FIG. 1

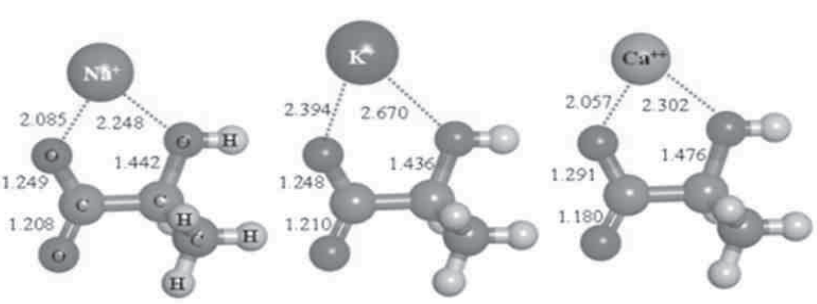



**Table 1.** Binding free energy of Metal-Lactate complexes

| | Metal (Hatree) | Lactate (Hatree) | Binding Energy (ΔE, kcal/mol) | TΔS (kcal/mol) | ΔG (kcal/mol) |
|---|---|---|---|---|---|
| **$Na^+$-Lactate** | -161.664286 | -341.163438 | -126.21 | -8.03 | -118.18 |
| **$K^+$-Lactate** | -599.001916 | -341.163438 | -106.85 | -7.06 | -99.79 |
| **$Ca^{2+}$-Lactate** | -676.13655 | -341.163438 | -290.86 | -8.20 | -282.66 |

FIG. 2

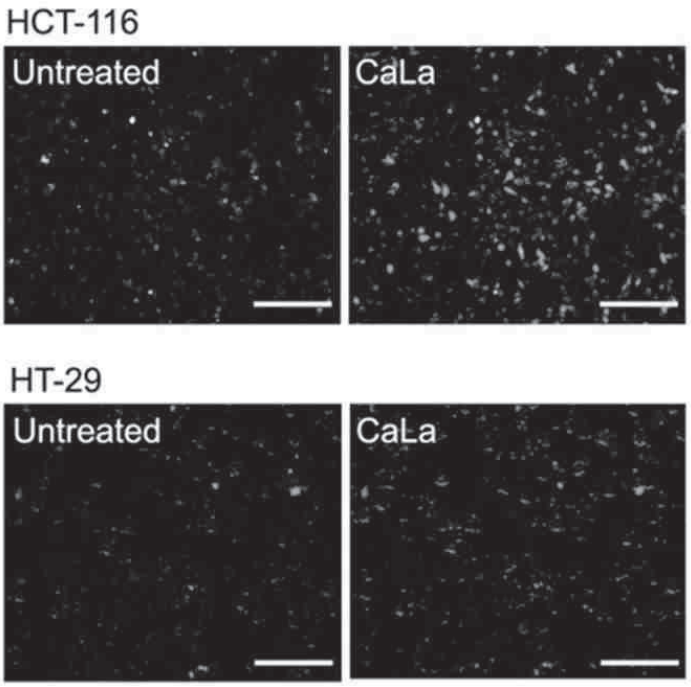


FIG. 3

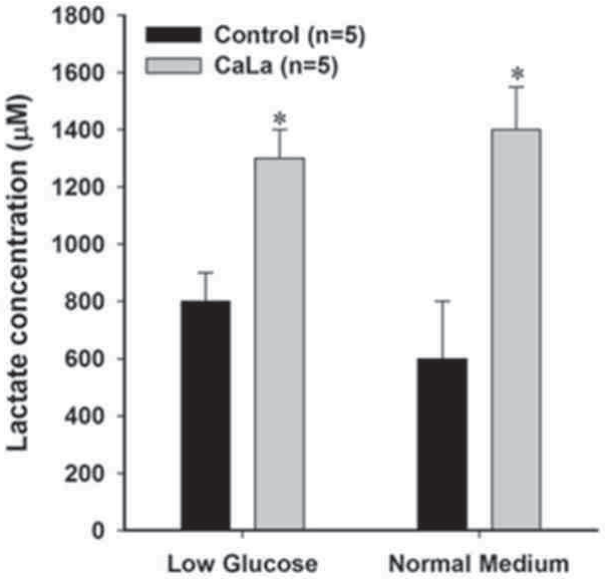

Control (n=5)
CaLa (n=5)
Lactate concentration (μM)
1800
1600
1400
1200
1000
800
600
400
200
0
*
*
Low Glucose
Normal Medium

FIG. 4

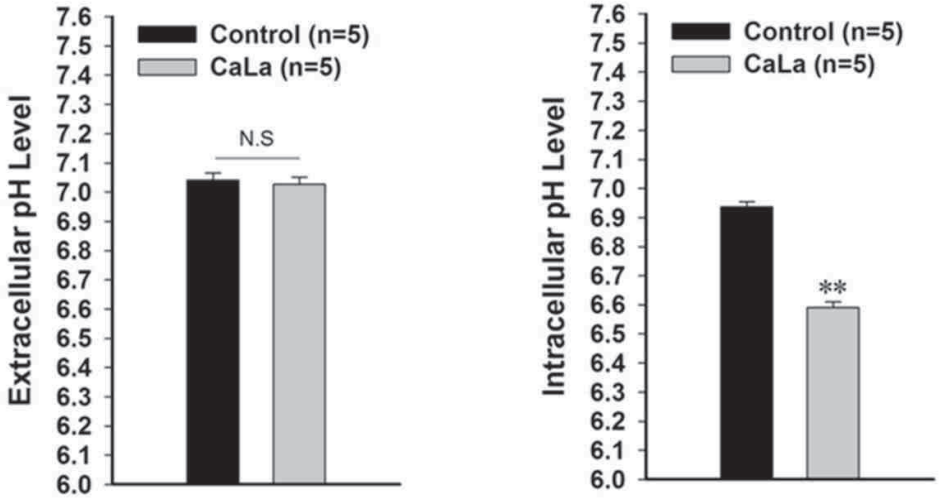

Control (n=5)
CaLa (n=5)
Extracellular pH Level
7.6
7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
6.7
6.6
6.5
6.4
6.3
6.2
6.1
6.0
N.S
Control (n=5)
CaLa (n=5)
Intracellular pH Level
7.6
7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
6.7
6.6
6.5
6.4
6.3
6.2
6.1
6.0
**

FIG. 5

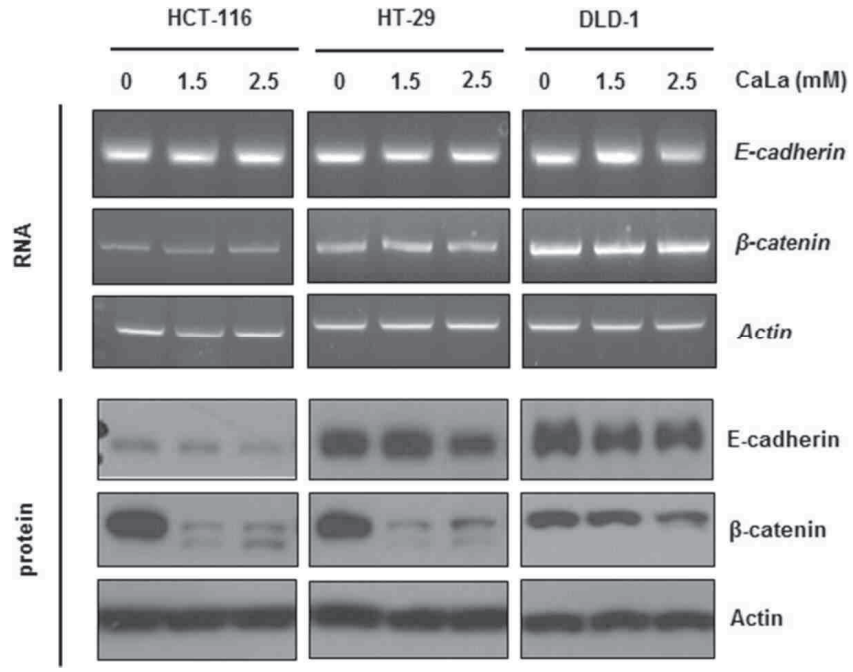

HCT-116
HT-29
DLD-1
0
1.5
2.5
0
1.5
2.5
0
1.5
2.5
CaLa (mM)
RNA
E-cadherin
β-catenin
Actin
protein
E-cadherin
β-catenin
Actin

FIG. 6

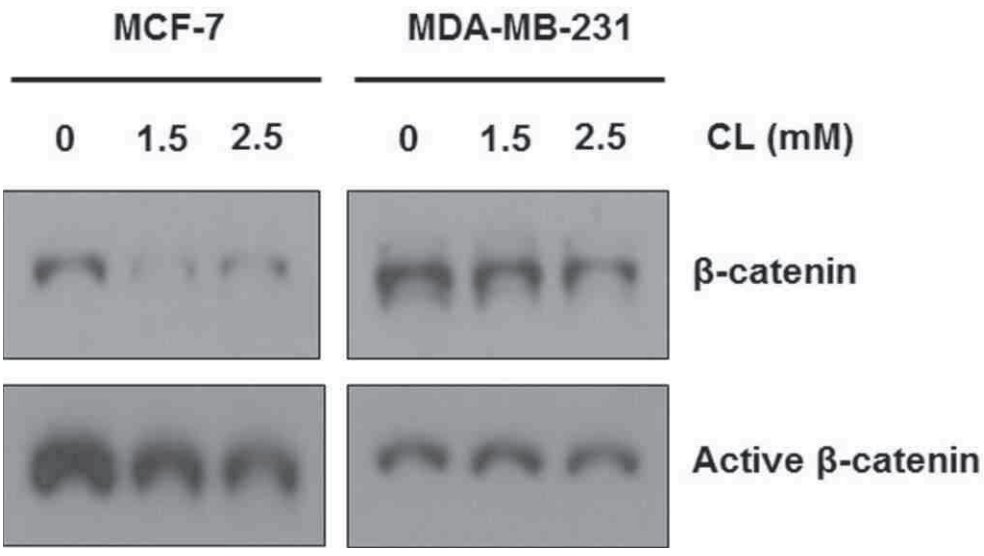

MCF-7
MDA-MB-231
0
1.5
2.5
0
1.5
2.5
CL (mM)
β-catenin
Active β-catenin

FIG. 7

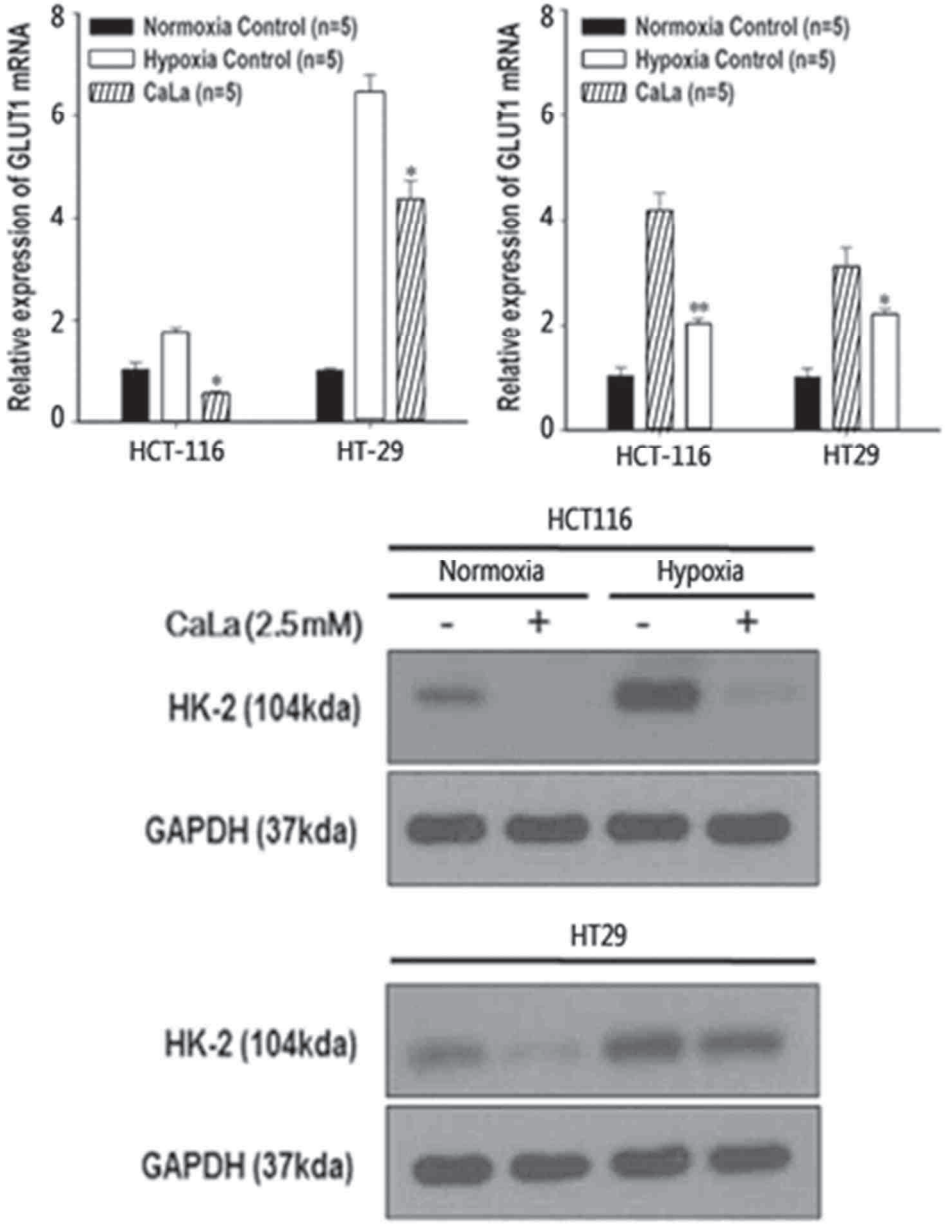

Normoxia Control (n=5)
Hypoxia Control (n=5)
CaLa (n=5)
Relative expression of GLUT1 mRNA
HCT-116
HT-29
HT29
HCT116
Normoxia
Hypoxia
CaLa (2.5mM)
HK-2 (104kda)
GAPDH (37kda)

