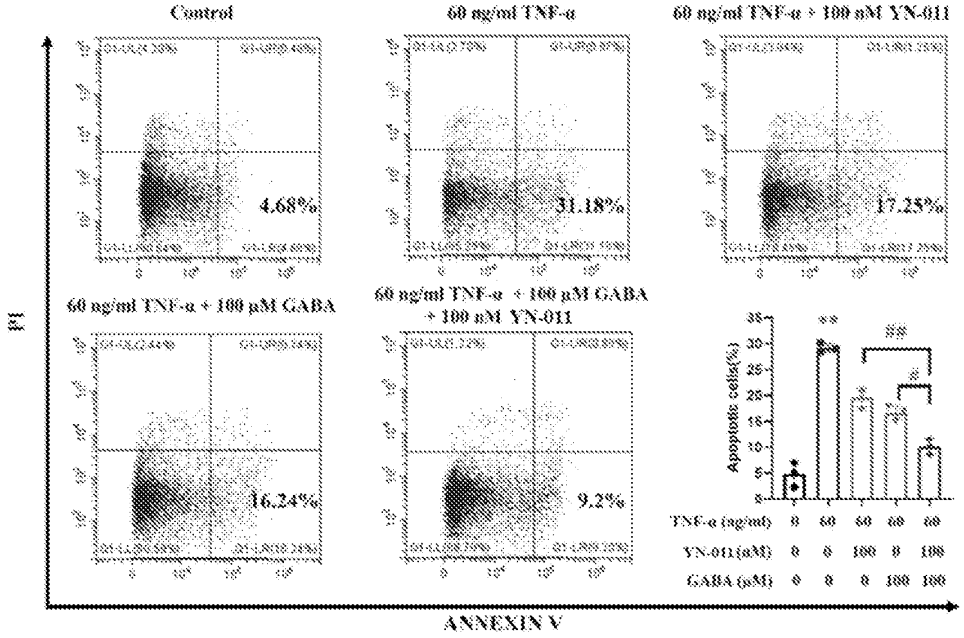
[图 22]


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
2.14%
33.53%
20.99%
16.98%
12.59%
PI
ANNEXIN V
Apoptotic cells(%)
**
#
TNF-α (ng/ml) 0 60 60 60 60
YN-011 (nM) 0 0 10 100 500

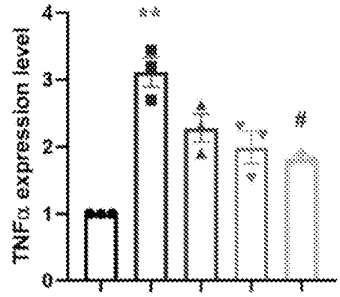
[图 23]

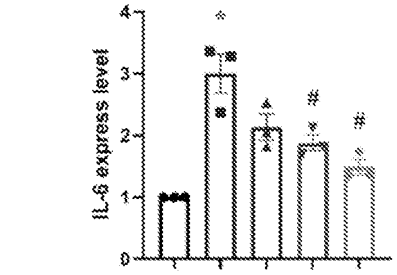

Control
60 ng/ml TNF-α
60 ng/ml TNF-α + 1 μM GABA
5.66%
31.67%
22.02%
60 ng/ml TNF-α + 10 μM GABA
60 ng/ml TNF-α + 100 μM GABA
16.58%
12.82%
Apoptotic cells(%)
TNF-α (ng/ml) 0 60 60 60 60
GABA (μM) 0 0 1 10 100
PI
ANNEXIN V

[图 24]

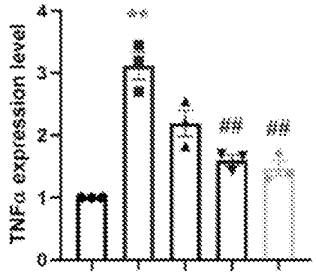

Control
60 ng/ml TNF-α
60 ng/ml TNF-α + 100 nM YN-011
4.68%
31.18%
17.25%
60 ng/ml TNF-α + 100 μM GABA
60 ng/ml TNF-α + 100 μM GABA + 100 nM YN-011
16.24%
9.2%
Apoptotic cells(%)
TNF-α (ng/ml) 0 60 60 60 60
YN-011 (nM) 0 0 100 0 100
GABA (μM) 0 0 0 100 100
PI
ANNEXIN V

