Supplementary material

Supp. Fig. 1. MGE does not cause apoptosis in TNBC cells. Apoptosis was determined by caspase 3/7 activation, quantified by the amount of cells fluorescently stained with green nuclear DNA (Caspase 3/7 Count). 4T1 (**A**), MDA-MB-231 (**B**) and BT-549 (**C**) cells were treated with 5 µg phenolics/mL, 10 µg phenolics/mL, or 20 µg phenolics/mL of MGE in the presence of the IncuCyte® Caspase-3/7 Apoptosis Reagent for 24 h, 48 h, and 48 h, respectively. Staurosporine (Stauro) was used as a positive control for apoptosis and untreated cells without the Caspase-3/7 apoptosis reagent (Casp 3/7) were used as a negative control. n=3; **P* < 0.05, ***P* < 0.01, ****P* < 0.001 and *****P* < 0.0001 compared to the control with Casp 3/7. MGE, muscadine grape extract; TNBC, triple negative breast cancer.

Supp. Fig. 2. Schematic of MGE's effect on TNBC molecular signaling. MGE reduced the receptor tyrosine kinase (RTK) c-Met in TNBC cells. Activation of c-Met stimulates the AKT pathway and MGE reduced p-AKT, which is phosphorylated by PI3 kinase (PI3K) and de-phosphorylated by the lipid phosphatase PTEN. Activation of c-Met also activates the MAPK/ERK pathway, by sequentially stimulating the phosphorylation (P) and activation of Ras, Raf, MEK and ERK. MGE reduced p-Raf, p-MEK and p-ERK. Activation of the AKT and MAPK/ERK pathways increases transcription of *CCND1*, which encodes cyclin D1. MGE reduced both *CCDN1* and cyclin D1. Cyclin D1 associates with cyclin dependent kinase (CDK4/6) to phosphorylate and inactivate the retinoblastoma protein (Rb) and prevent its association with E2F, which inhibits the

transcription of E2F target genes. MGE reduced phosphorylation of Rb to abrogate its association with E2F. The MGE-mediated reduction in the AKT and MAPK/ERK oncogenic pathways was associated with a decrease in proliferation. The purple arrows indicate MGE inhibitory effects identified in TNBC cells and the reduction in cyclin D1, Ki67 and tumor burden in triple negative breast tumors *in vivo*. MGE, muscadine grape extract; TNBC, triple negative breast cancer; AKT, protein kinase B; PI3K, Phosphoinositide 3-kinase; PTEN, phosphatase and tensin homolog; ERK, extracellular-regulated kinase; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; CDK, cyclin dependent kinase; Rb, retinoblastoma protein.

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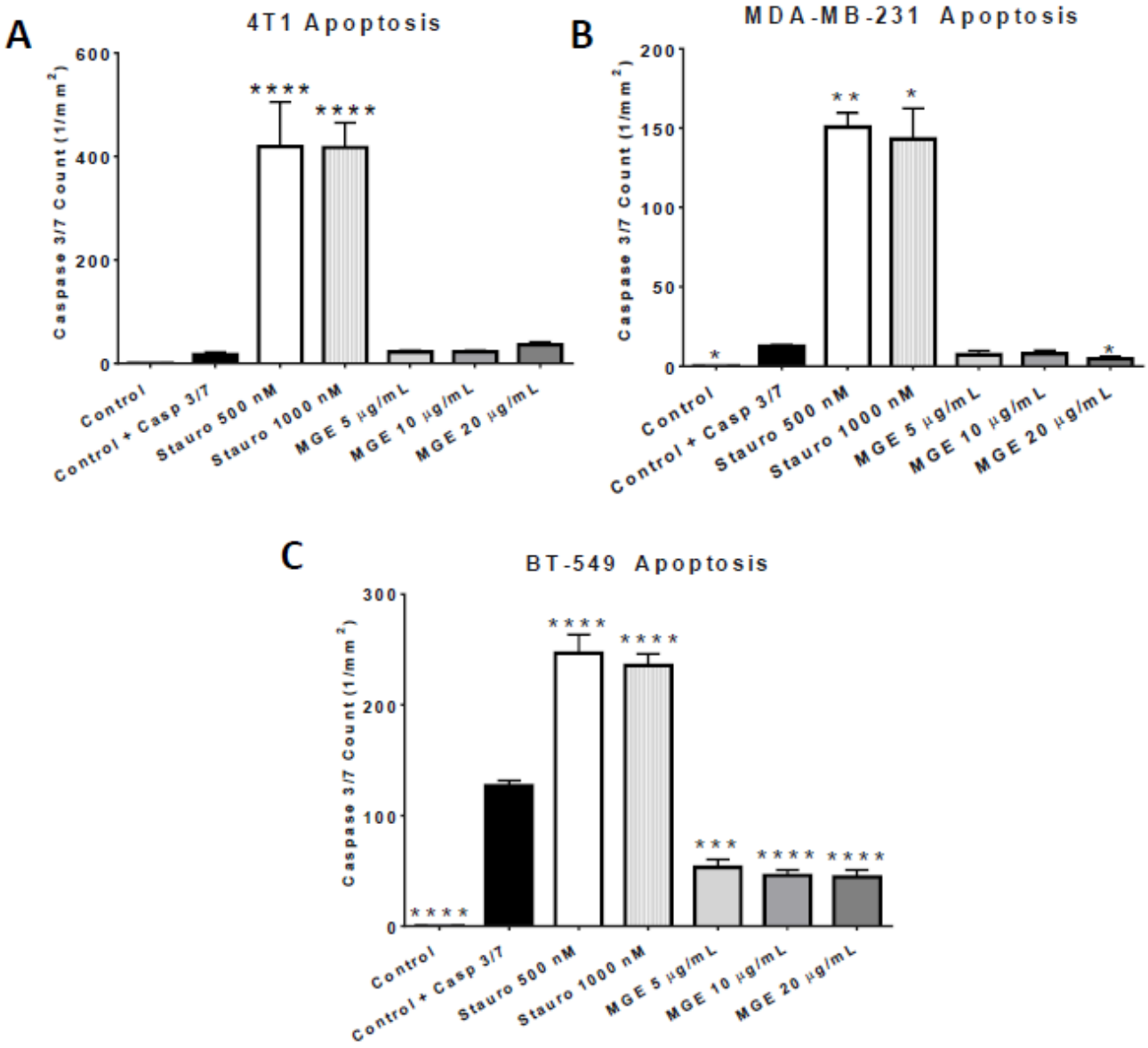

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