FIG. 8

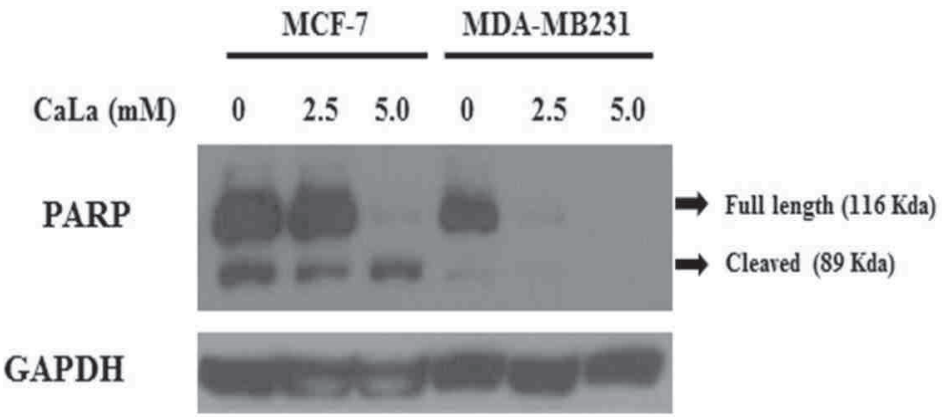

MCF-7
MDA-MB231
CaLa (mM)
0
2.5
5.0
0
2.5
5.0
PARP
Full length (116 Kda)
Cleaved (89 Kda)
GAPDH

FIG. 9

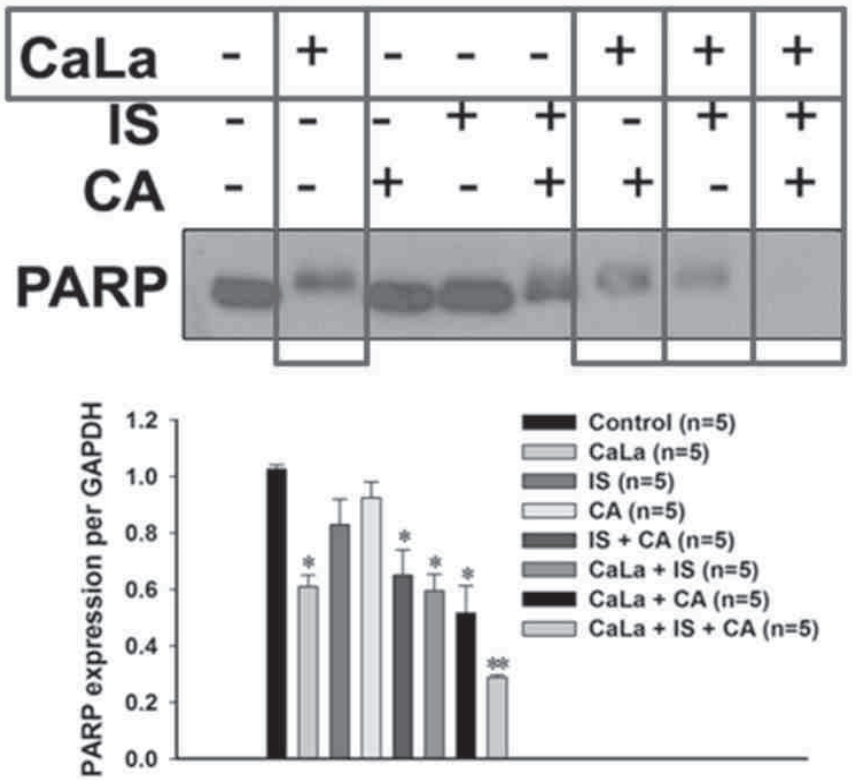

CaLa
IS
CA
PARP
PARP expression per GAPDH
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Control (n=5)
CaLa (n=5)
IS (n=5)
CA (n=5)
IS + CA (n=5)
CaLa + IS (n=5)
CaLa + CA (n=5)
CaLa + IS + CA (n=5)

FIG. 10

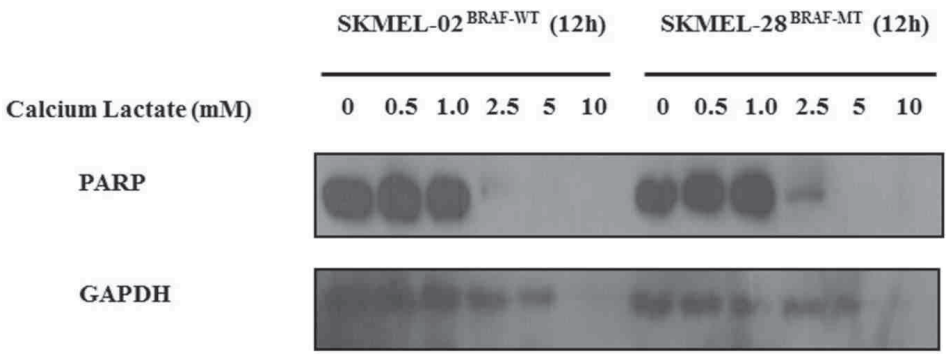



FIG. 11a

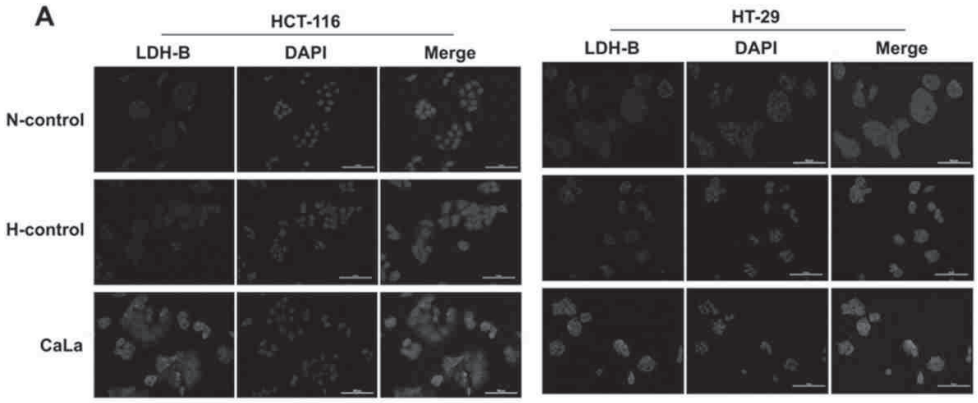


FIG. 11b

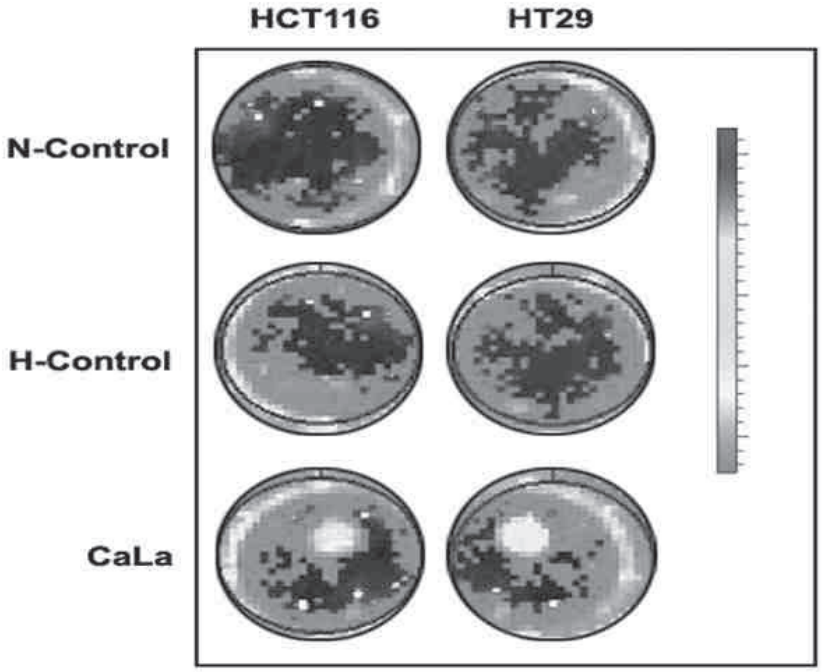



FIG. 11c

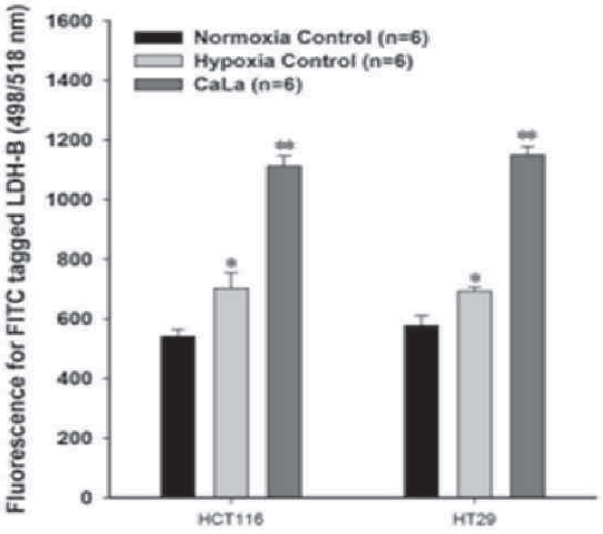


FIG. 12

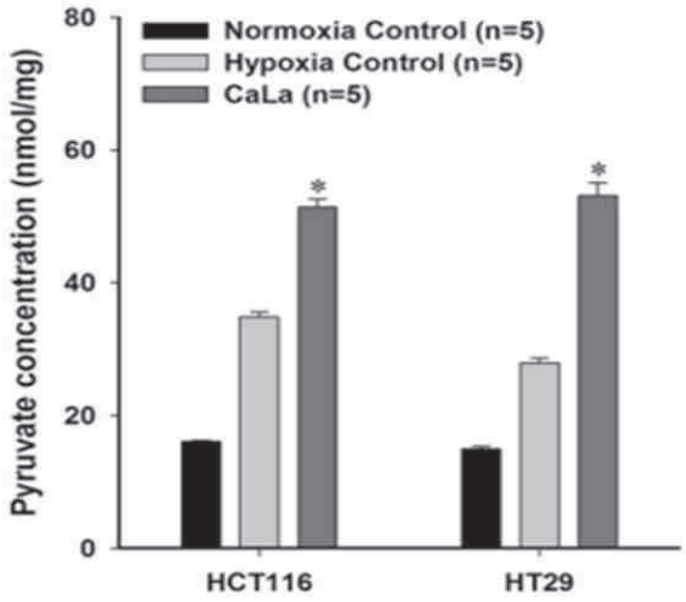



FIG. 13a

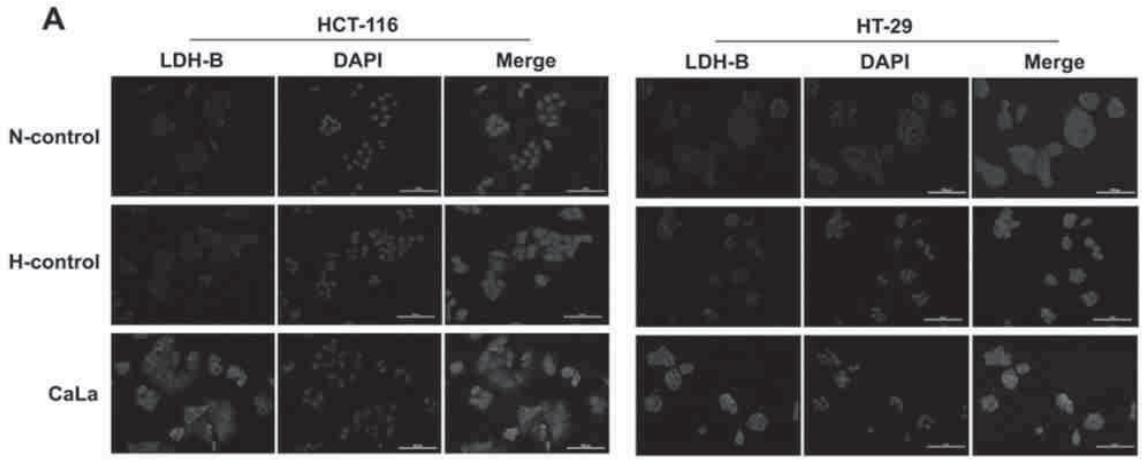


FIG. 13b

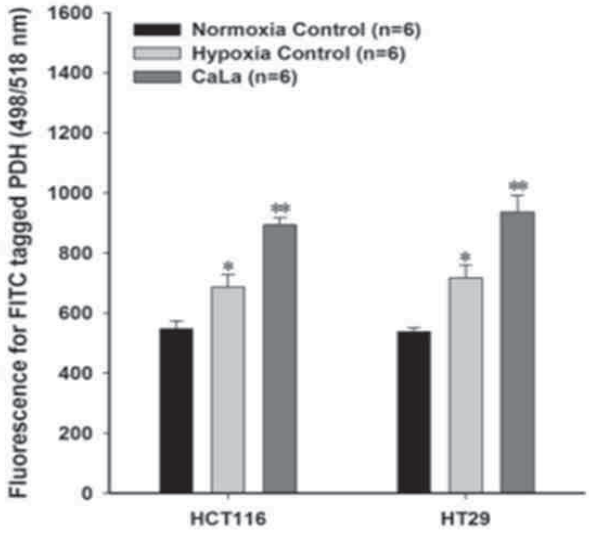



FIG. 14a

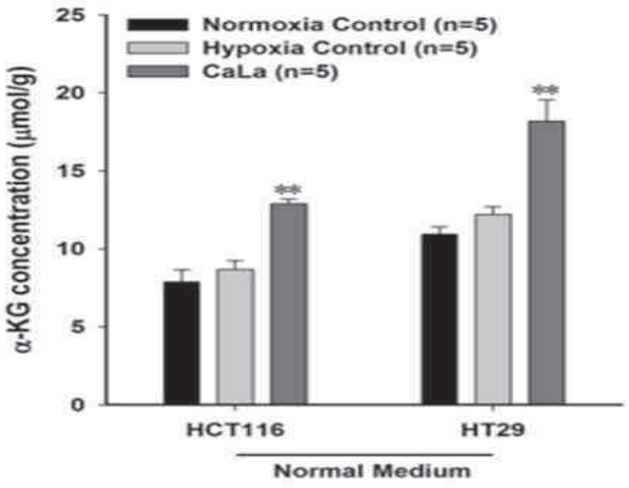


FIG. 14b

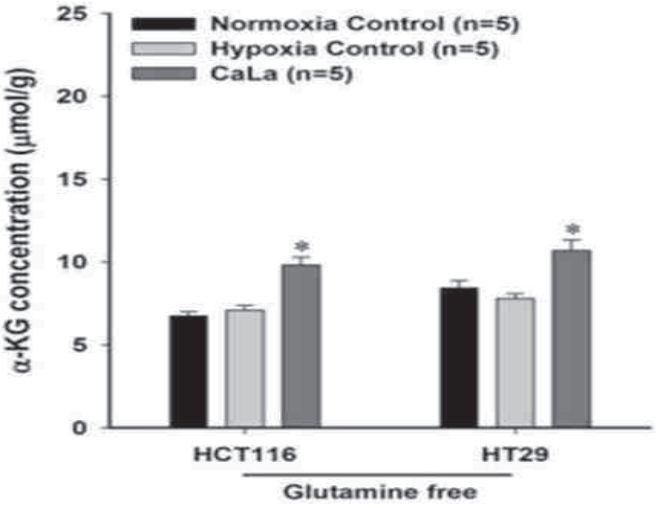

Normoxia Control (n=5)
Hypoxia Control (n=5)
CaLa (n=5)
α-KG concentration (µmol/g)
25
20
15
10
5
0
*
*
HCT116
HT29
Glutamine free

