

Role of SIRT1 in maintaining mitochondrial health through mitochondrial biogenesis and mitophagy in oral cancer

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Abstract

Mitochondria, the ATP generators, are involved in a wide variety of cellular functions like metabolism, redox signaling, calcium homeostasis, and regulated death pathways. These are the major players in maintaining oxidative stress, generating succinate and fumarate metabolites, and regulating mitochondrial outer membrane permeability. Studies have found these to be the drivers of mitochondria-associated occurrence and progression of cancer in an environment of compromised mitochondrial health. In this connection, SIRT1, a NAD-dependent histone deacetylase, is known to regulate mitochondrial biogenesis. Along with this, SIRT1 is also involved in regulating cell cycle, metabolism, genetic modifications, stress response, and aging. In this study, we have identified butein as a natural small molecule activator of SIRT1. Butein, a potent phytochemical found in the plant *Butea monosperma*, has recently gained the attention of researchers because of its anti-oxidant, anti-neoplastic, anti-angiogenic, and apoptosis-inducing properties. Butein has been found to down-regulate various oncogenes like NF- κ B, EGFR, JNK, Ras, Bcl2, c-Myc regulating proliferation, invasion, and chemoresistance in a variety of cancer models. All these hallmarks link cancer with mitochondria because of their multifunctional role in cellular homeostasis. Thus, maintaining a healthy mitochondrial population is the need of the hour to put a break on the oncogenic outcomes. In this connection, mitochondrial biogenesis is a driving tool for maintaining mitochondrial health to curtail cancerous outcomes. In our study, we have investigated the mitochondrial biogenesis and mitochondrial integrity maintenance potential of butein in Cal33 and FaDu cells. We found that butein regulates the SIRT1-PGC1 α signaling axis for mitochondrial biogenesis. Along with this, butein was also found to induce mitophagy during a decrease in MMP. We have also investigated the anti-oxidant role of butein in arecoline-induced ROS to mitigate oxidative stress in oral cancer cell lines.

Keywords: Mitophagy, Mitochondrial biogenesis, SIRT1, Butein

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OUTLINES

□ Introduction

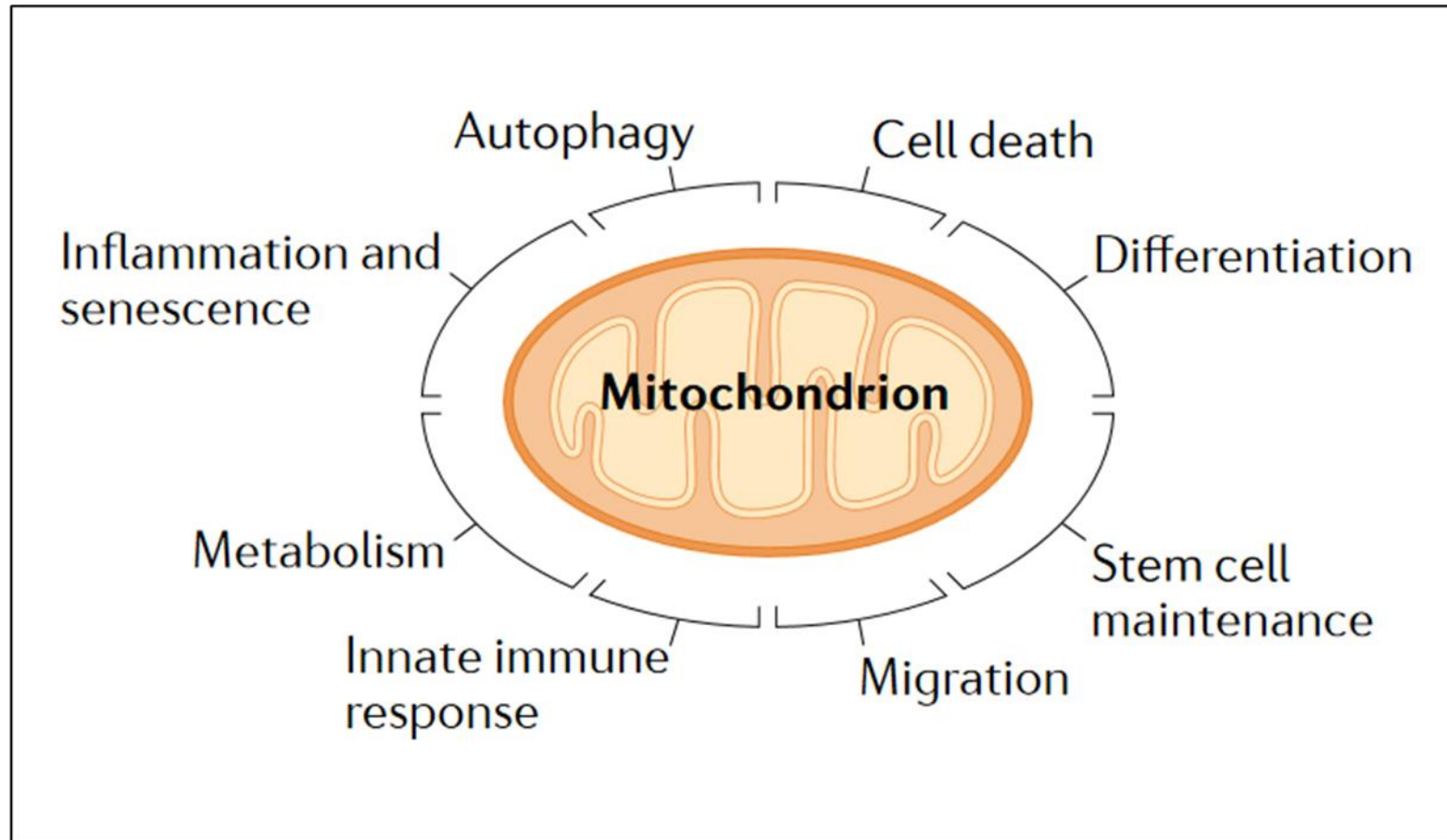
- **Mitochondria in general**
- **Mitochondrial dysfunction**
- **Maintenance of mitochondrial health**

