**Repurposing Cyclovirobuxine D as a Novel Inhibitor of Colorectal Cancer Progression via Modulating the CCT3/YAP Axis**

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**Background and aims.** Colorectal cancer (CRC) ranks second in mortality worldwide and requires effective and affordable remedies. Cyclovirobuxine D (CVB-D) is the main effective component of Huangyangning tablet, an approved traditional patent medicine, which is mainly used for cardiovascular treatment. As a multibioactive natural compound, CVB-D possesses underlying anticancer activities.

**Methods.** Cell viability and clone-forming ability were determined in human CRC lines. Western blot, immunofluorescence assay, transmission electron microscopy and senescence-associated β-galactosidase (SA-β-Gal) staining were utilized to investigate cell autophagy and senescence. The molecular mechanisms were explored by virtual prediction and experimental validation. Patient-derived xenograft (PDX), dextran sulfate sodium salt (DSS), and azomethane (AOM)/DSS mouse models were employed for in vivo studies.

**Results.** CVB-D inhibited the growth and development of advanced CRC cells/mice by inducing autophagic and senescent activities through the chaperonin containing TCP1 subunit 3 (CCT3)/yes-associated protein (YAP) axis. CVB-D acted as a promising inhibitor of CCT3 by interacting with its ATP site. In PDX tumours, CVB-D showed potential therapeutic effects by targeting CCT3. Treatment with CVB-D alleviated the mouse model of colitis induced by DSS and attenuated AOM/DSS-induced formation of adenomatous polyps by its action on CCT3.

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**Figure 1.** CVB-D impedes CRC progress by regulation of autophagy and senescence machinery via targeting CCT3. In terms of preventive effect, CVB-D alleviates DSS-induced murine colitis and attenuates AOM/DSS-induced adenomatous polyps formation.

**Conclusion/Discussion.** Our study has provided a scientific basis for the suggestion that CVB-D may be recognized as a prospective drug candidate for the therapy of CRC in patients.

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