FIG. 15

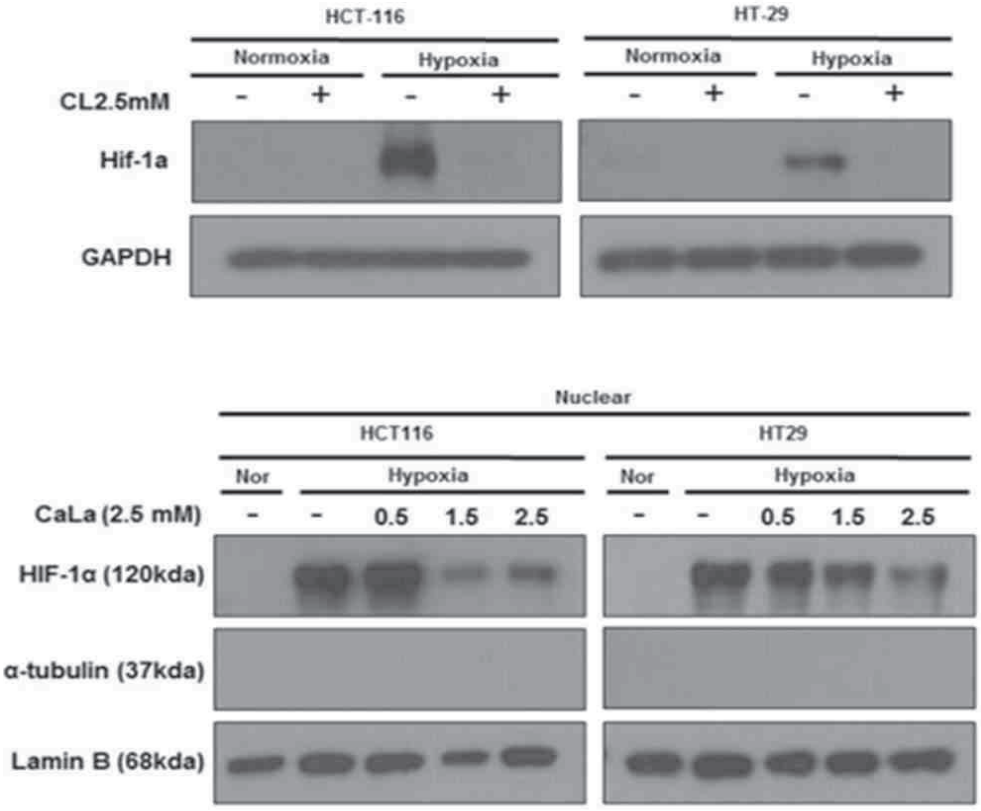

HCT-116
HT-29
Normoxia
Hypoxia
Normoxia
Hypoxia
CL2.5mM
- + - + - + - +
Hif-1a
GAPDH
Nuclear
HCT116
HT29
Nor
Hypoxia
Nor
Hypoxia
CaLa (2.5 mM)
- - 0.5 1.5 2.5 - - 0.5 1.5 2.5
HIF-1α (120kda)
α-tubulin (37kda)
Lamin B (68kda)

FIG. 16a

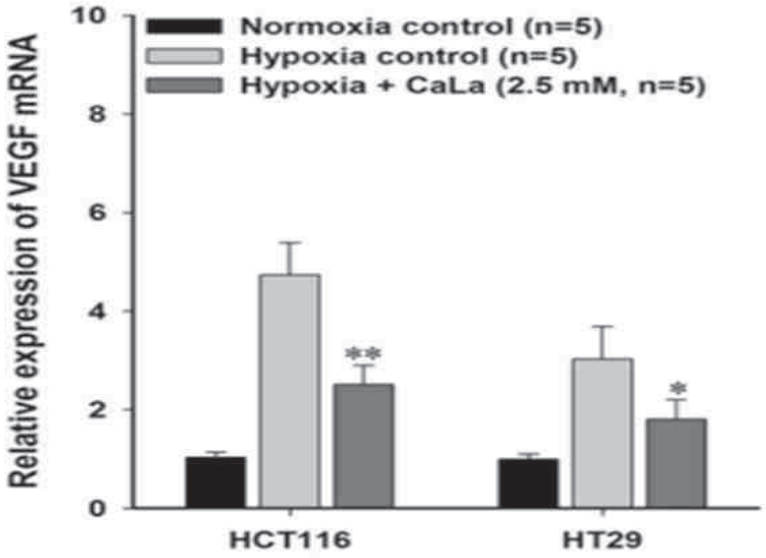



FIG. 16b

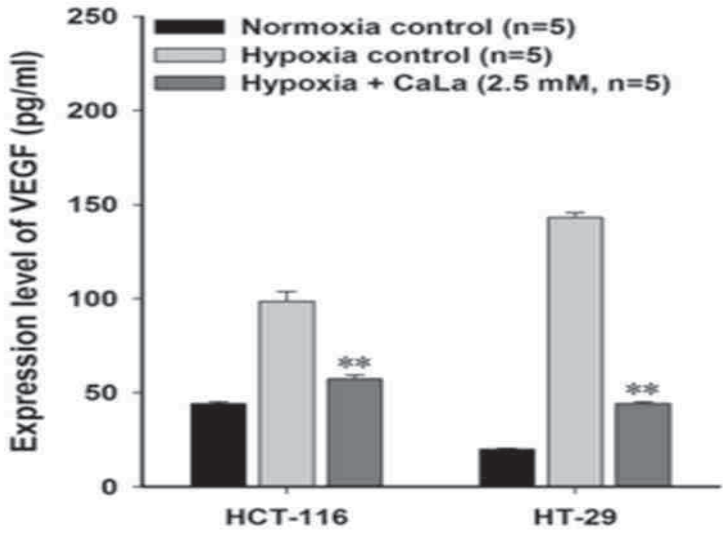


FIG. 17

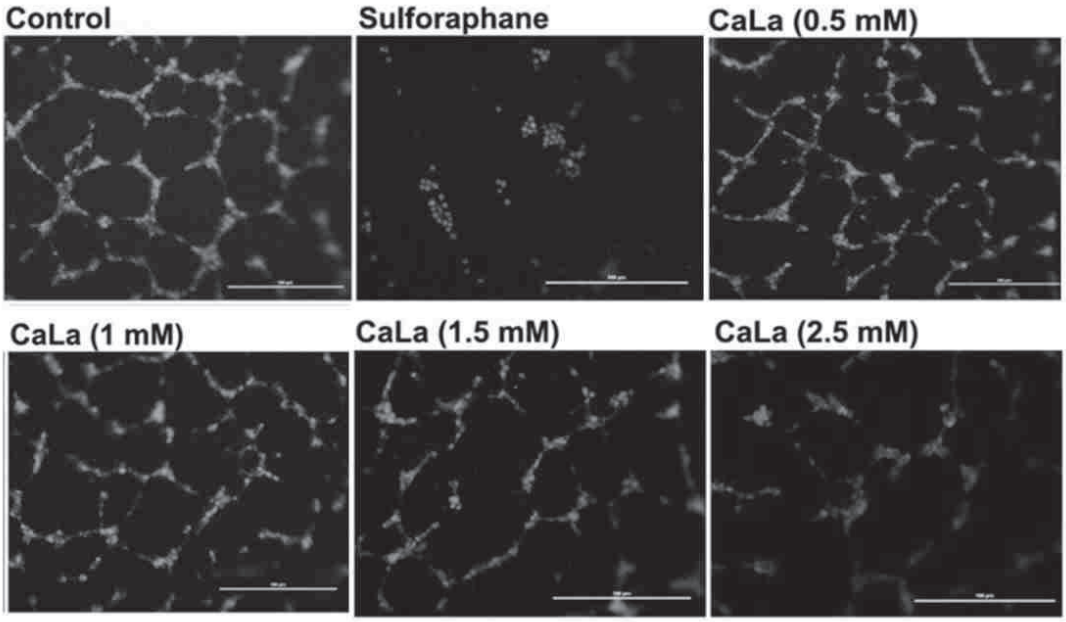

Control
Sulforaphane
CaLa (0.5 mM)
CaLa (1 mM)
CaLa (1.5 mM)
CaLa (2.5 mM)

FIG. 18

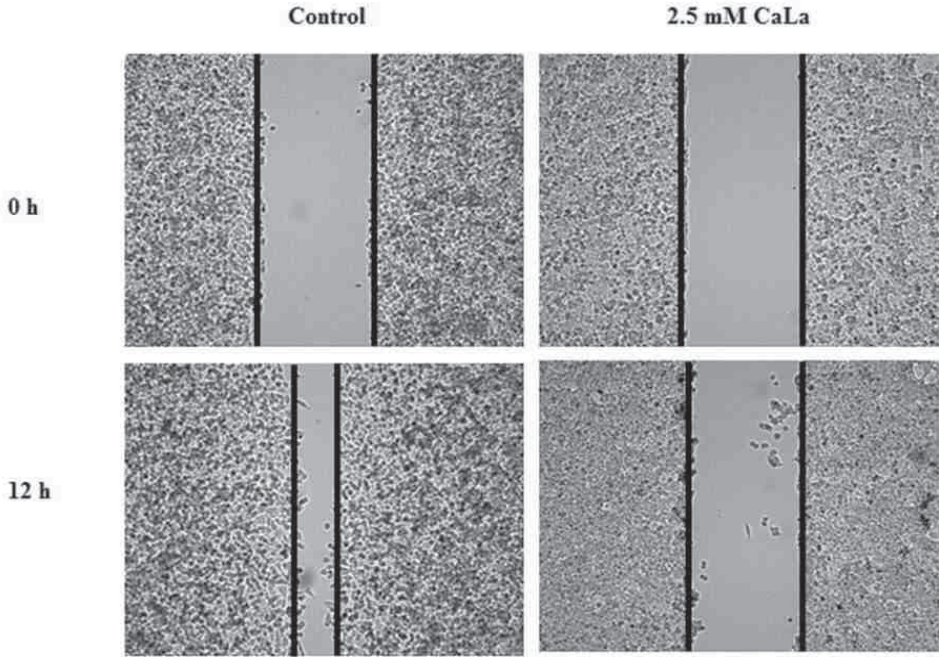

Control
2.5 mM CaLa
0 h
12 h

FIG. 19

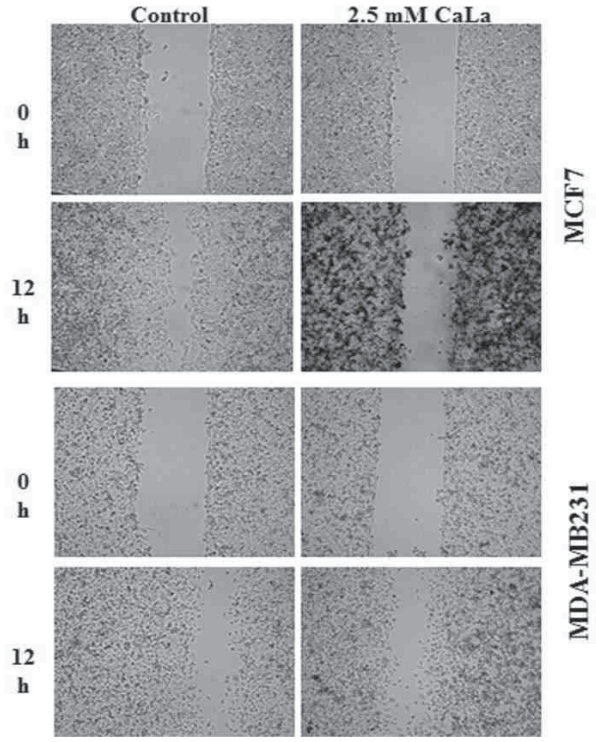

Control
2.5 mM CaLa
0 h
12 h
MCF7
0 h
12 h
MDA-MB231

FIG. 20

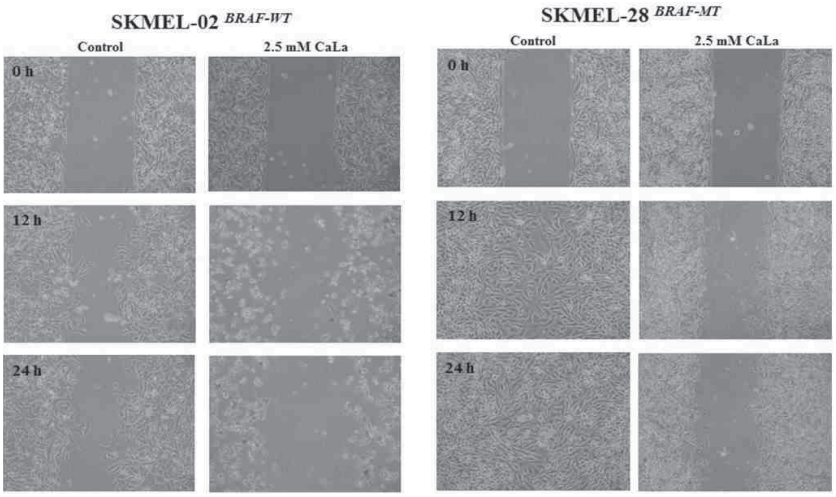

SKMEL-02 BRAF-WT
Control
2.5 mM CaLa
0 h
12 h
24 h
SKMEL-28 BRAF-MT
Control
2.5 mM CaLa
0 h
12 h
24 h