□ Results

□ Summary

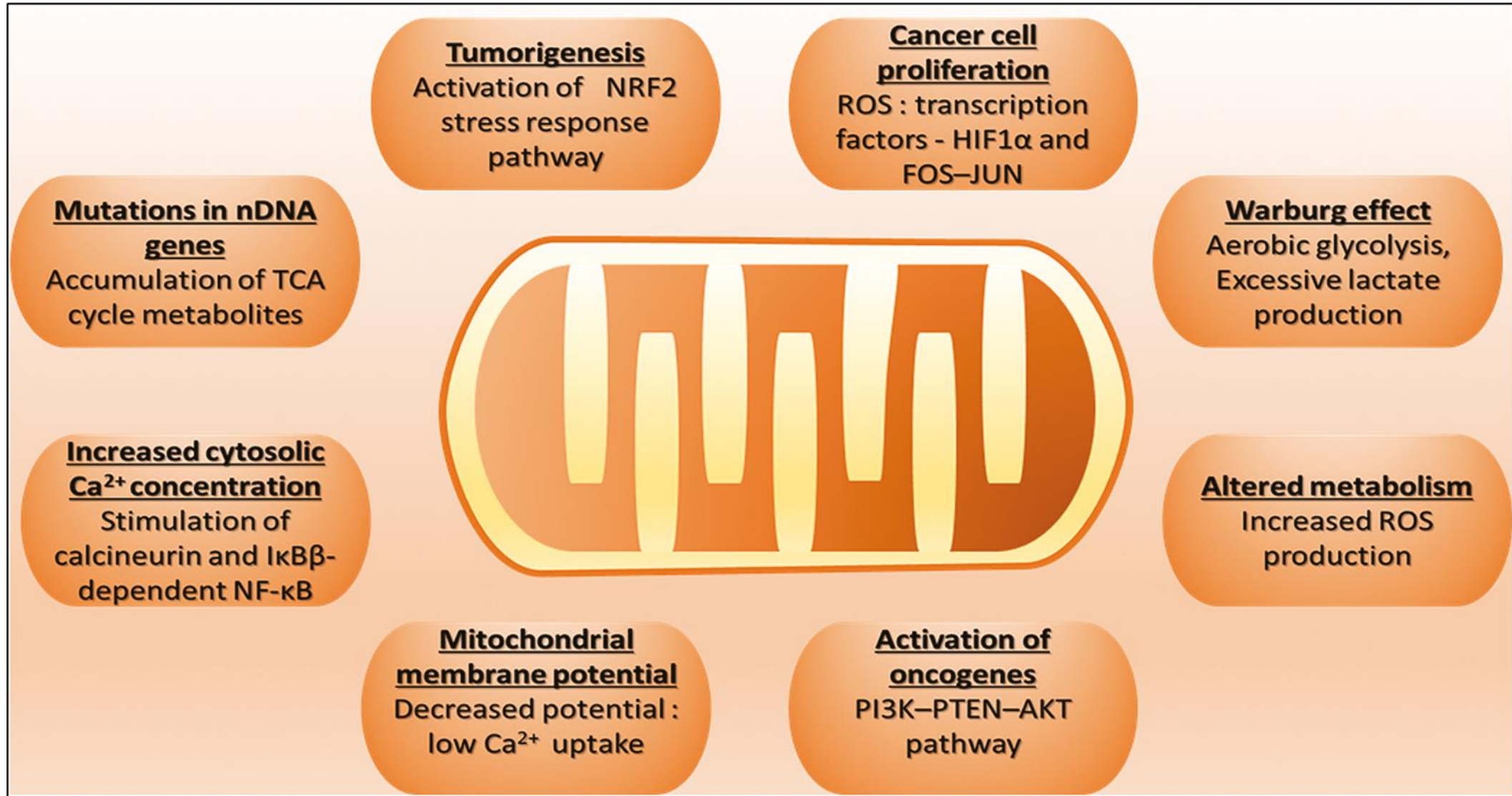
Mitochondria

- Mitochondria are the double membraned cellular organelles with their own genetic material.
- These are known as the power house of the cell.