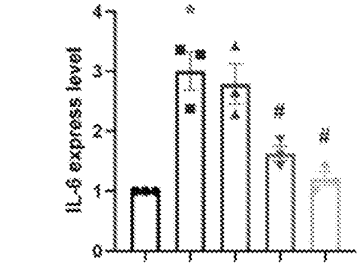
[图 25]


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

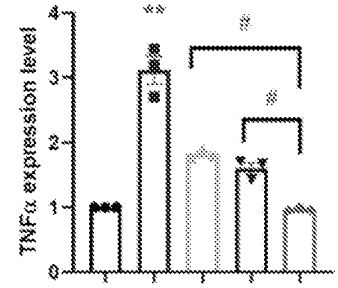

IL-6 express level
*
#
Aβ1-42 (μM) 0 10 10 10 10
GABA (μM) 0 0 1 10 100

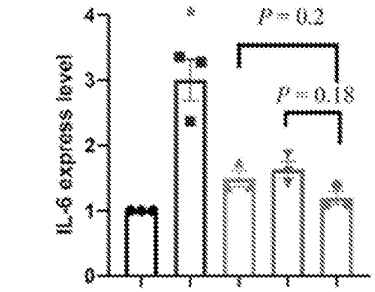
[图 26]


TNFα expression level
**
##
Aβ1-42 (μM) 0 10 10 10 10
YN-011 (nM) 0 0 10 100 500

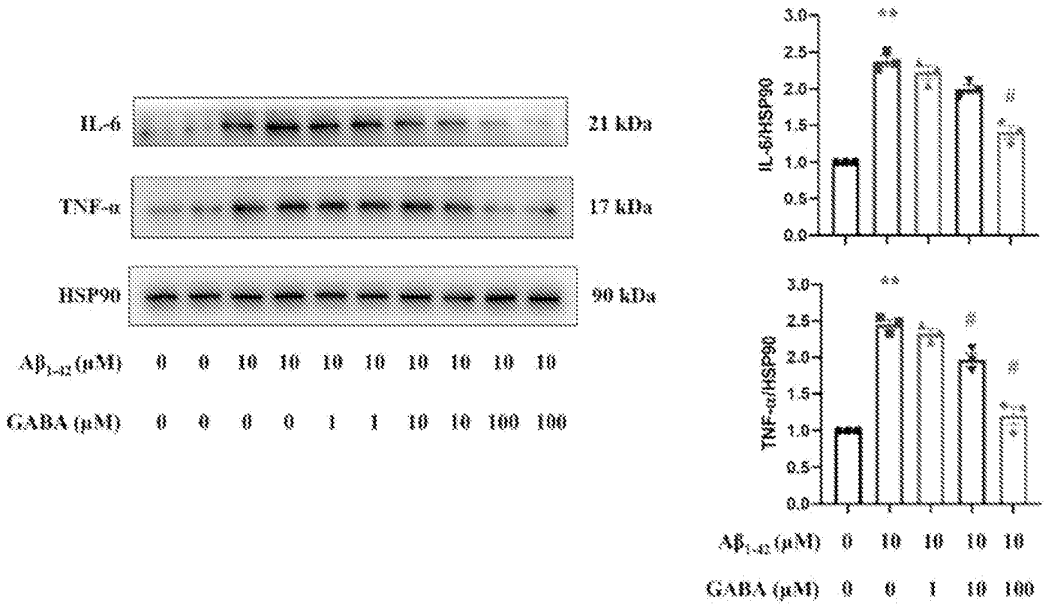

IL-6 express level
*
#
Aβ1-42 (μM) 0 10 10 10 10
YN-011 (nM) 0 0 10 100 500

[图 27]