FIG. 21a

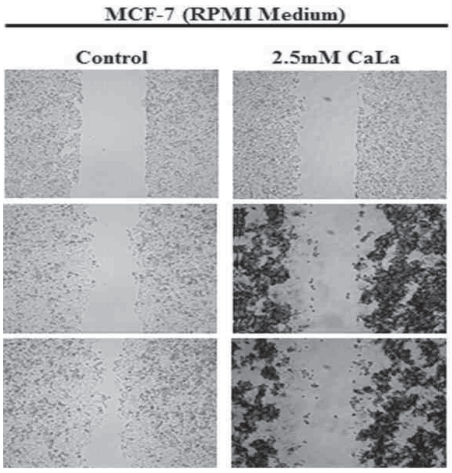



FIG. 21b

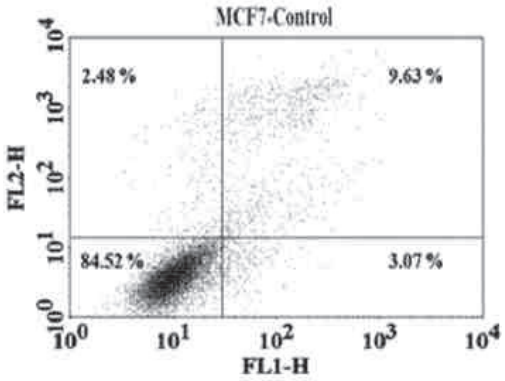



FIG. 21c

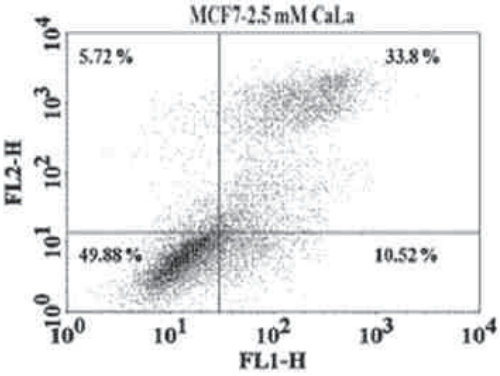


FIG. 21d

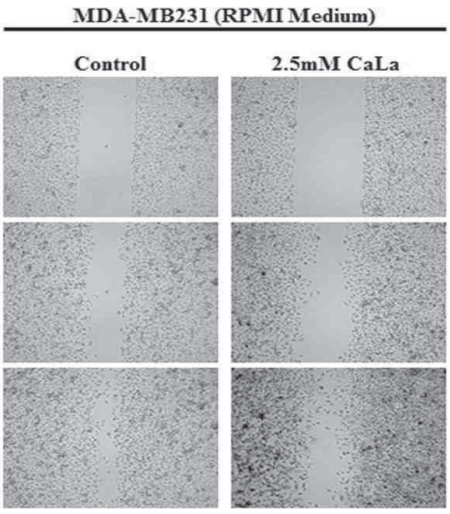



FIG. 21e

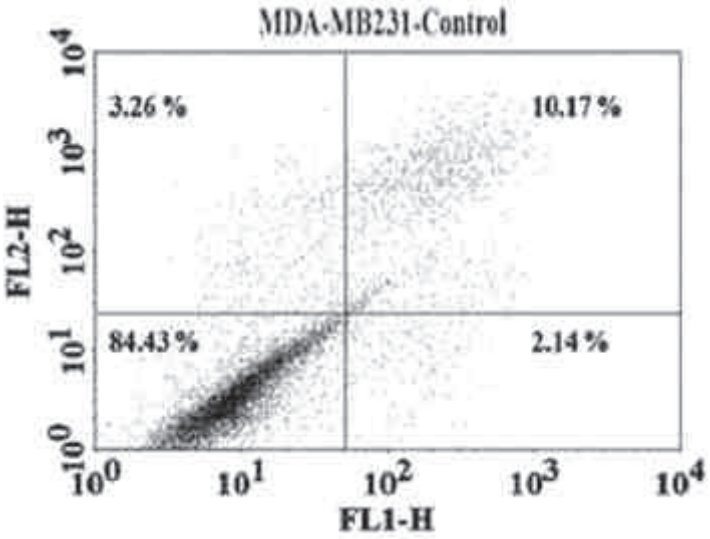


FIG. 21f

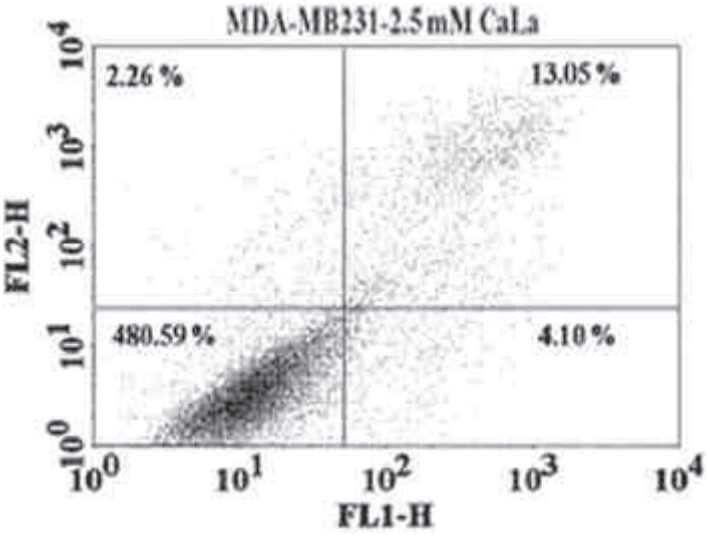



FIG. 22

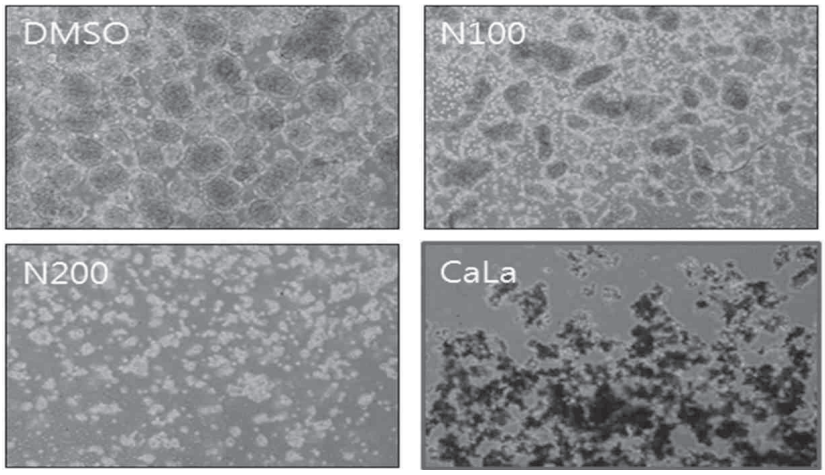


FIG. 23

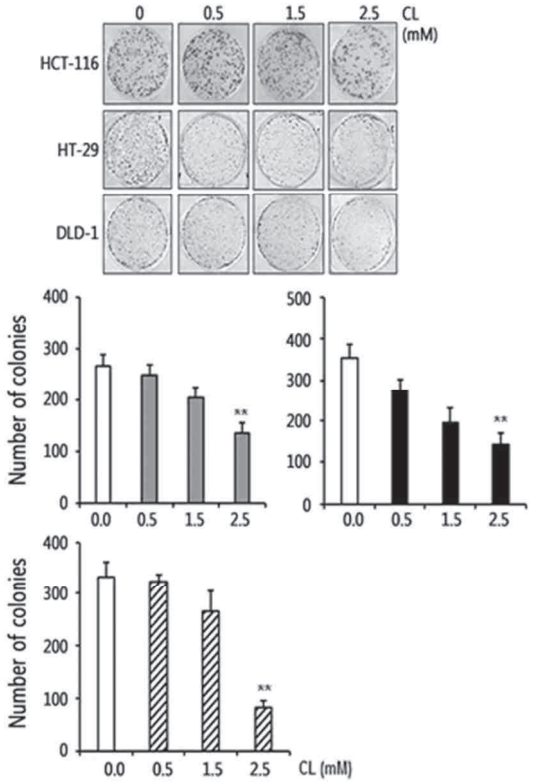
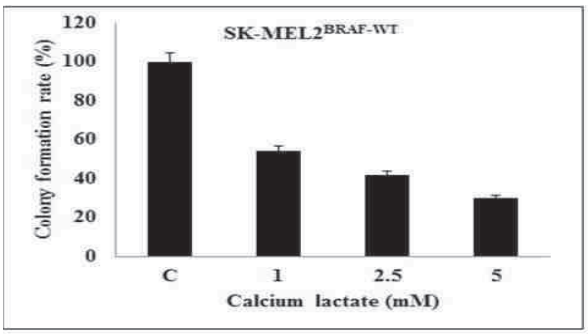
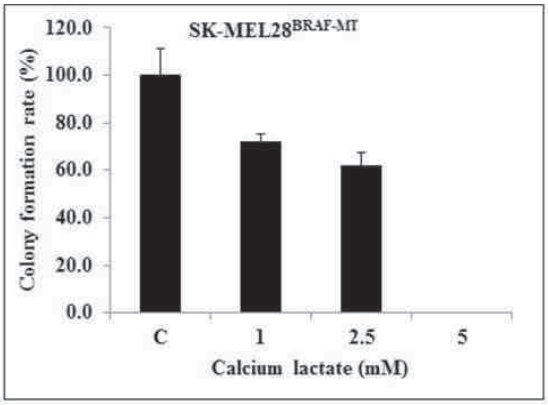



FIG. 24a




| SK-MEL2$^{BRAF-WT}$ | Average | CfR % | SD |
|---|---|---|---|
| Control | 167 | 100 | 18.52 |
| CaLa 1 mM | 90.7 | 53.8922 | 20.11 |
| CaLa 2.5 mM | 69.7 | 41.3174 | 8.5 |
| CaLa 5 mM | 49.7 | 29.3413 | 11.72 |

FIG. 24b




| SK-MEL28$^{BRAF-MT}$ | Average | CfR % | SD |
|---|---|---|---|
| Control | 105.3 | 100.3 | 10.97 |
| CaLa 1 mM | 75.7 | 72.1 | 3.51 |
| CaLa 2.5 mM | 65.3 | 62.2 | 5.51 |
| CaLa 5 mM | 0.0 | 0.0 | 0.00 |

FIG. 25a

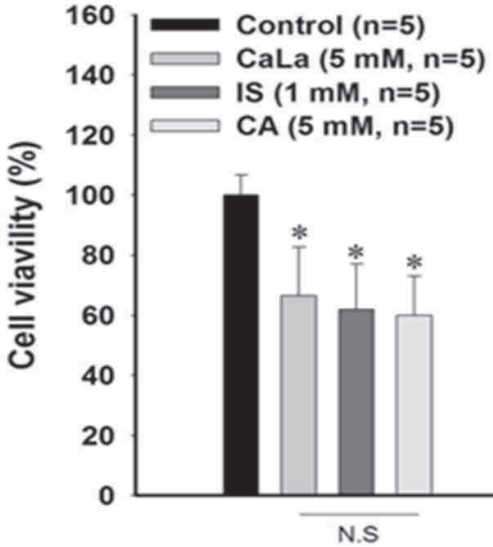


FIG. 25b

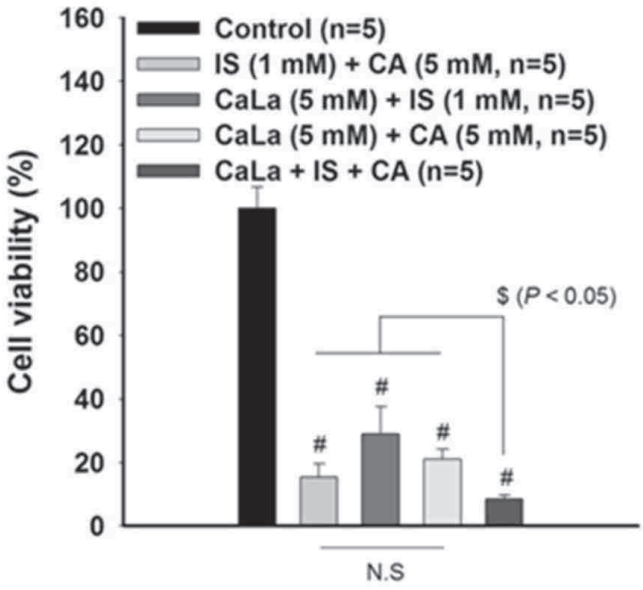



FIG. 26

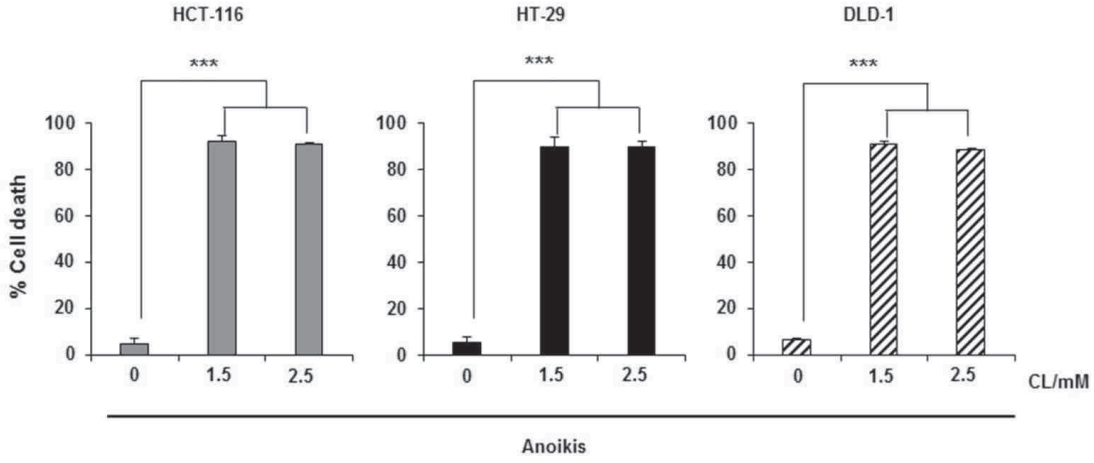


FIG. 27

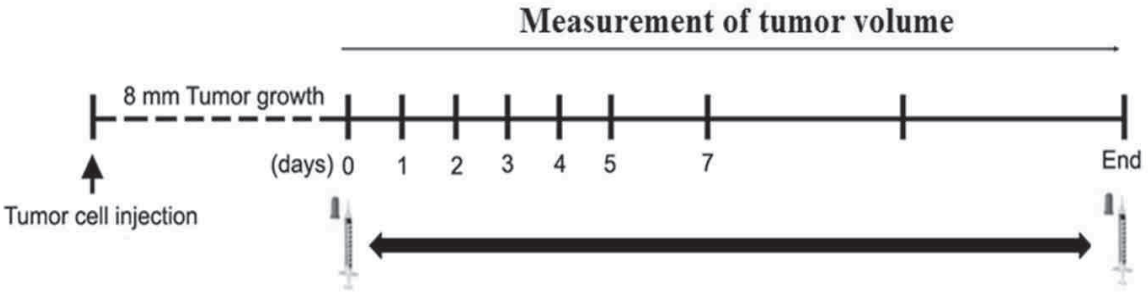
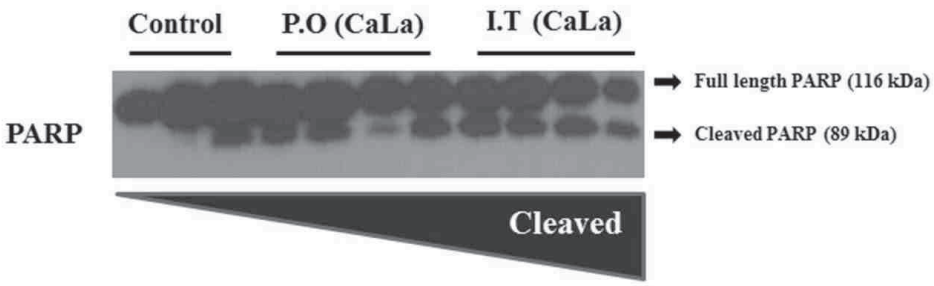
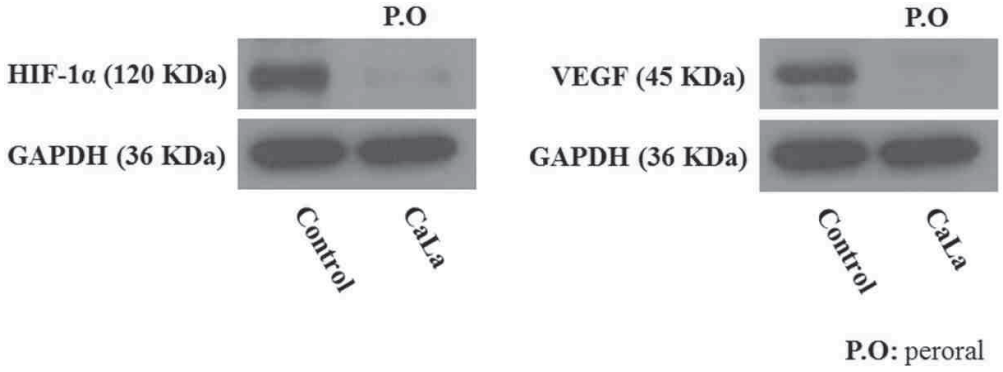