Giacomello, et al., Nat Rev Mol Cell Biol, 2020

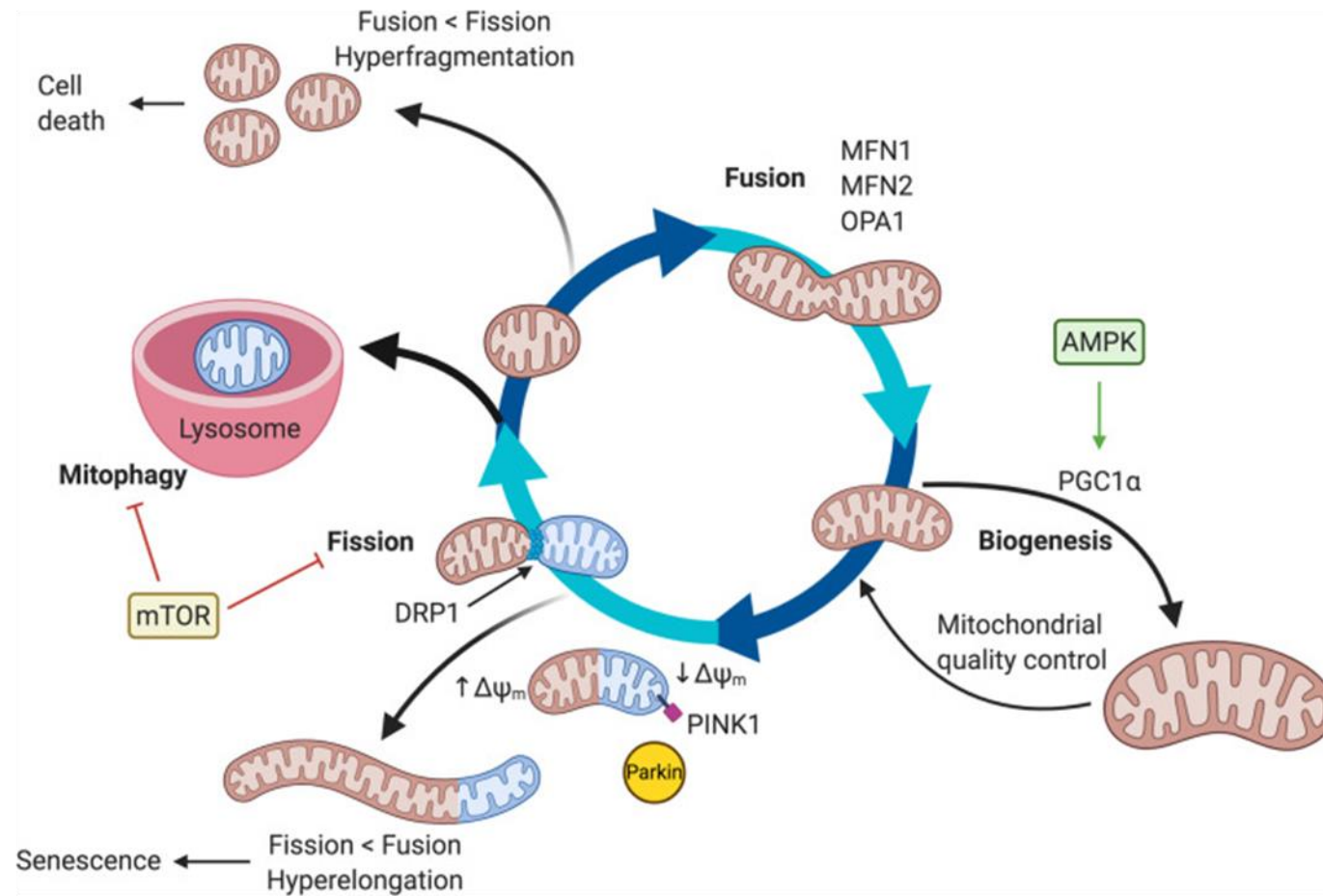
Mitochondrial dysfunction and Cancer



Badrinath, et al., Carcinogenesis. 2018

Maintenance of mitochondrial health

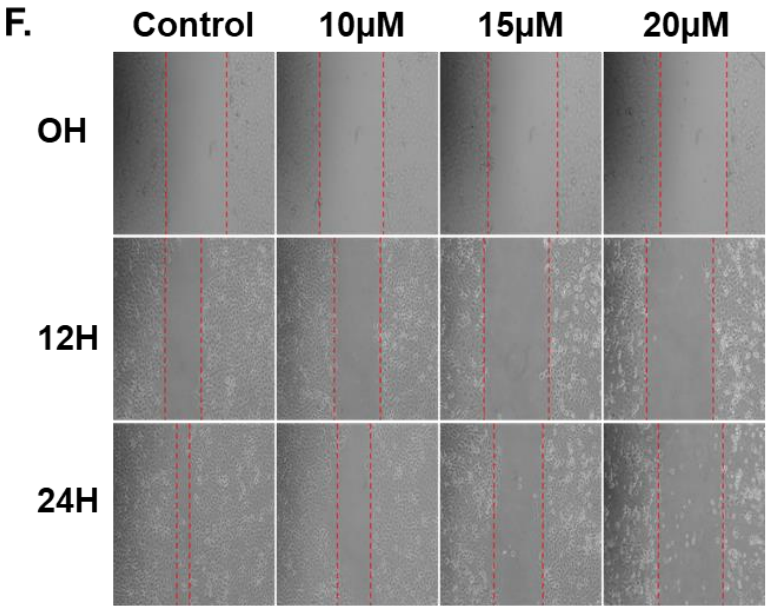
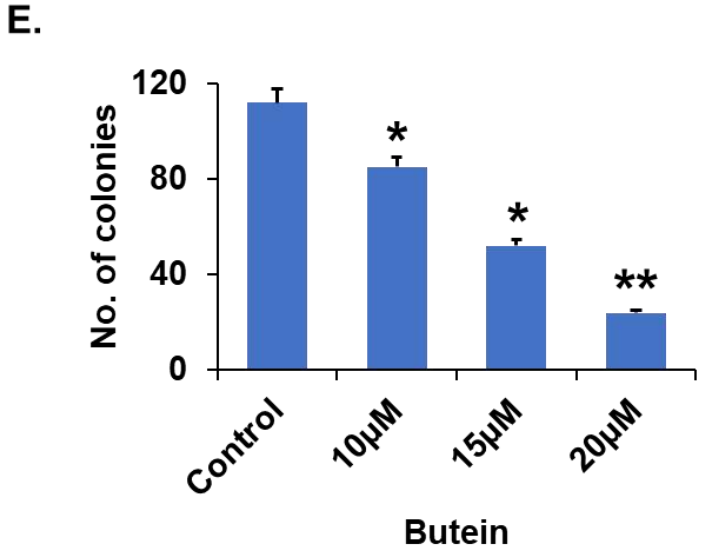
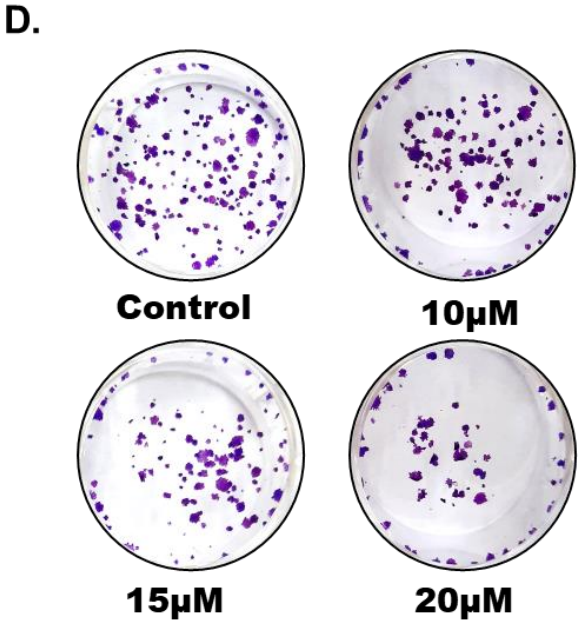
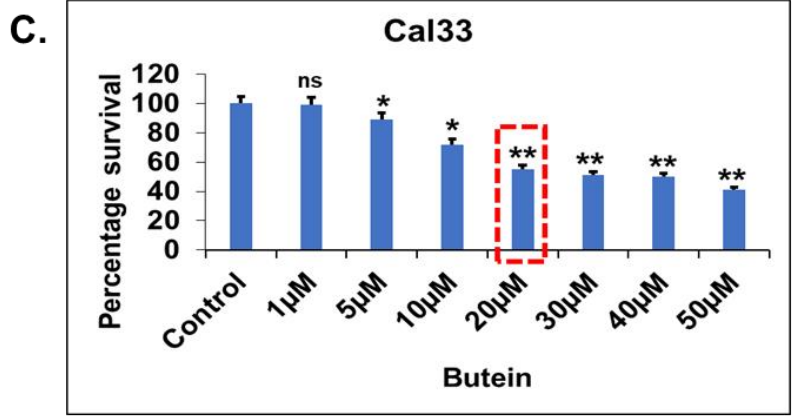
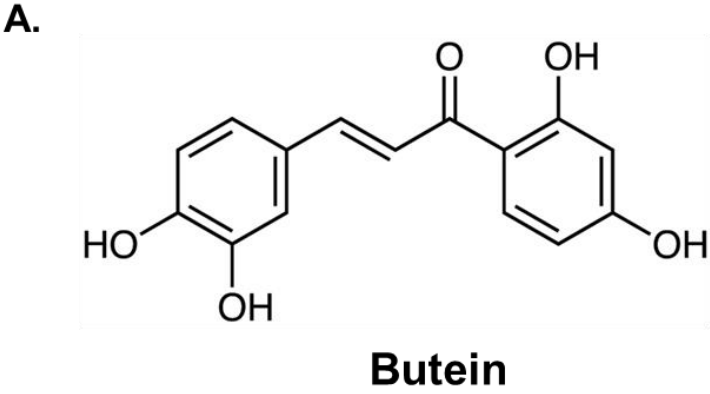
- Mitochondrial dynamics (fusion and fission cycle) and mitochondrial biogenesis are the two key factors that regulate mitochondrial health.



