UNIVERSITY of MARYLAND
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Synergy Between Andrographolide and Melatonin for Metastatic Colon Cancer Treatment

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ABSTRACT

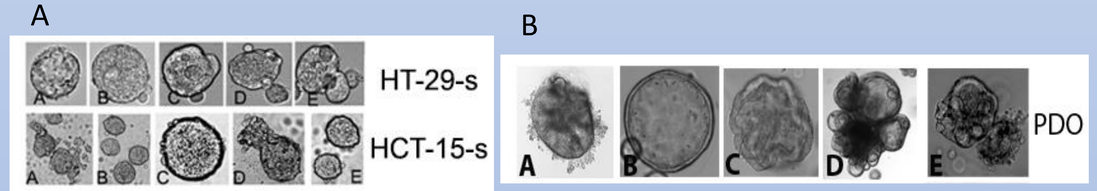
A Metastatic colorectal cancer (mCRC) is predicted to increase by 90% among young adults by 2030 due to delayed diagnosis. Colon cancer metastasis and drug resistance are colospheroids (CSCs) driven. Aberrant β-catenin signaling, and angiogenesis are crucial for CSCs development. Therefore, a new therapeutic approach is needed to overcome CSCs. It is well-documented that andrographolide (AGP) and melatonin (MLT) have anti-carcinogenic properties. We found that this combination has a therapeutic impact by synergistically inhibiting: i) the CSCs phenotype derived from mCRC cells, ii) a panel of mCRC proliferation, iii) patient-derived organoids (PDO) proliferation iv) 5FU-resistant cell proliferation, vi) β-catenin and its downregulatory signals, viii) xenograft tumor growth and ix) microvascular density and tumor index. Therefore, this novel compound has a potential therapeutic candidate for mCRC.

GOALS

Potential benefits of combinatorial drug therapy on metastatic colon cancer.

RESULTS

Models of Colon Cancer Metastasis



Characterization of Stemness

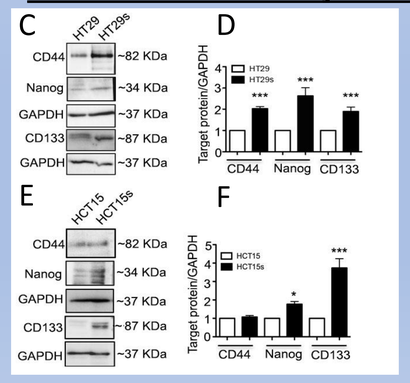
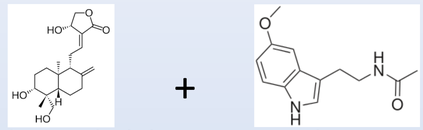


Figure 1. Organoids were grown on poly-L-lysine coated plates in Advanced DMEM:F12 reduced serum media containing growth factors including EGF, fibroblast with N2 and NAC (Refs. 1-3). A. Chronological development of HT-29 and HCT-15 Colospheroids (HT-29-s and HCT-15-s) from HT-29 and HCT-15 mCRC cells. B. Organoids from mCRC tissue. C and E:. CSCs (HT-29-s and HCT-15-s) marker protein expression as indicated by western blot; D and F. Quantification by densitometry and normalized with GAPDH. (*p<.05, ***p<.001). Data generated from three independent experiments

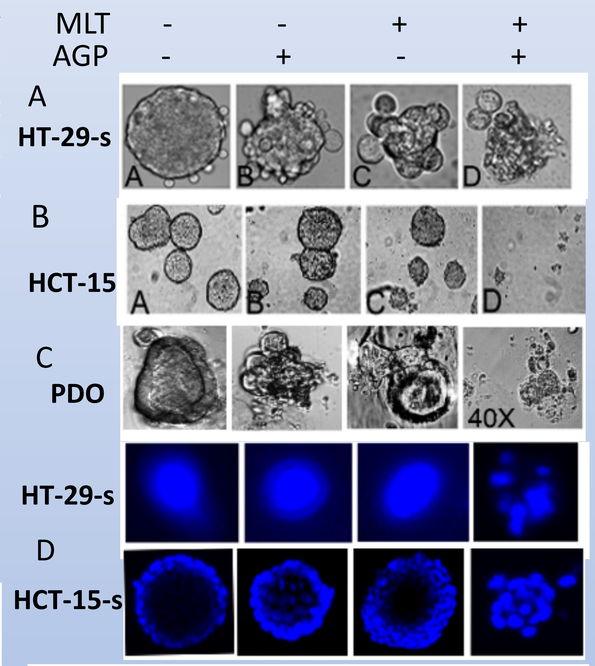
REFERENCES

1. Sokolov D., et al. Journal of Pineal Research., 2022
2. Sharda N., et al. Clinical Medicine Insights Oncology, 2021
3. Banerjee V., et al. European Journal of Pharmacology, 2021