FIG. 28



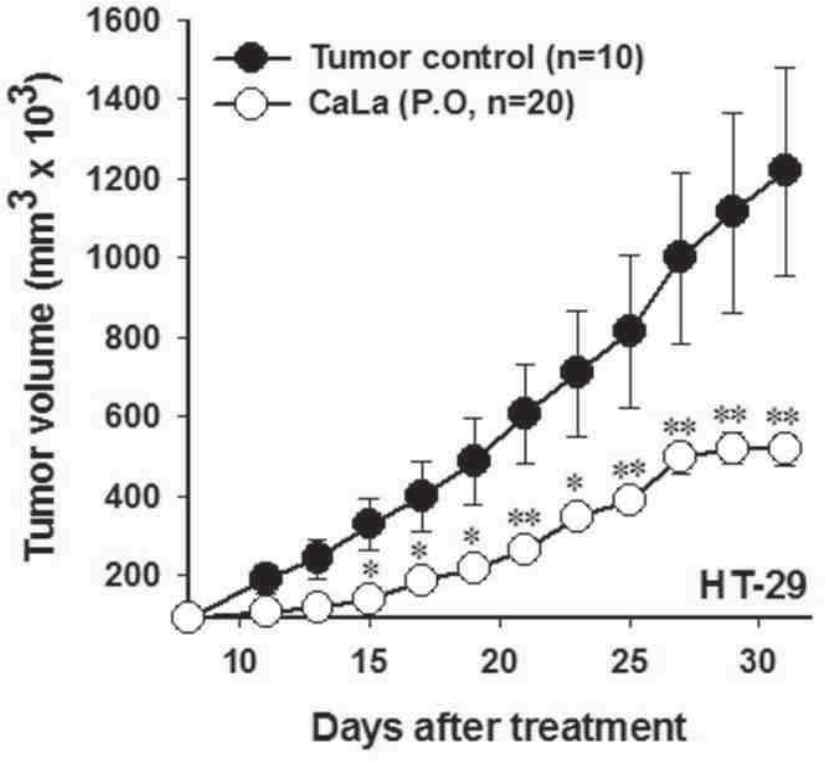

**P.O:** peroral
**I.T:** intra tumoral

FIG. 29



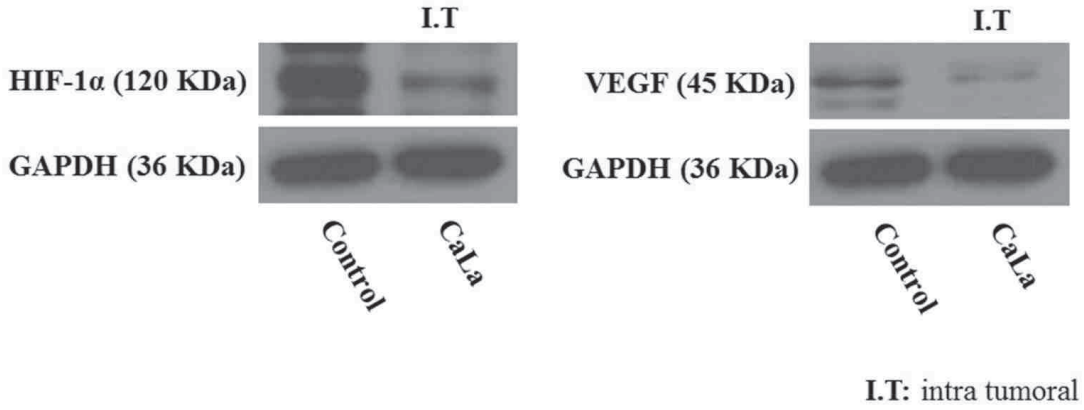

**P.O:** peroral

FIG. 30




**P.O:** peroral

FIG. 31




**I.T:** intra tumoral

FIG. 32

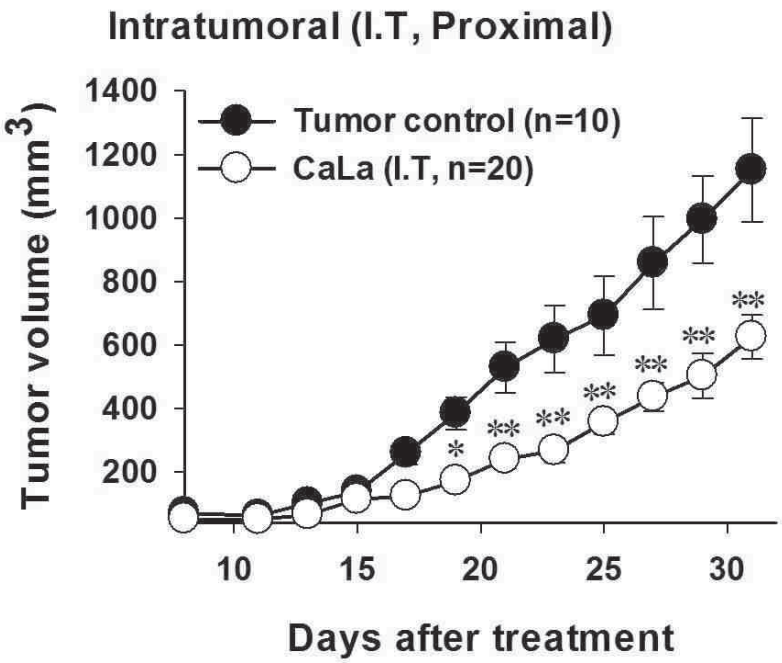


FIG. 33

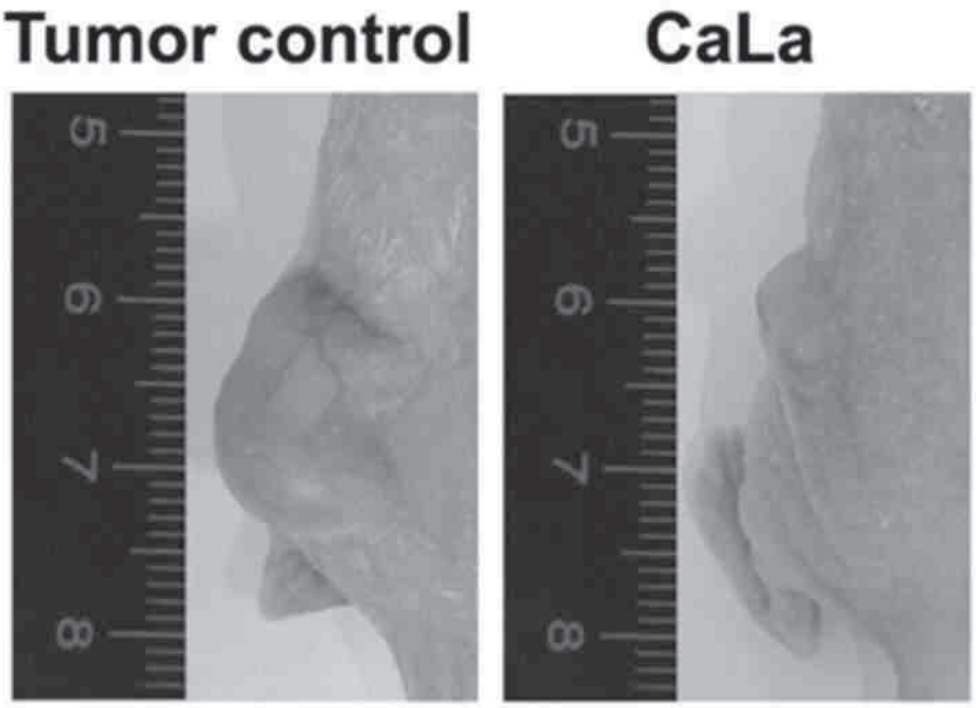

Tumor control
CaLa

FIG. 34

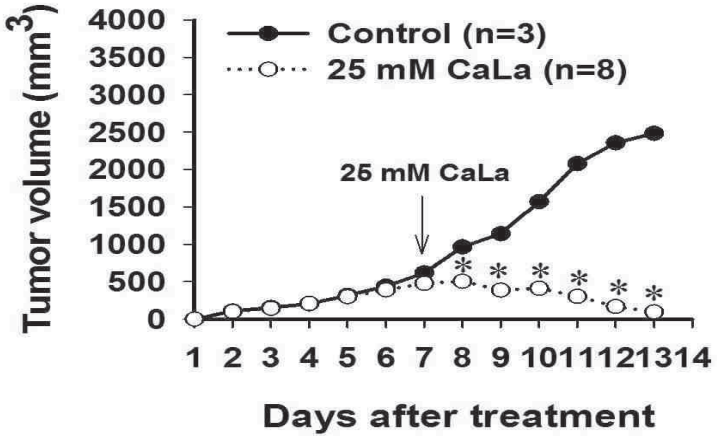

Tumor volume (mm3)
4000
3500
3000
2500
2000
1500
1000
500
0
Control (n=3)
25 mM CaLa (n=8)
25 mM CaLa
1 2 3 4 5 6 7 8 9 10 11 12 13 14
Days after treatment

FIG. 35

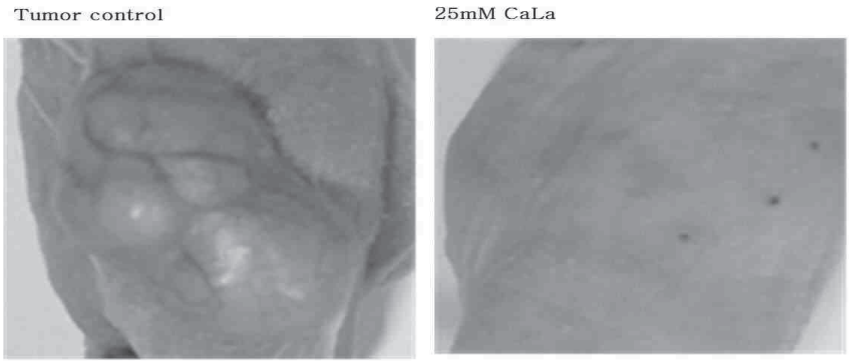

Tumor control
25mM CaLa

FIG. 36

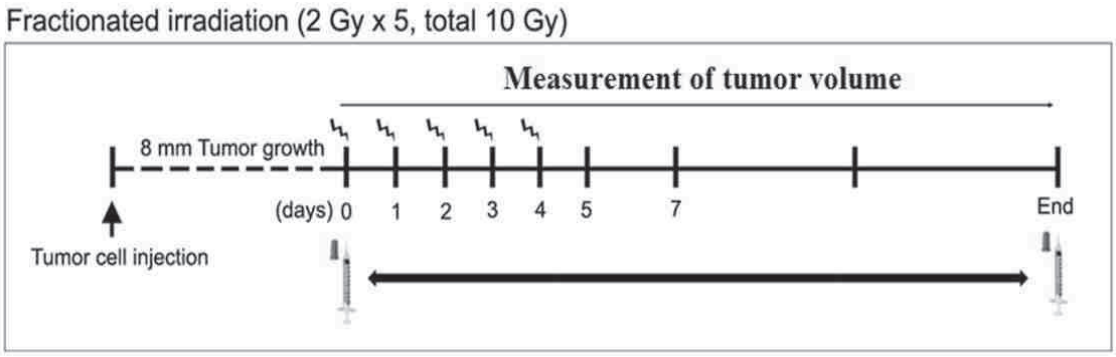

Fractionated irradiation (2 Gy x 5, total 10 Gy)
Measurement of tumor volume
8 mm Tumor growth
(days) 0 1 2 3 4 5 7
End
Tumor cell injection