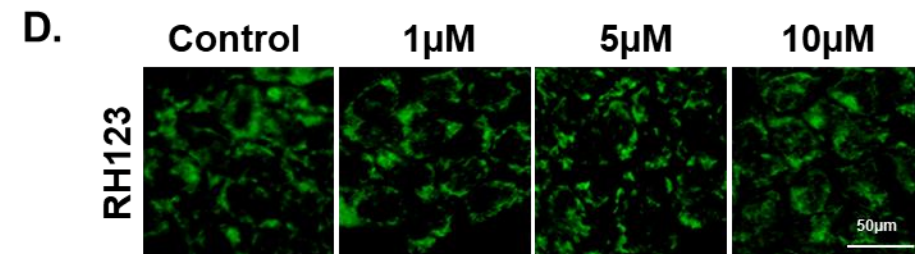
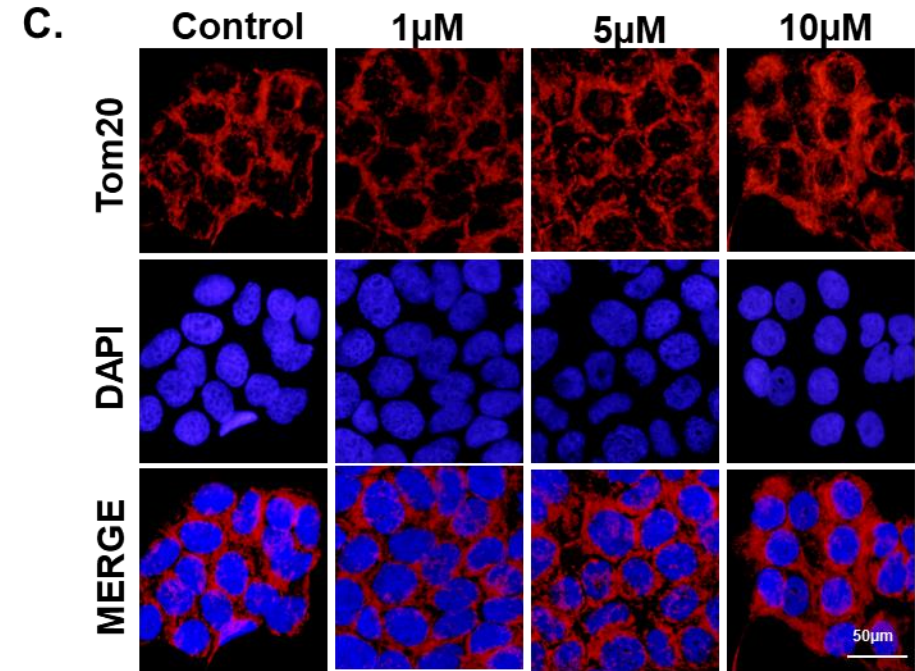
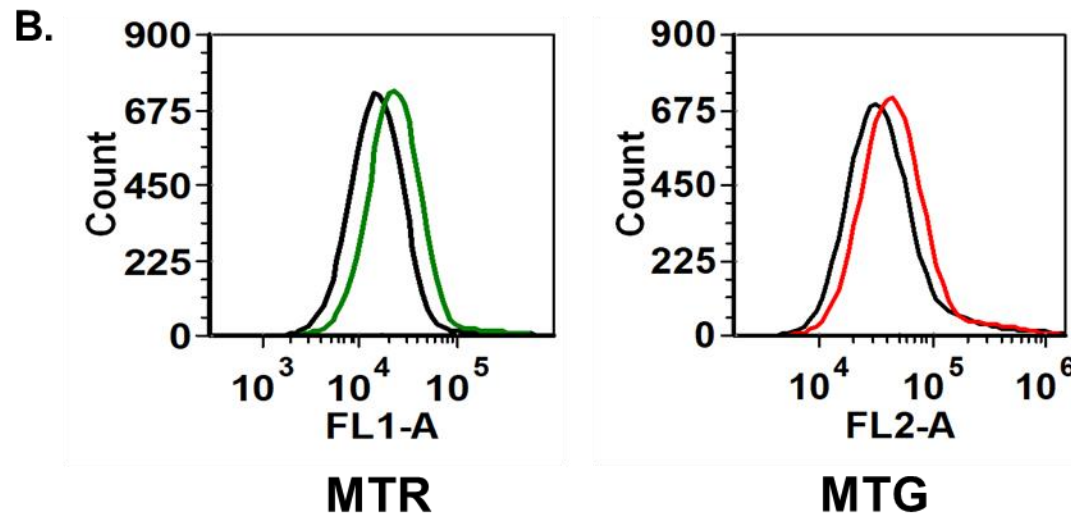
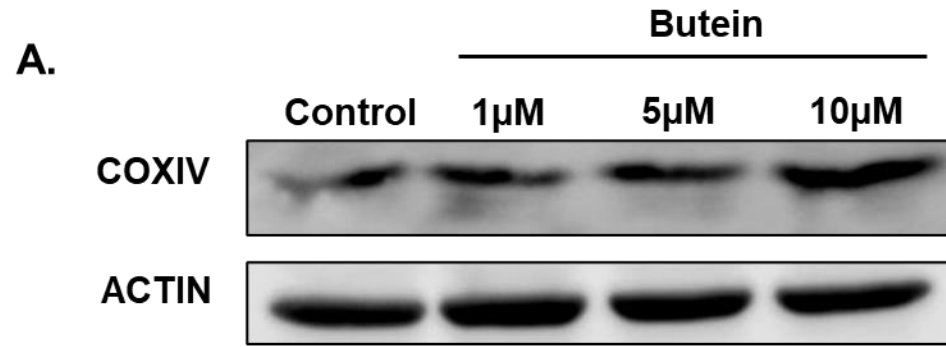
Garbern, et al., Stem Cell Res Ther., 2021