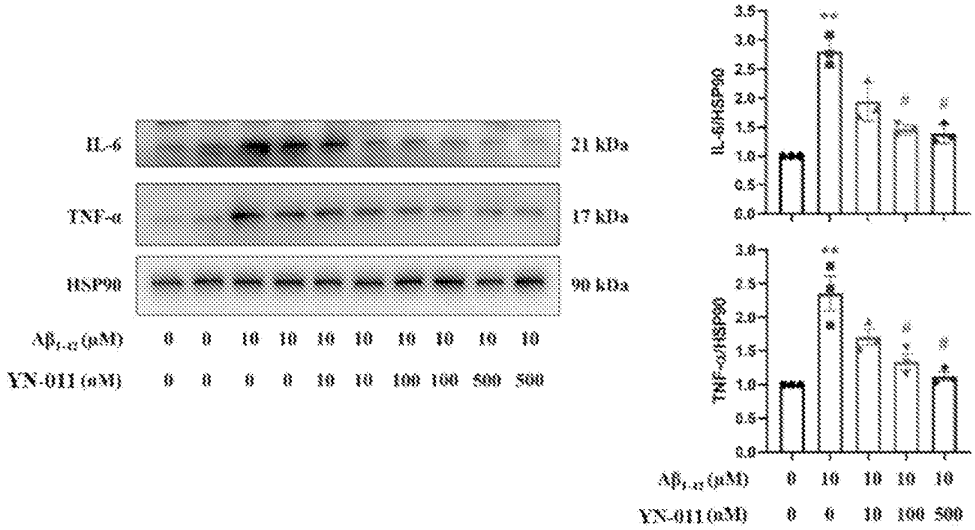

TNFα expression level
**
#
Aβ1-42 (μM) 0 10 10 10 10
GABA (μM) 0 0 100 0 100
YN-011 (nM) 0 0 0 100 100


IL-6 express level
*
P = 0.2
P = 0.18
Aβ1-42 (μM) 0 10 10 10 10
GABA (μM) 0 0 100 0 100
YN-011 (nM) 0 0 0 100 100

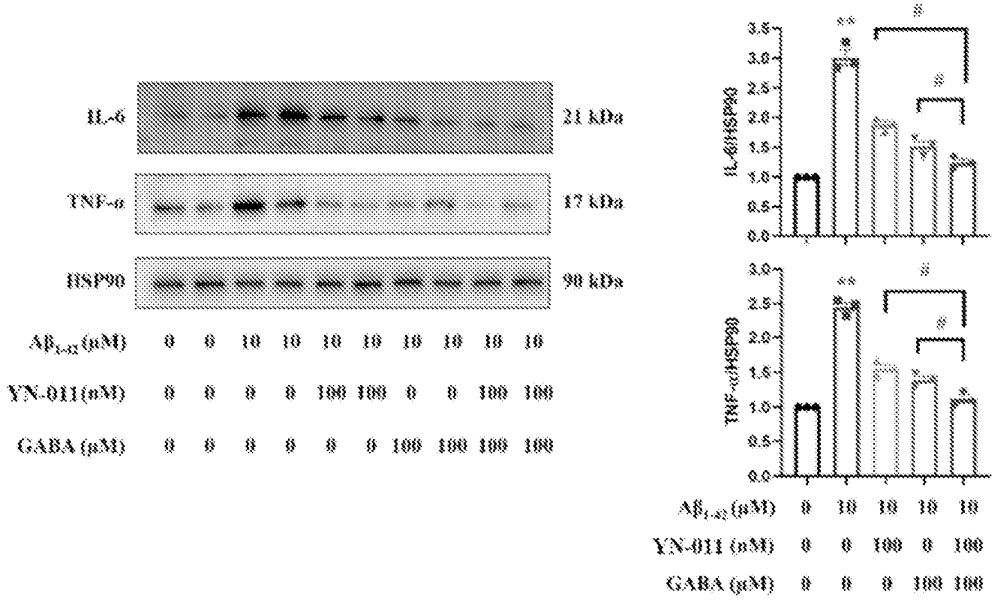
[图 28]


IL-6
TNF-α
HSP90
21 kDa
17 kDa
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
Aβ1-42 (μM) 0 10 10 10 10
GABA (μM) 0 0 1 10 100

[图 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

[图 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