Potential enhancement of host immunity and anti-tumor efficacy of nanoscale curcumin and resveratrol in colorectal cancers by modulated electro-hyperthermia

Ming Kuo[1,†], Jih-Jong Lee[2,†], Yu-Shan Wang[3,4], Hsin-Chien Chiang[4], Cheng-Chung Huang[4], Pei-Jong Hsieh[4], Winston Han[4], Chiao-Hsu Ke[1], Albert TC Liao[1], Chen-Si Lin[1]

[1]Department of Veterinary Medicine, School of Veterinary Medicine, National Taiwan University, Taipei, Taiwan
[2]Graduate Institute of Veterinary Clinical Science, School of Veterinary Medicine, National Taiwan University, Taipei, Taiwan
[3]Institute of Molecular Medicine and Bioengineering, National Chiao Tung University, Hsinchu, Taiwan
[4]JohnPro Biotech Inc., Taipei, Taiwan

Citation: Kuo M. et al. (2020): Potential enhancement of host immunity and anti-tumor efficacy of nanoscale curcumin and resveratrol in colorectal cancers by modulated electro-hyperthermia, Oncothermia Journal 29: 125 – 134,
www.oncotherm.com/sites/oncotherm/files/2021-02/Kuo_Potentialenhancement

Abstract

Background: Modulated electro-hyperthermia (mEHT) is a form of hyperthermia used in cancer treatment. mEHT has demonstrated the ability to activate host immunity by inducing the release of heat shock proteins, triggering apoptosis, and destroying the integrity of cell membranes to enhance cellular uptake of chemo-drugs in tumor cells. Both curcumin and resveratrol are phytochemicals that function as effective antioxidants, immune activators, and potential inhibitors of tumor development. However, poor bioavailability is a major obstacle for use in clinical cancer treatment.

Methods: This purpose of this study was to investigate whether mEHT can increase anti-cancer efficacy of nanosized curcumin and resveratrol in in vitro and in vivo models. The in vitro study included cell proliferation assay, cell cycle, and apoptosis analysis. Serum concentration was analyzed for the absorption of curcumin and resveratrol in SD rat model. The in vivo CT26/BALB/c animal tumor model was used for validating the safety, tumor growth curve, and immune cell infiltration within tumor tissues after combined mEHT/curcumin/resveratrol treatment.

Results: The results indicate co-treatment of mEHT with nano-curcumin and resveratrol significantly induced cell cycle arrest and apoptosis of CT26 cells. The serum concentrations of curcumin and resveratrol were significantly elevated when mEHT was applied. The combination also inhibited the growth of CT26 colon cancer by inducing apoptosis and HSP70 expression of tumor cells while recruiting CD3+ T-cells and F4/80+ macrophages.

Conclusions: The results of this study have suggested that this natural, non-toxic compound can be an effective anti-tumor strategy for clinical cancer therapy. mEHT can enable cellular uptake of potential anti-tumor materials and create a favorable tumor microenvironment for an immunological chain reaction that improves the success of combined treatments of curcumin and resveratrol.

Keywords: Modulated electro-hyperthermia (mEHT), curcumin, resveratrol, nanosized, apoptosis, tumor microenvironment

38th Conference of the International Clinical Hyperthermia Society

November 5, 2020

Potential enhancement of host immunity and anti-tumor efficacy of nanoscale curcumin and resveratrol in colorectal cancers by modulated electro- hyperthermia (mEHT)

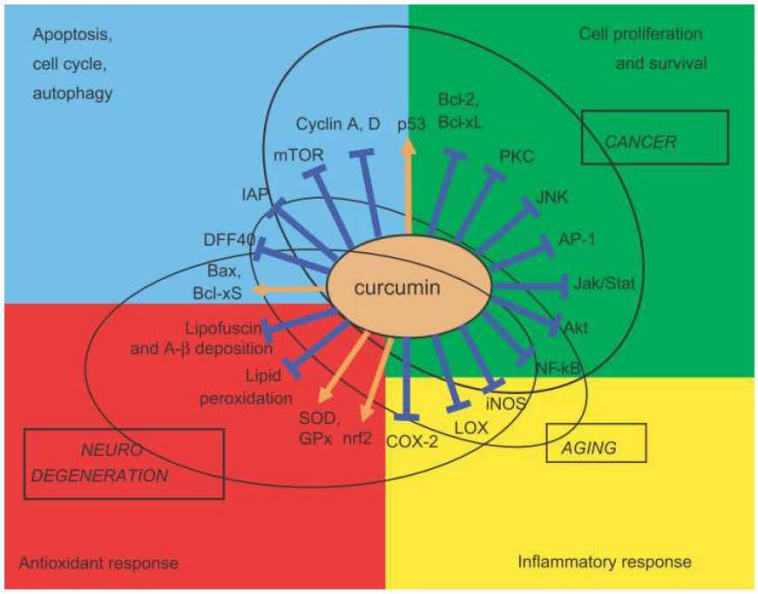
Samuel Yu-Shan Wang, PhD

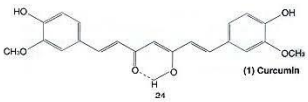
Molecular Medicine and Biochemical Engineering,
National Chiao Tung University, Hsinchu, Taiwan

Introduction

- mEHT was widely used to promote the synergistic effects in a variety of cancer therapies
- Both curcumin and resveratrol are phytochemicals that function as effective antioxidants, immune activators, and potential inhibitors of tumor development.
- Poor bioavailability is a major obstacle for the using of curcumin and resveratrol in clinical cancer treatment.
- We have developed a unique platform for nanosized curcumin and resveratrol.
- This purpose of this study was to investigate whether mEHT can increase anti-cancer efficacy of nanosized curcumin and resveratrol.