Results

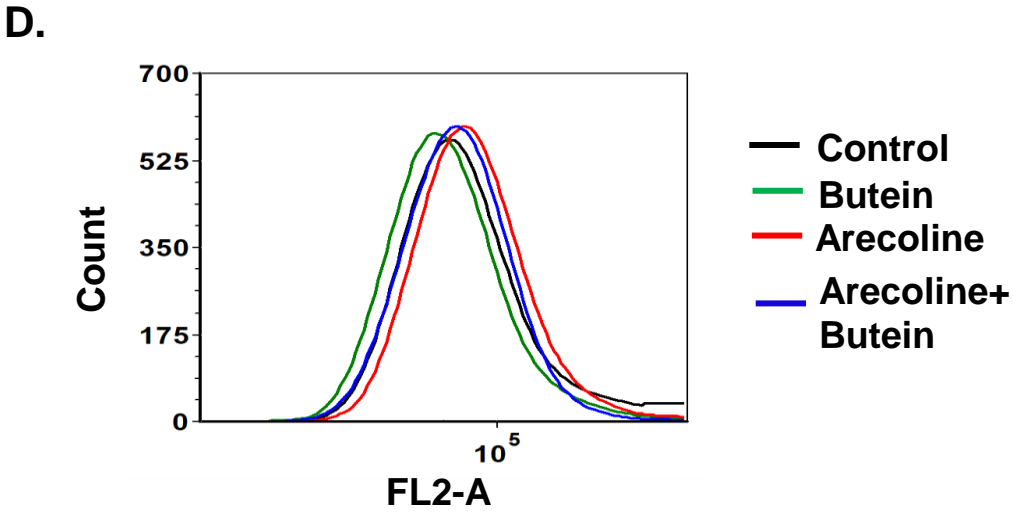
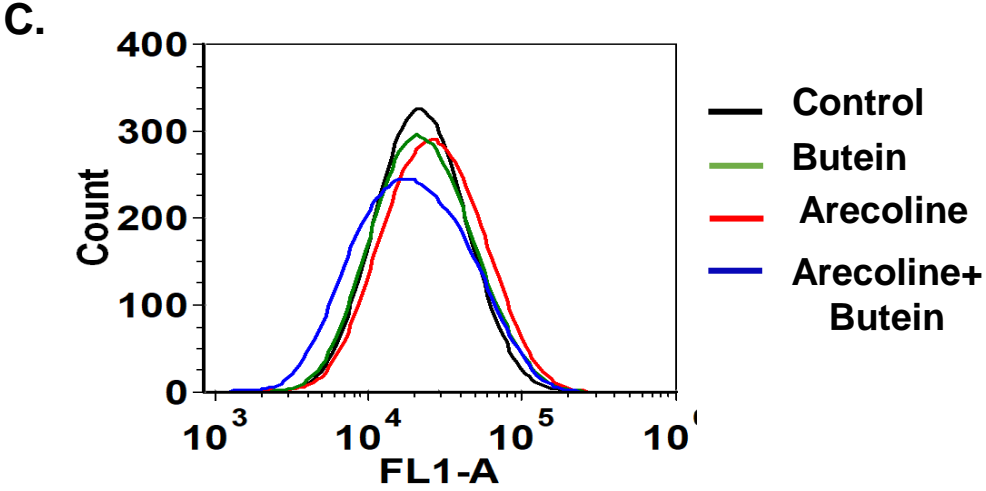
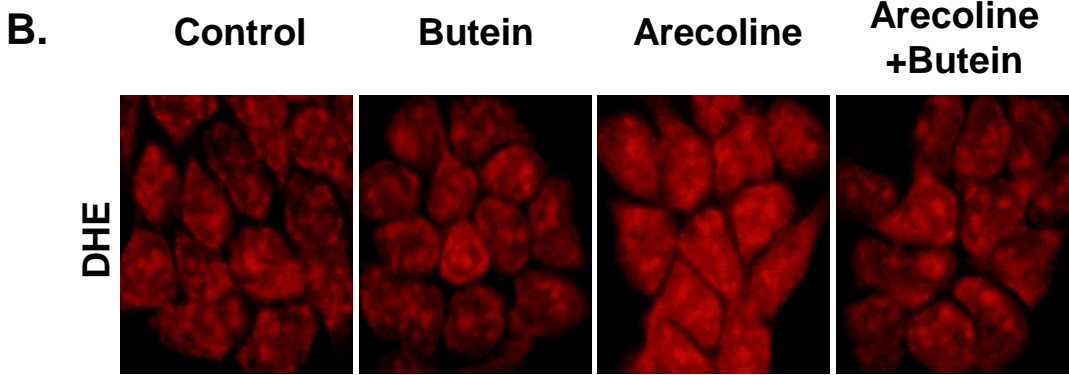
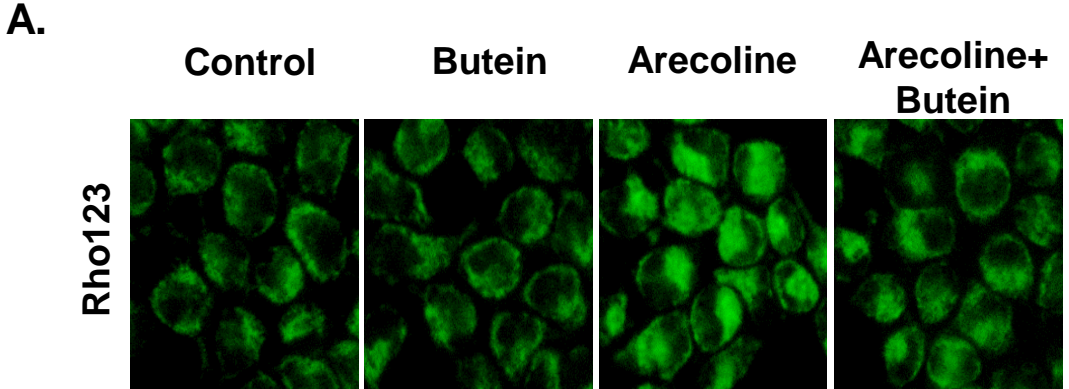
Butein exhibits anti-proliferative activity against oral cancer cells