Natural Bioactive Compound



Therapeutic Efficacy of AGP and MLT



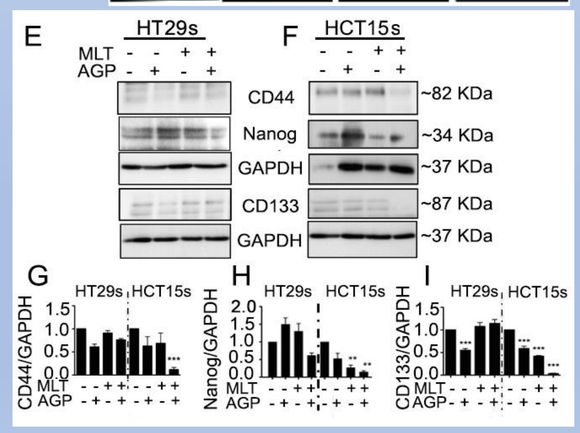
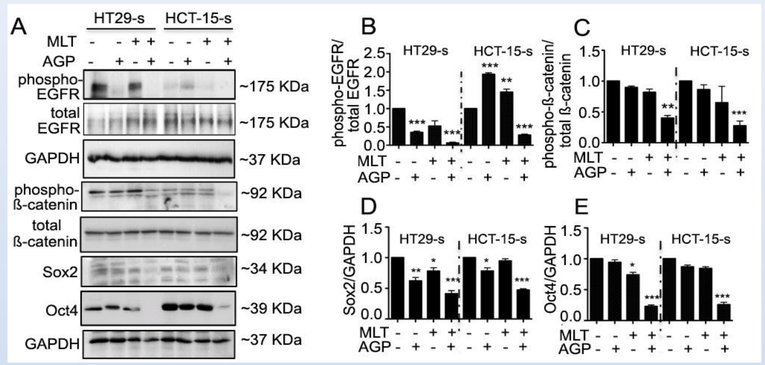


Figure 2. Morphological impact of AGP alone or in combination with MLT (A) HT-29-s (B) HCT-15-s (C) PDO (D) Apoptotic features by DAPI staining. (E-F): Stemness inhibition in combination treatment (AGP 9.3 µM, MLT 0.18 mM for 48h). (G-I) Quantification as indicated.



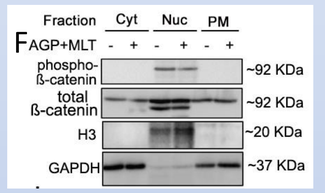
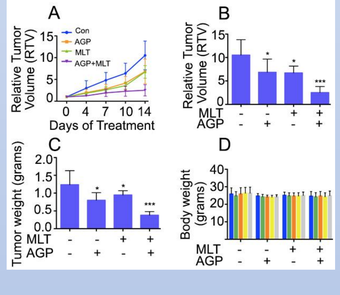


Figure 3. (A) AGP and MLT combination suppresses β-catenin signals as indicated proteins. (B-E) Quantification. (F) Translocation of β-catenin from cytoplasm to nucleus with reduced expression.



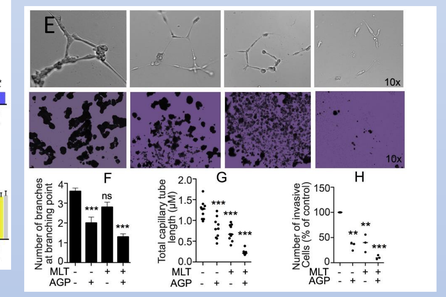


Figure 4. AGP and MLT combination inhibits HT-29 cell-generated subcutaneous xenografts tumor growth. A-B. tumor volume, after two weeks of drug treatment, C. Tumor weight, D. Body weight. E. AGP and MLT suppressed angiogenic branching (upper panel), Matrigel invasion of HT-29-s (lower panel). F-H. Quantification as indicated.

CONCLUSION

1. This drug combination significantly diminishes the stemness properties, β-catenin signal and angiogenesis.
2. The drug combination inhibits tumor growth in xenograft model.

REMAINING QUESTIONS

Effect of AGP and MLT combination in patient-derived-organoid xenograft model and its molecular mechanism.

PRESENT STATUS

International Patent Application No. PCT/US2021/030084