FIG. 37a

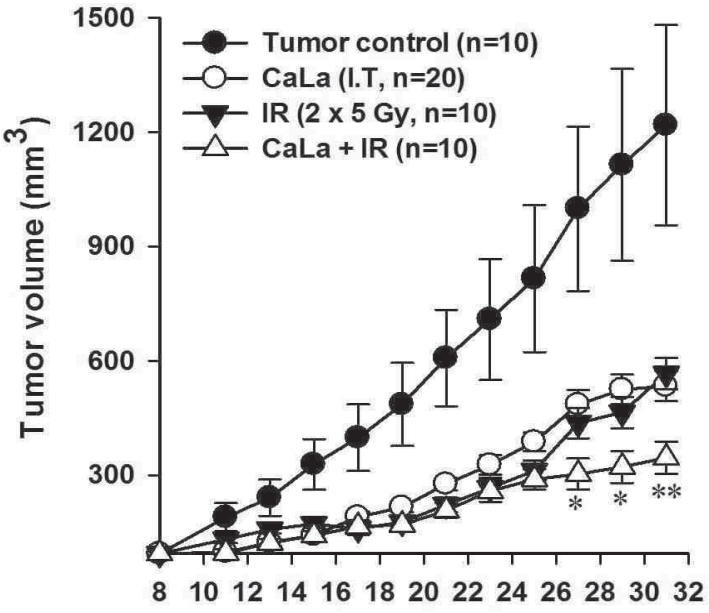



FIG. 37b

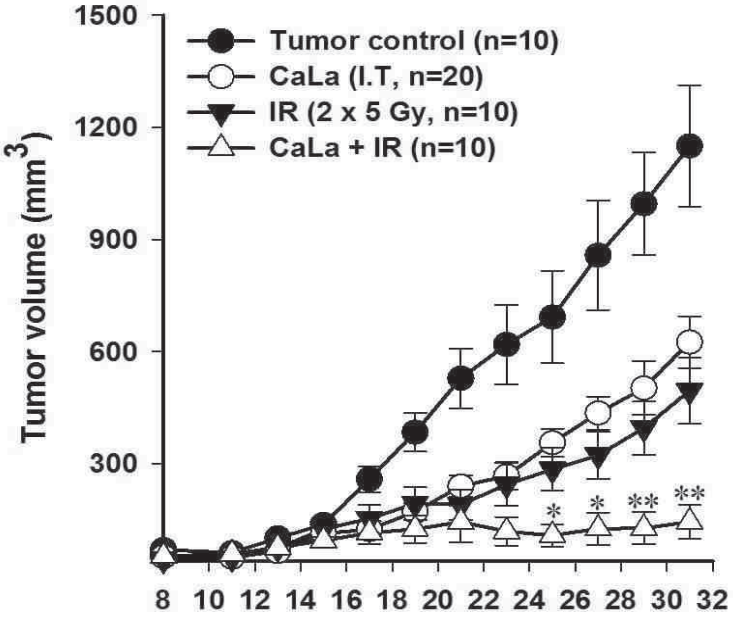


FIG. 38a

• Gastrointestinal stromal tumors

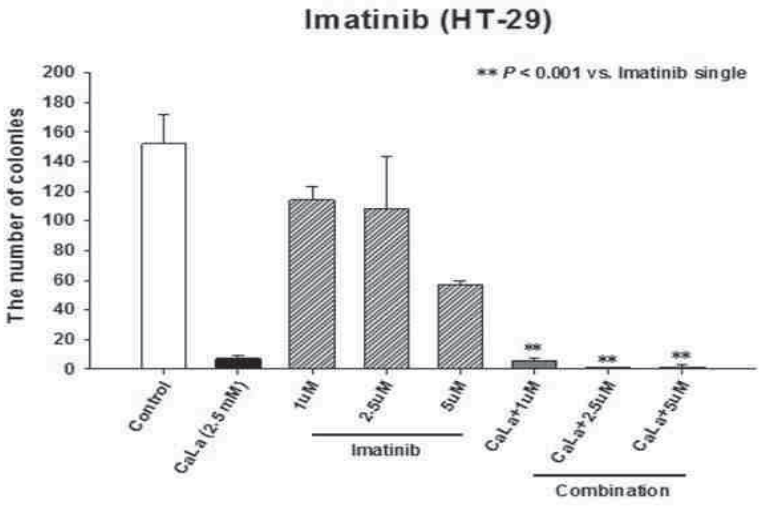



FIG. 38b

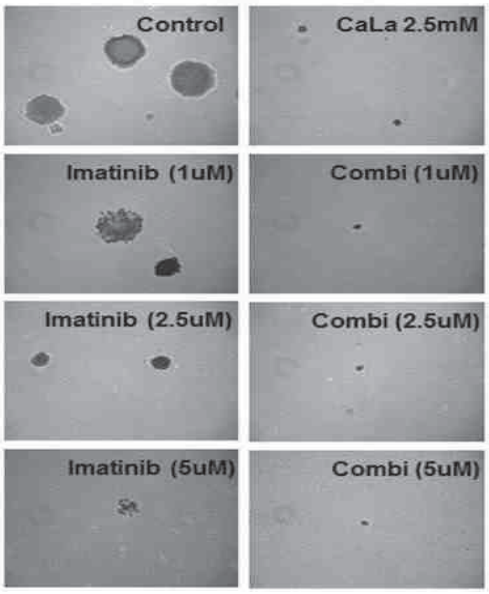


FIG. 39a

• Gastrointestinal stromal tumors

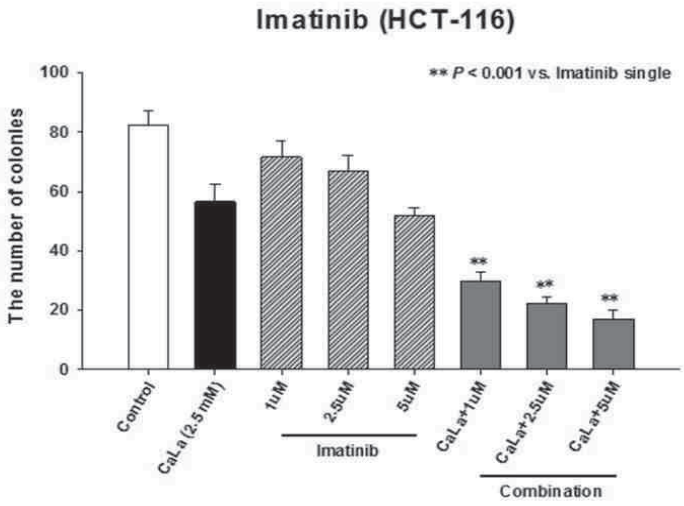



FIG. 39b

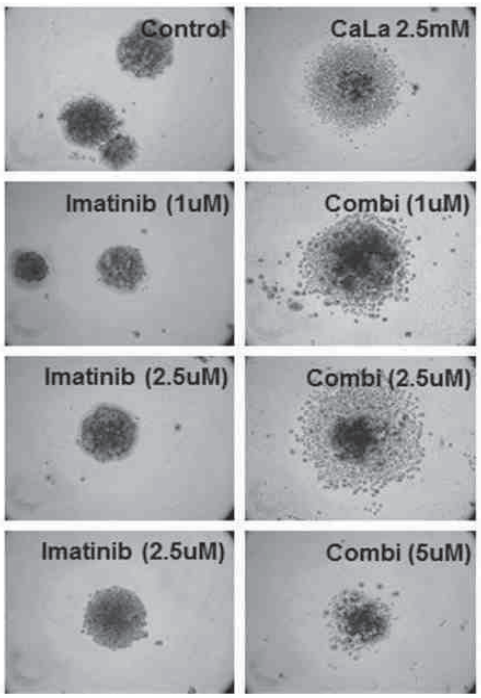


FIG. 40a

• Colorectal and oesophageal cancers

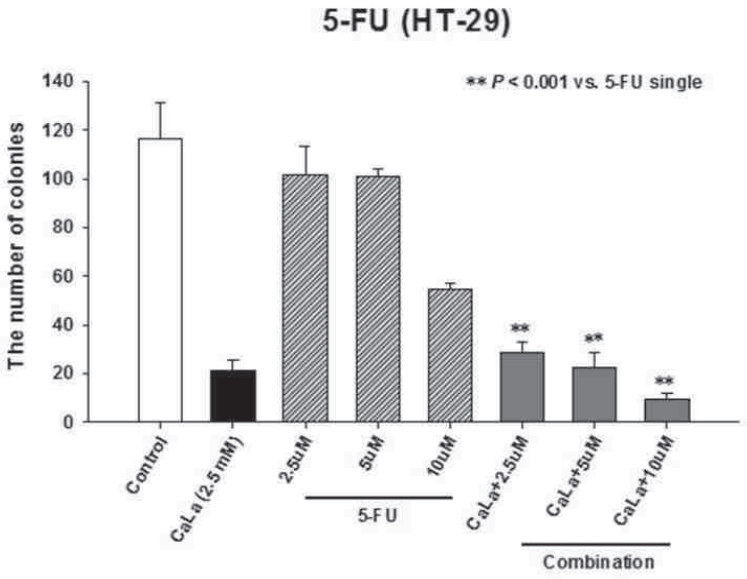


FIG. 40b

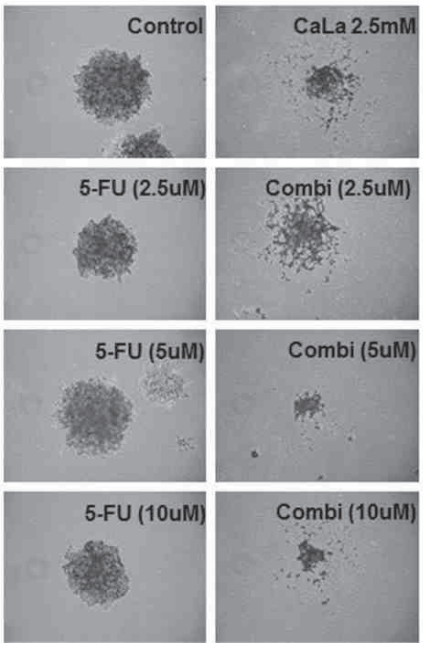



FIG. 41a

• Colorectal and oesophageal cancers

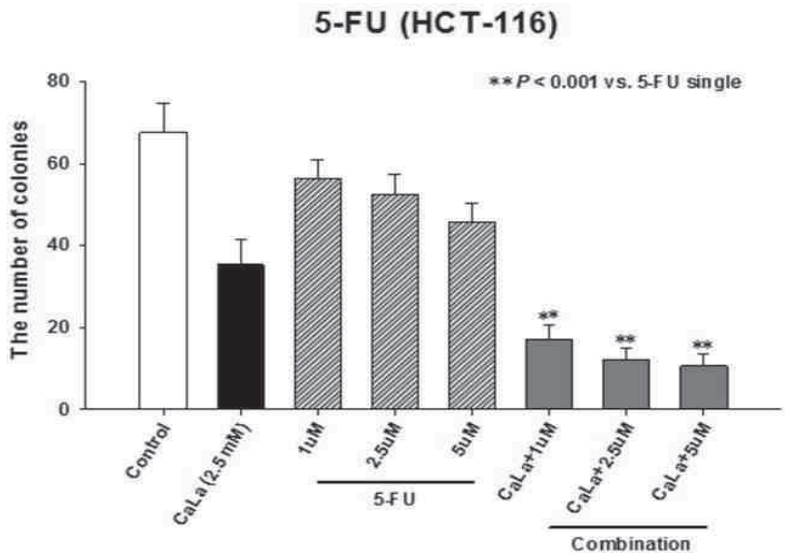


FIG. 41b

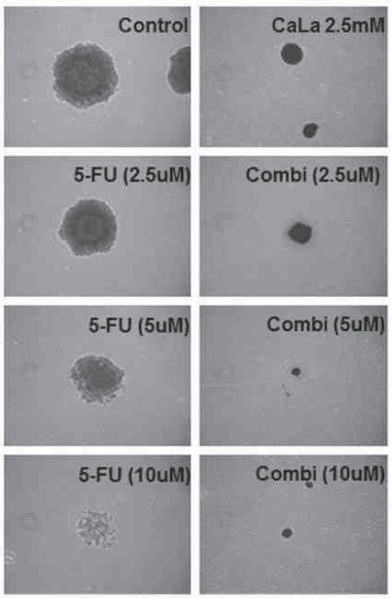



FIG. 42a

• Ovarian cancer, Breast cancer, Lung cancer cancer

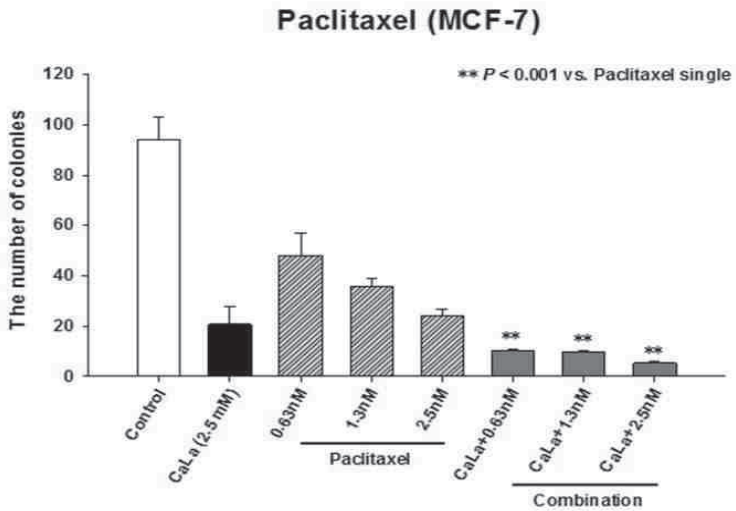


FIG. 42b

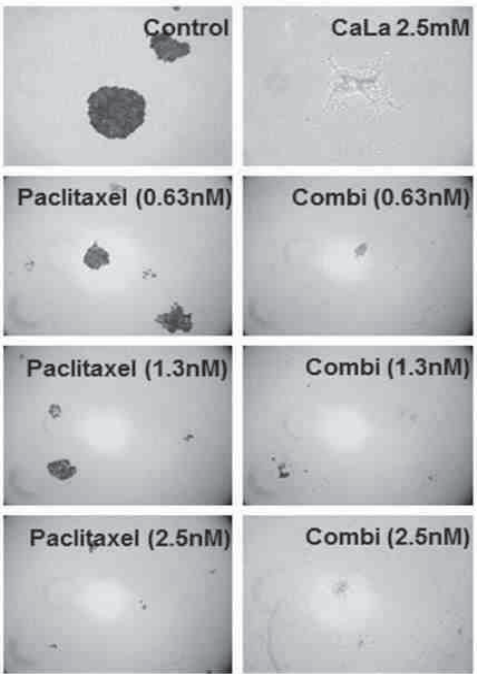



FIG. 43a

• Ovarian cancer, Breast cancer, Lung cancer cancer

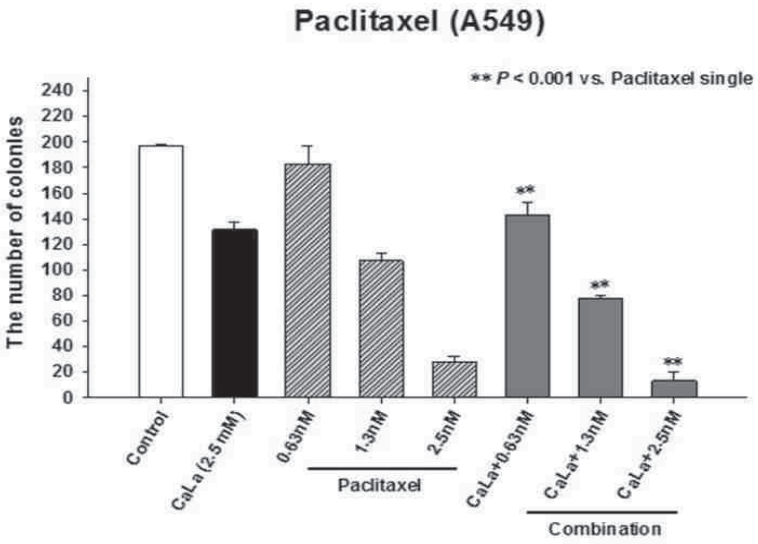


FIG. 43b

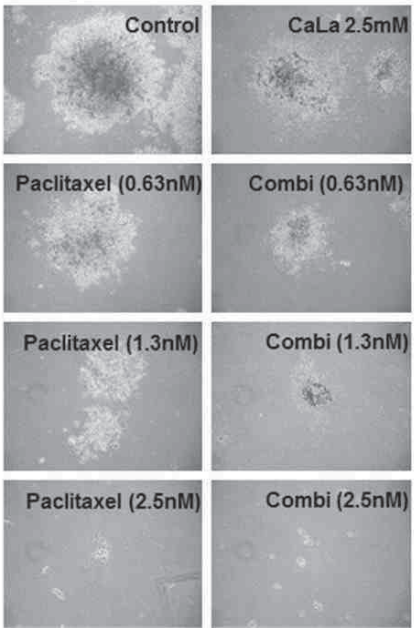



FIG. 44a

• Non-small-cell lung carcinoma

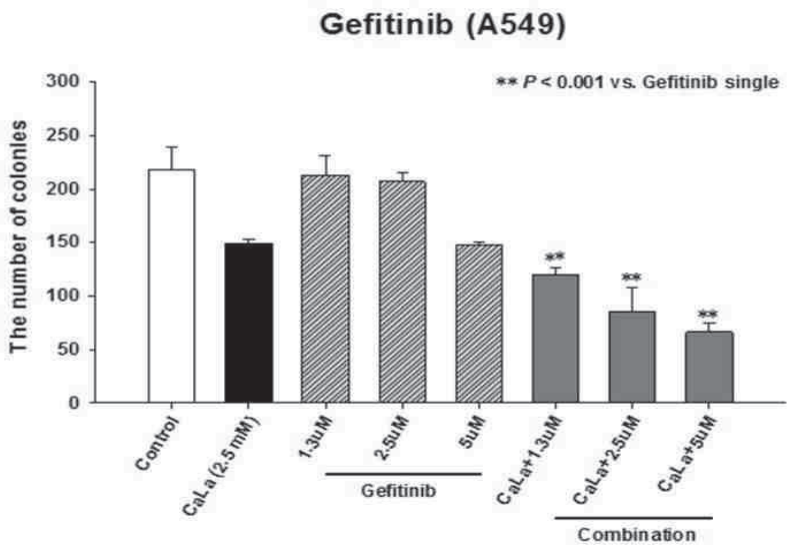


FIG. 44b

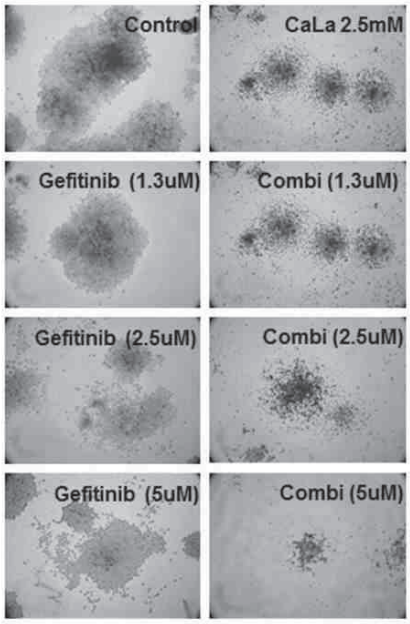



FIG. 45a

• Renal cell carcinoma, Hepatocellular carcinoma, Thyroid cancer.