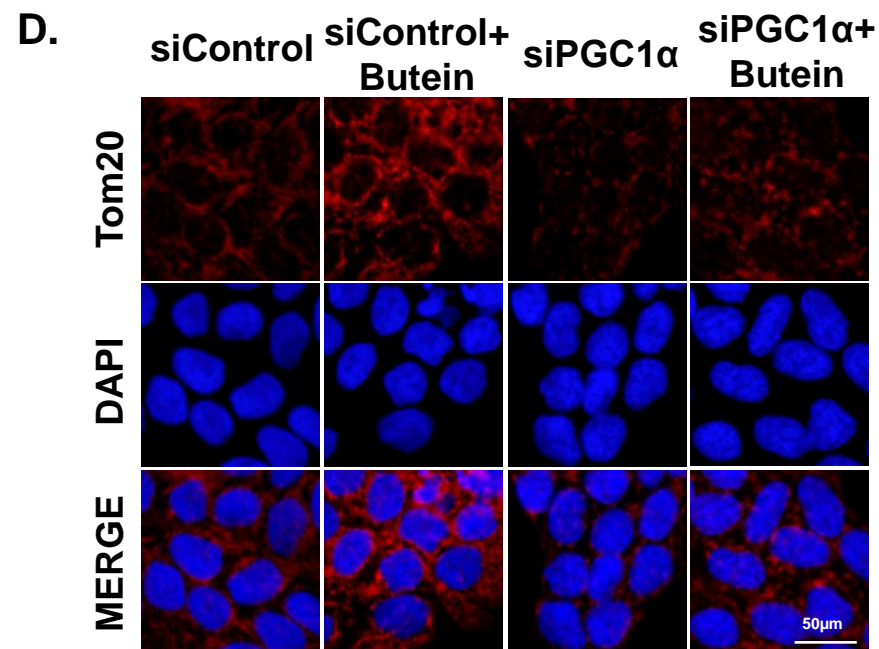
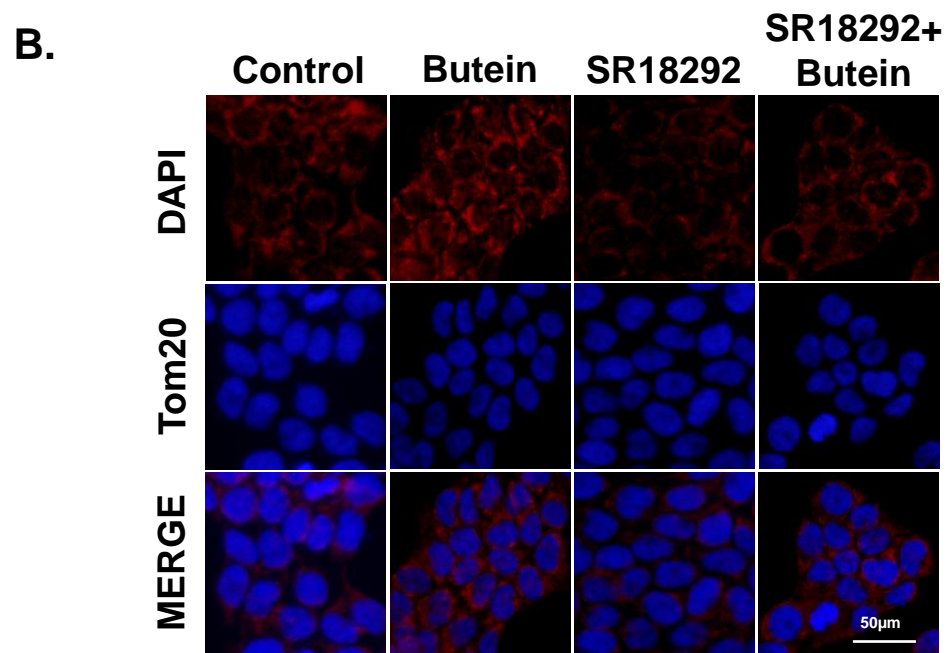
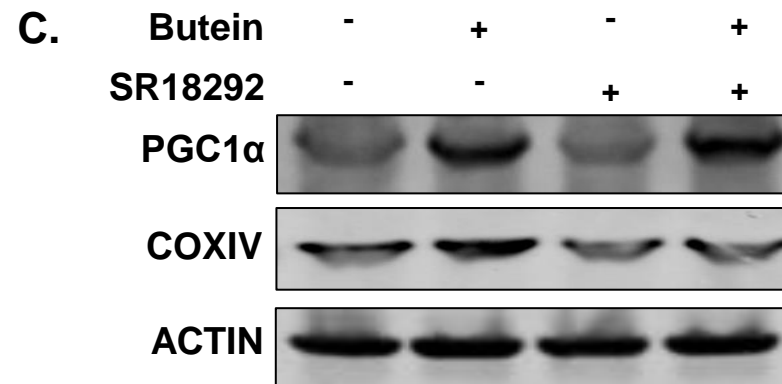
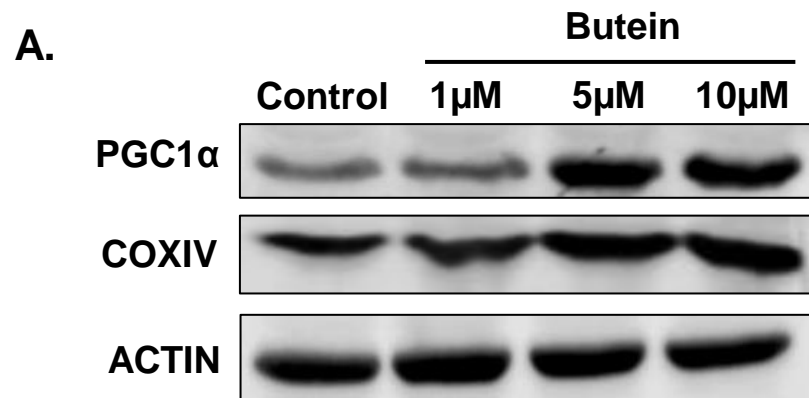
Butein promotes mitochondrial biogenesis



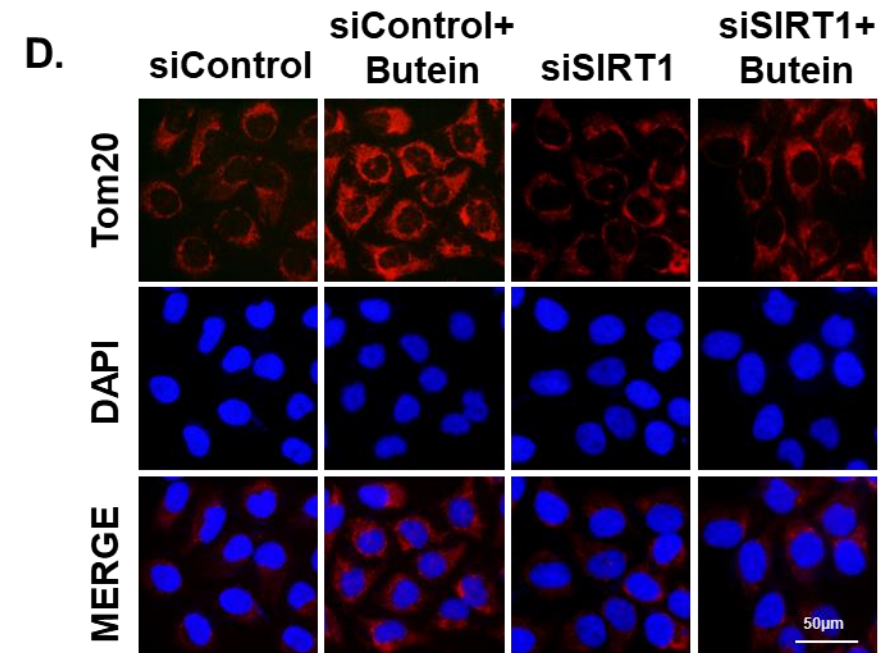
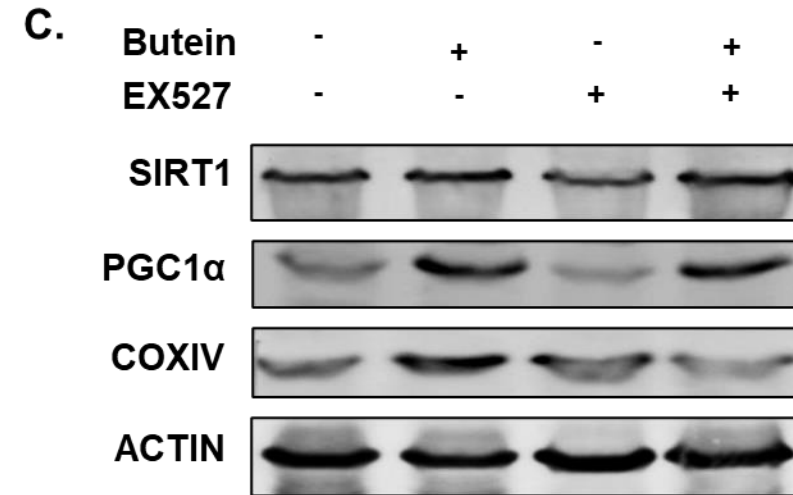
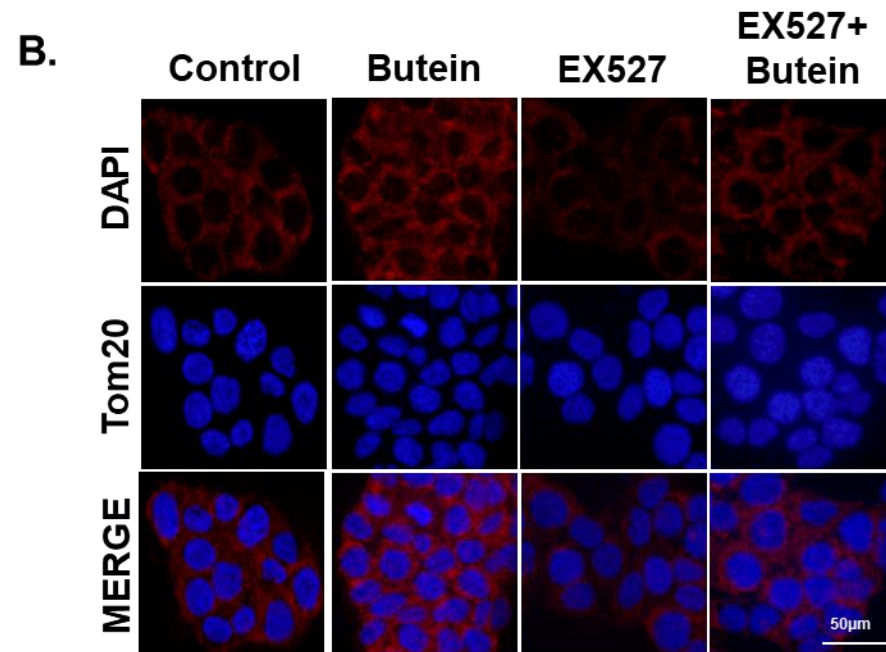
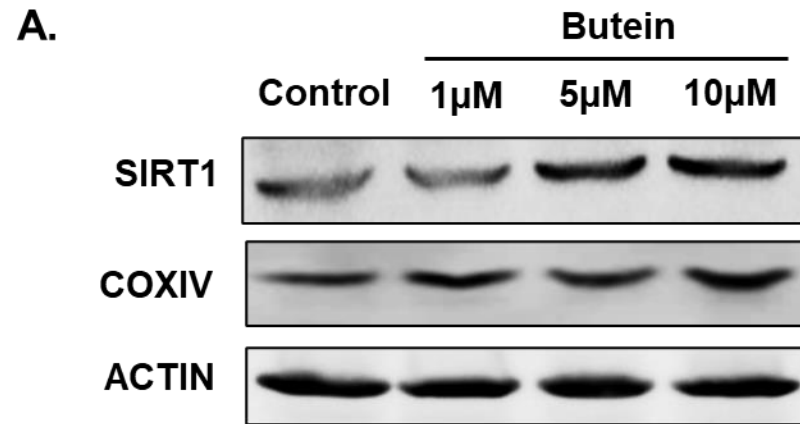
Butein maintains mitochondrial membrane potential and plays an anti-oxidant role