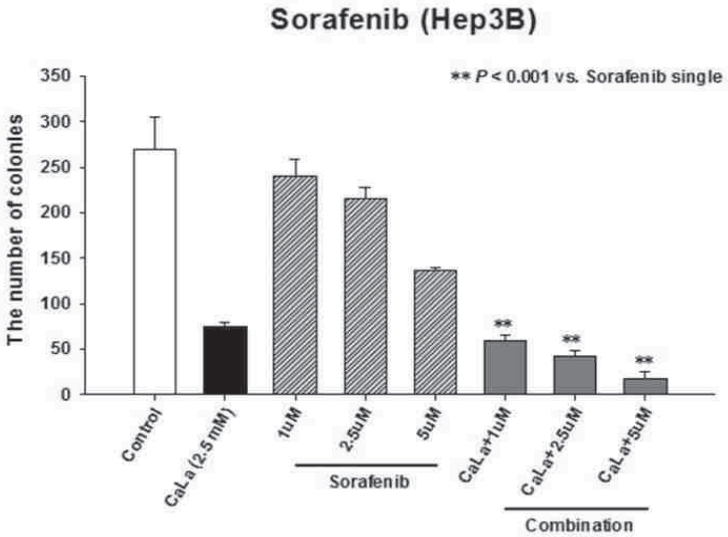


FIG. 45b

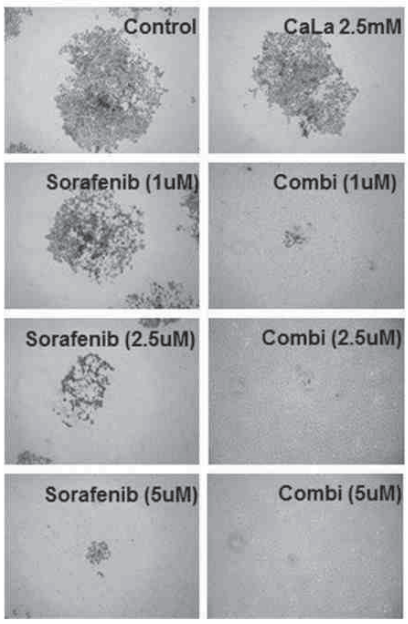



FIG. 46a

• Colorectal cancer

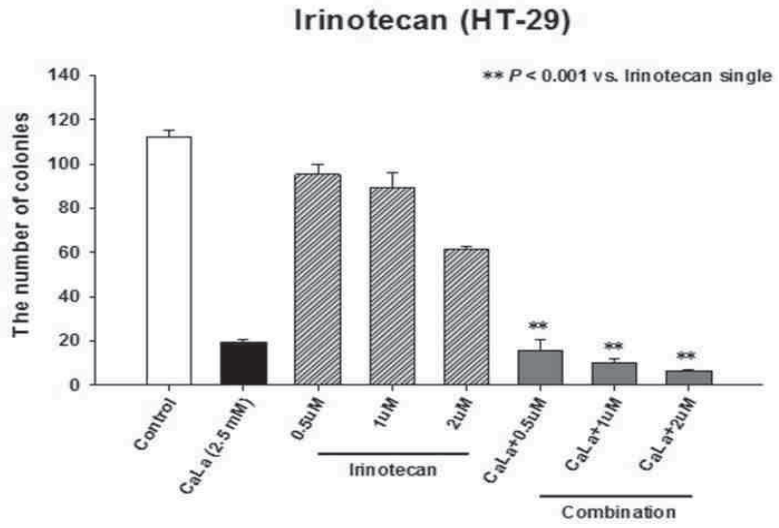


FIG. 46b

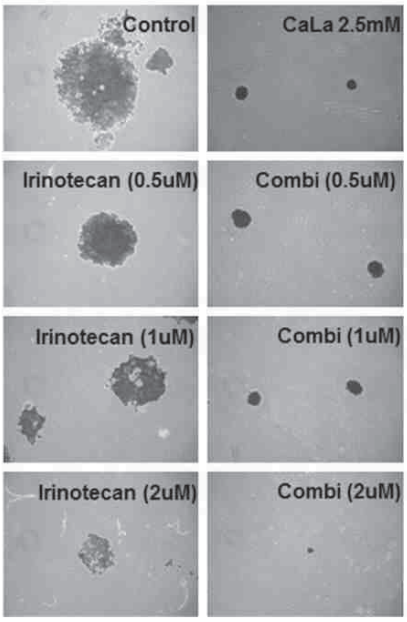



FIG. 47a

• Non-small cell lung cancer

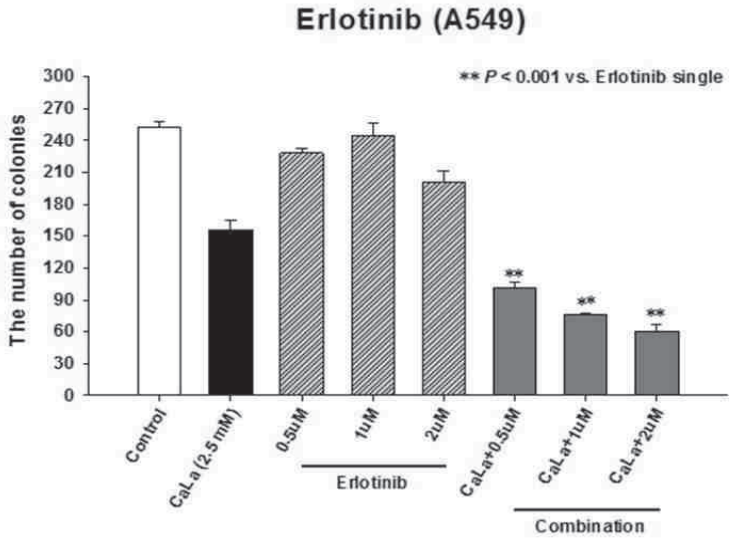


FIG. 47b

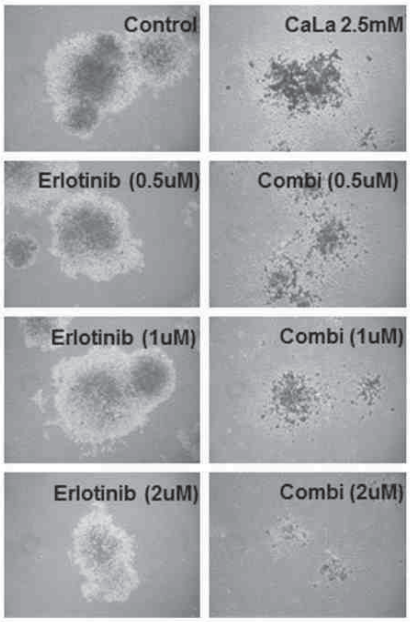



FIG. 48a

• Renal cell carcinoma, gastrointestinal stromal tumor

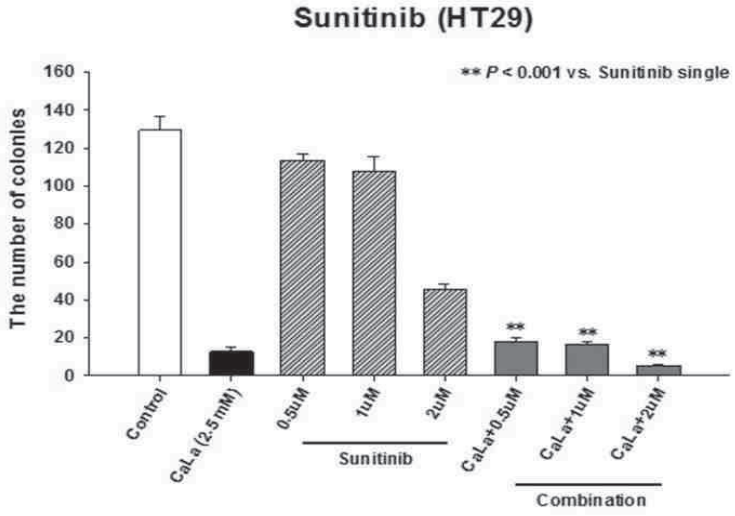


FIG. 48b

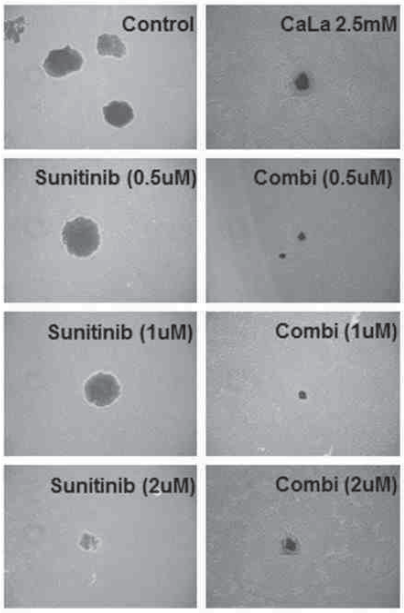



FIG. 49a

• Breast, lung cancer

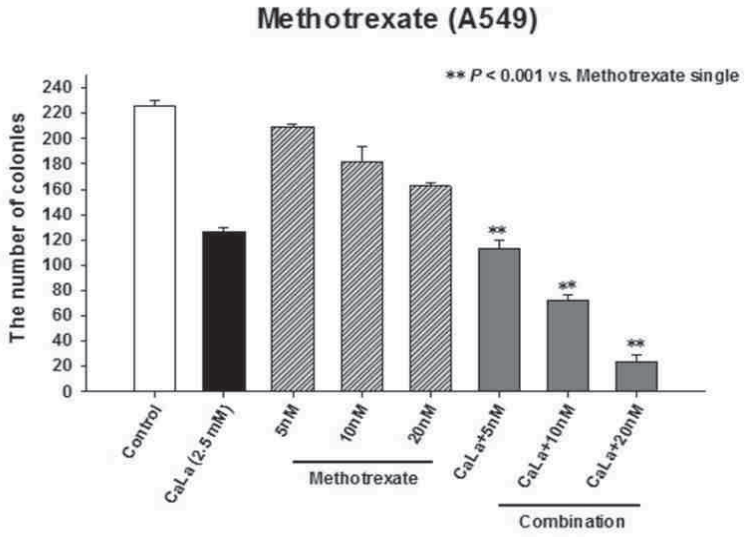


FIG. 49b

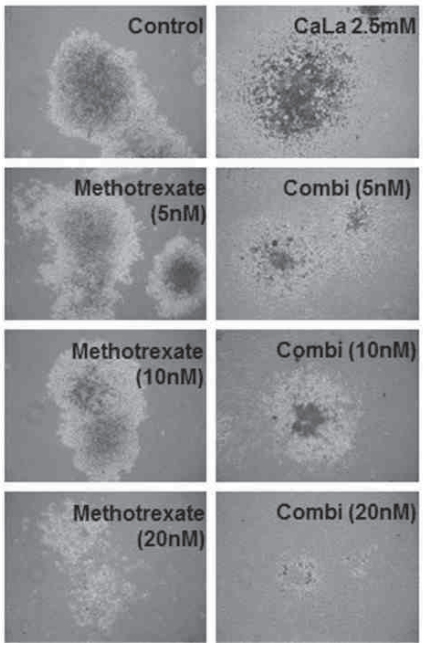



FIG. 50a

• Ovarian carcinoma, lung, head and neck cancers

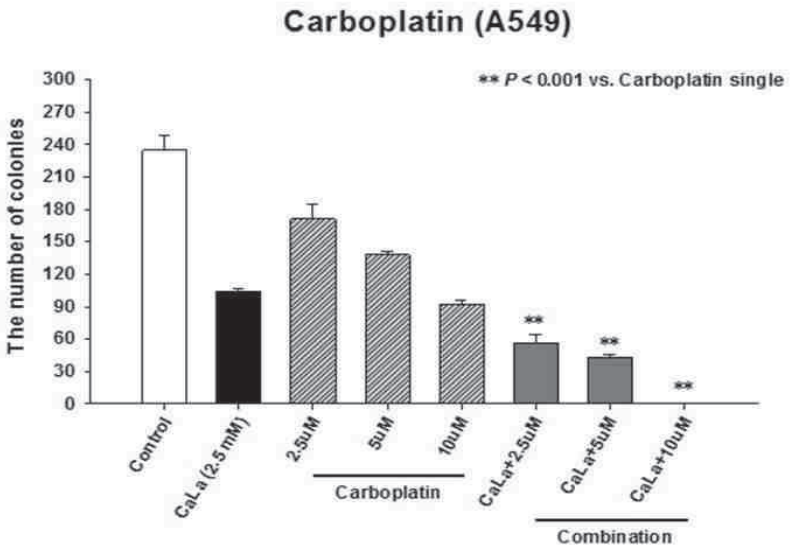


FIG. 50b