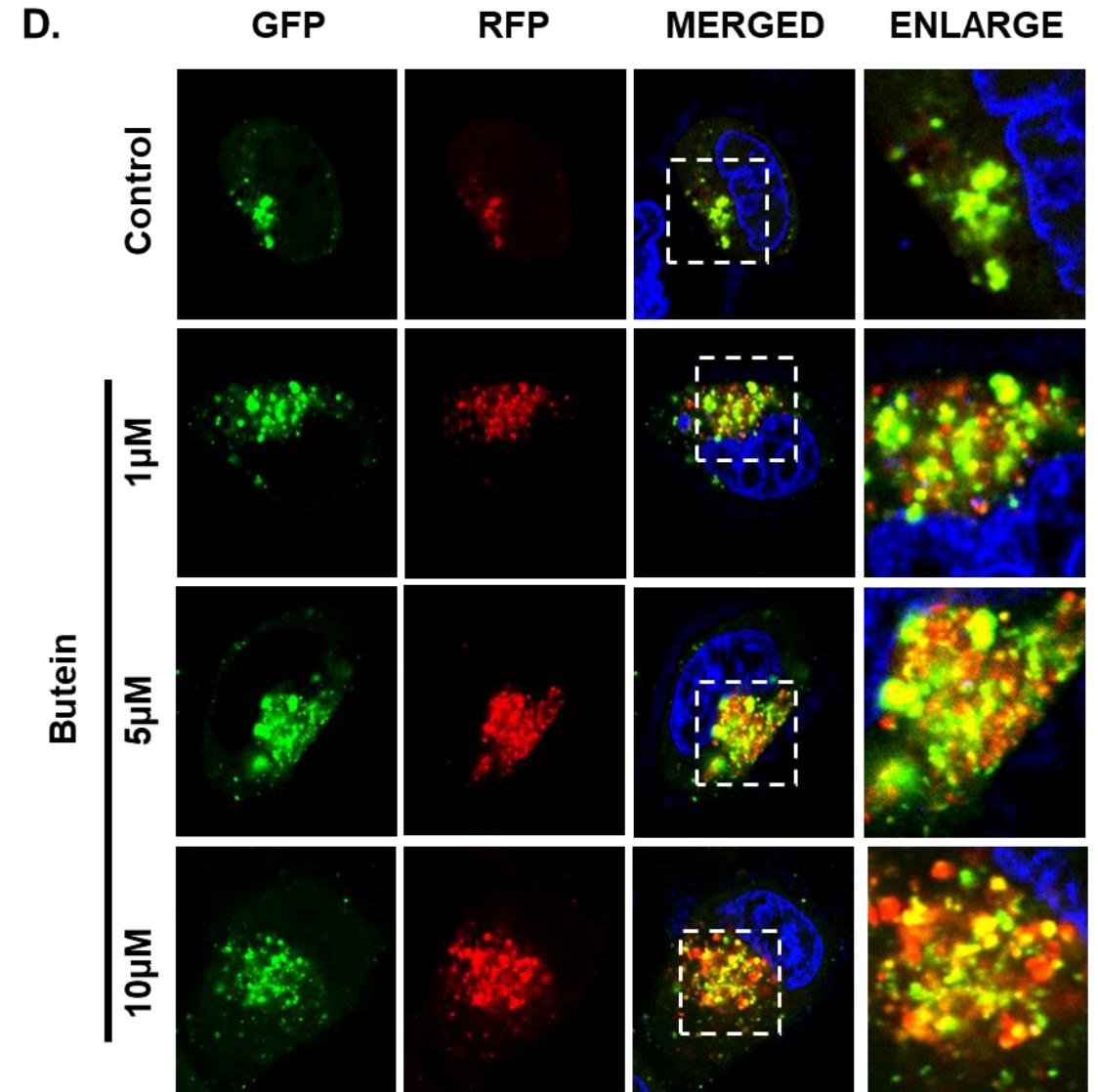
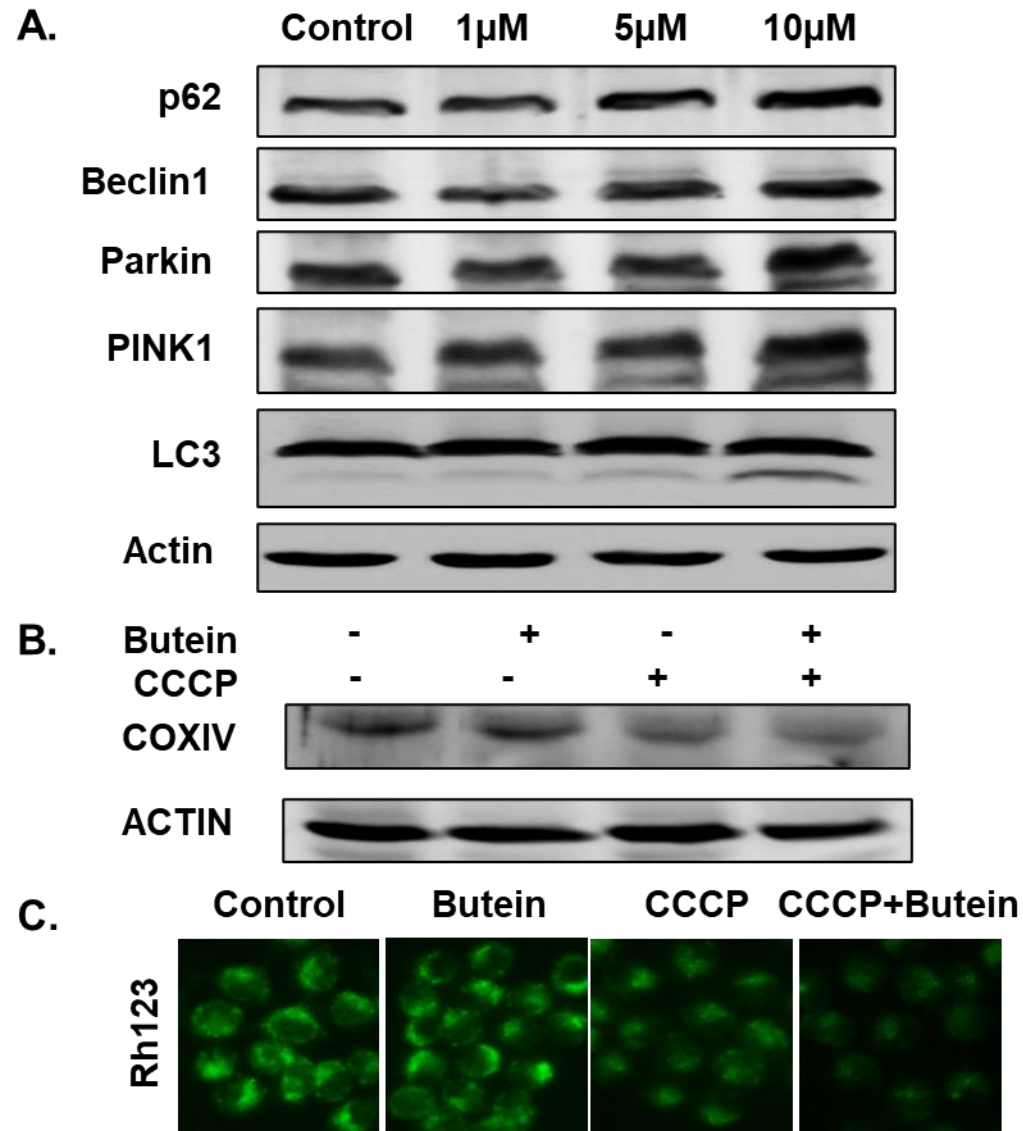
Butein activates PGC1 α for generation of new mitochondria



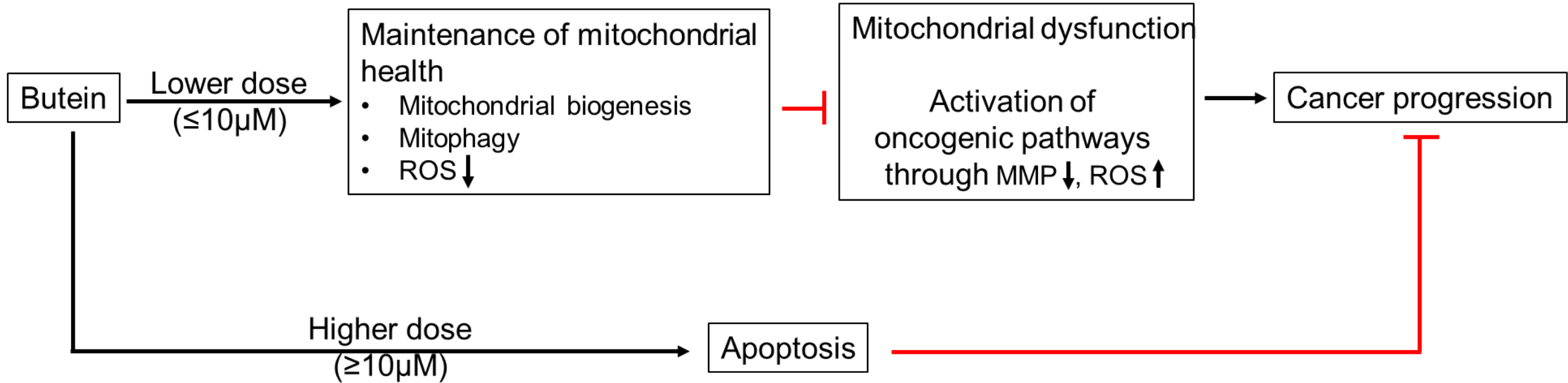
Butein regulates SIRT1-PGC1 α axis for generation of new mitochondria



Butein initiates mitophagy for maintenance of mitochondrial health



SUMMARY



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THANK YOU