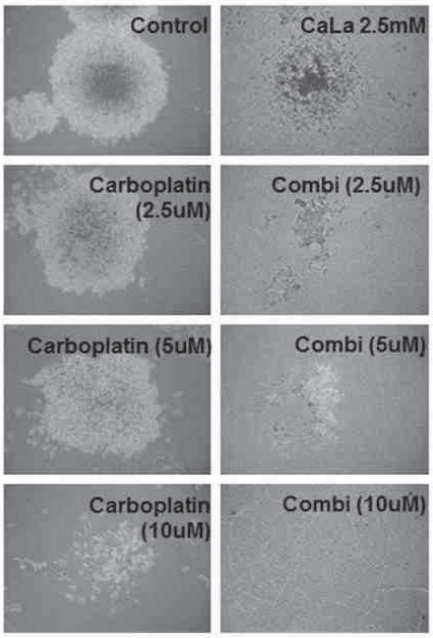



FIG. 51a

• Breast, lung, and ovarian cancer

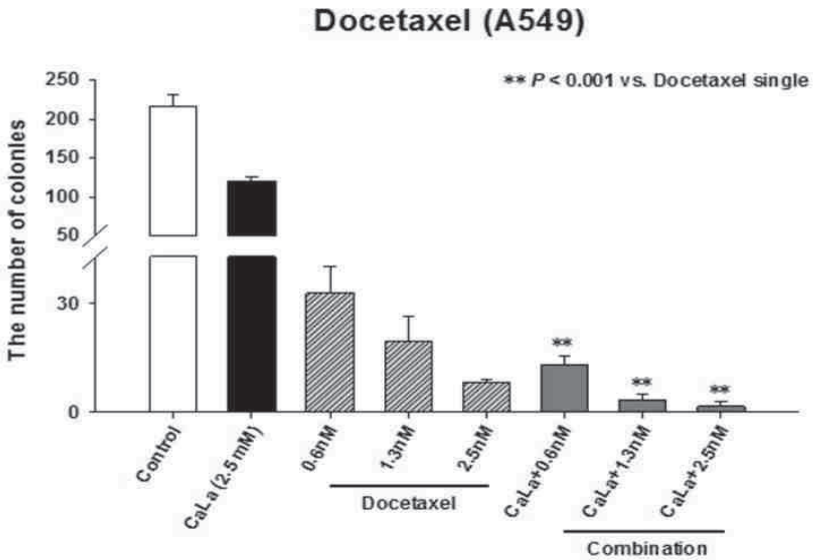


FIG. 51b

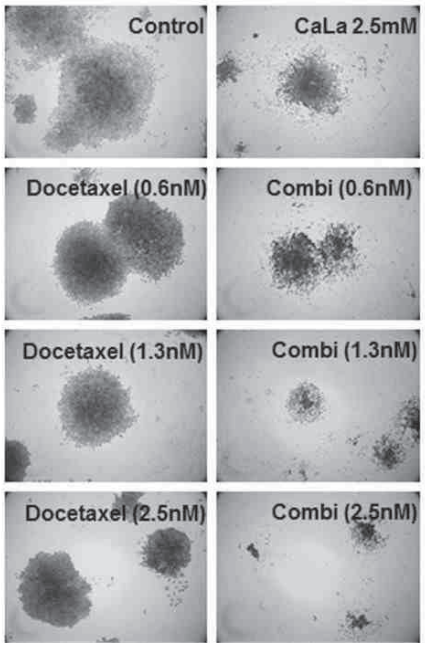



FIG. 52a

• Breast cancer

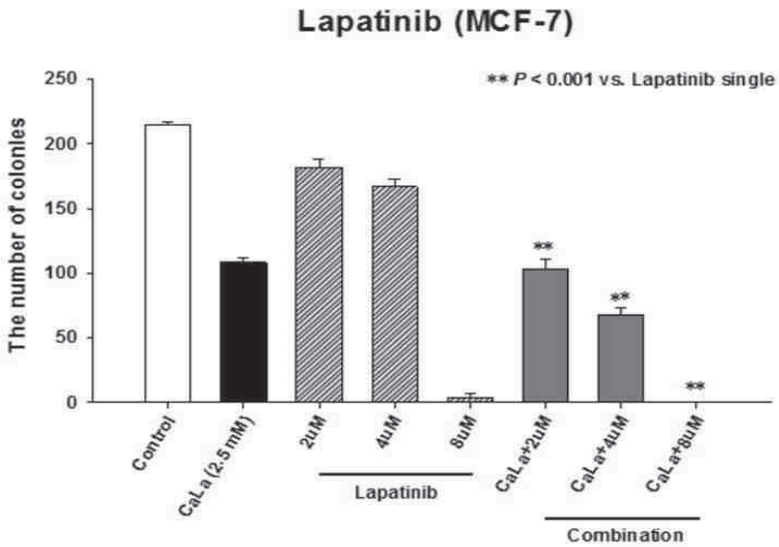


FIG. 52b

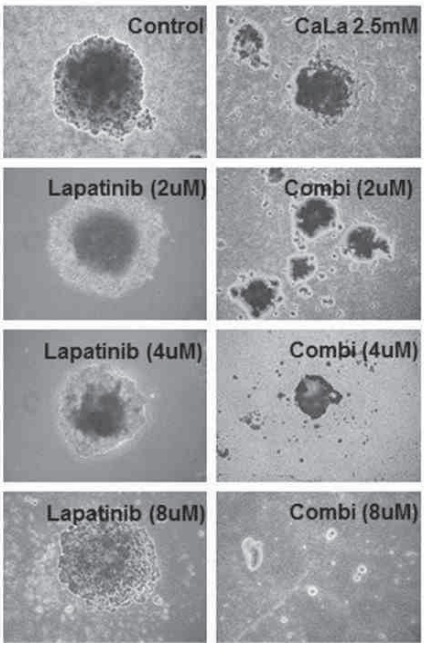



FIG. 53a

• Renal cell cancer

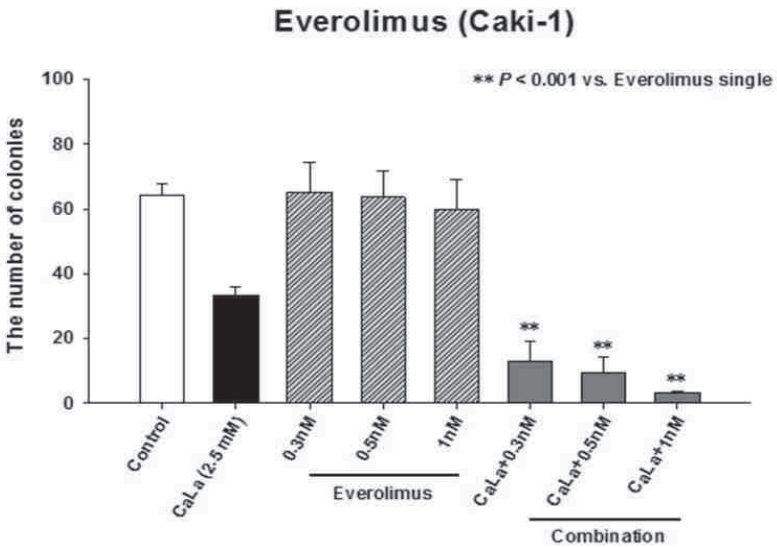


FIG. 53b

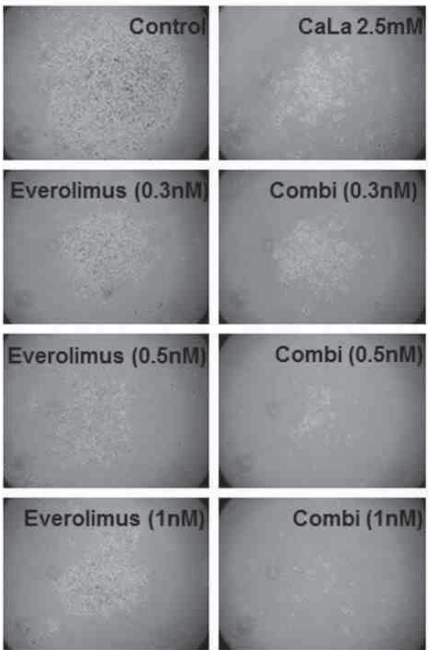



FIG. 54a

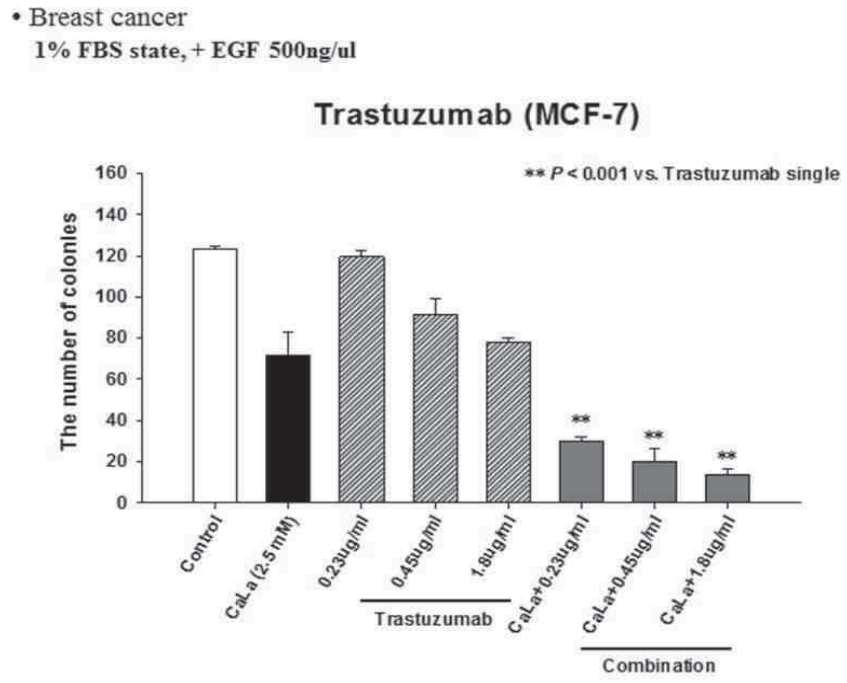


FIG. 54b

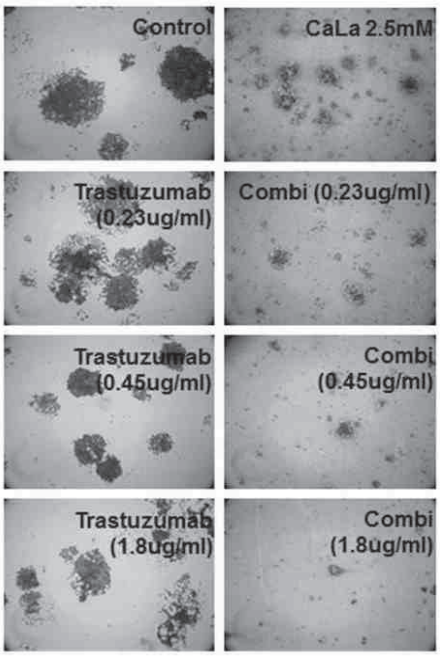



FIG. 55a

• Colorectal cancer

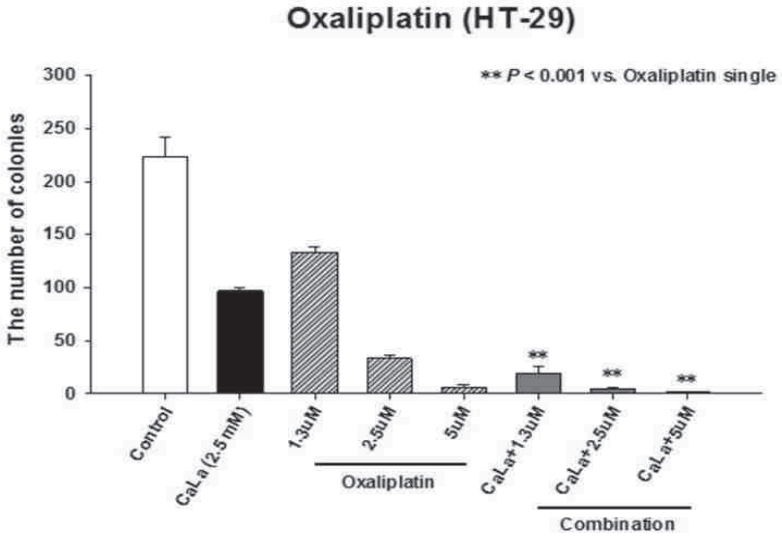
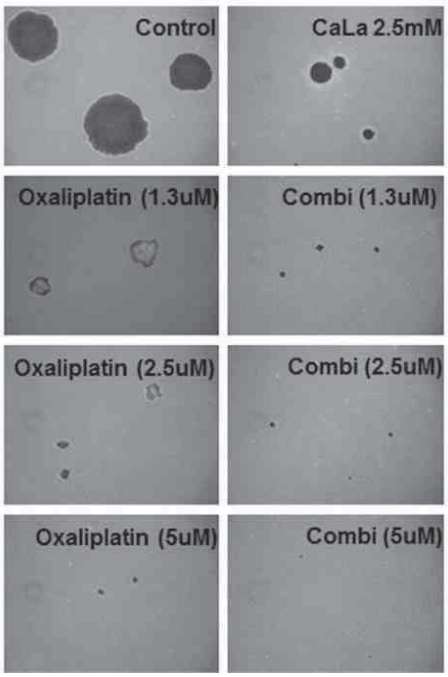


FIG. 55b


Control
CaLa 2.5mM
Oxaliplatin (1.3uM)
Combi (1.3uM)
Oxaliplatin (2.5uM)
Combi (2.5uM)
Oxaliplatin (5uM)
Combi (5uM)