Curcumin

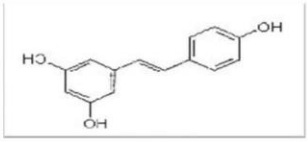


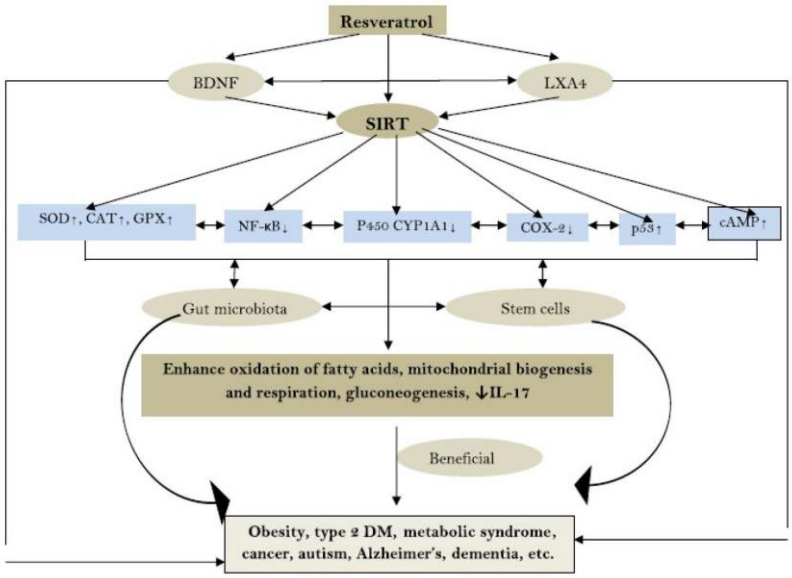


Evid Based Complement Alternat Med. 2007

3

Resveratrol



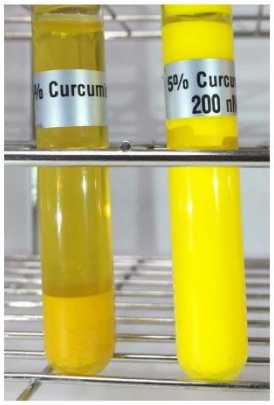


Nutrition 32 (2016) 174–178

4

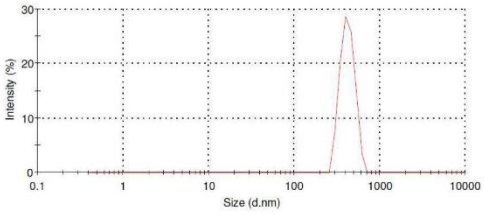
A unique platform for nanosized curcumin and resveratrol

Nano bead mills



Before and after nanosizing

Particle sizes after nanosizing



5

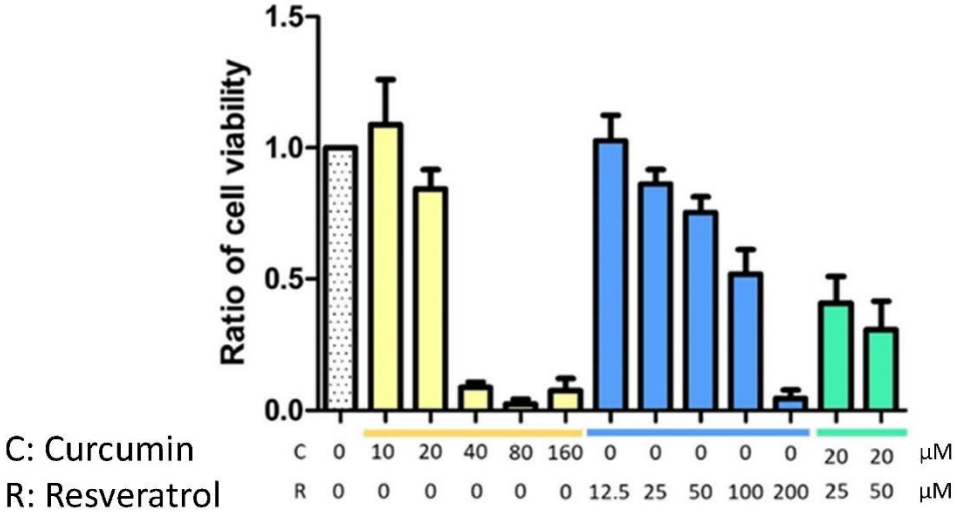
Nano formulation of curcumin plus resveratrol enhanced the absorption in serum of rat model

Table 1. Pharmacokinetic parameters derived from rat plasma. *

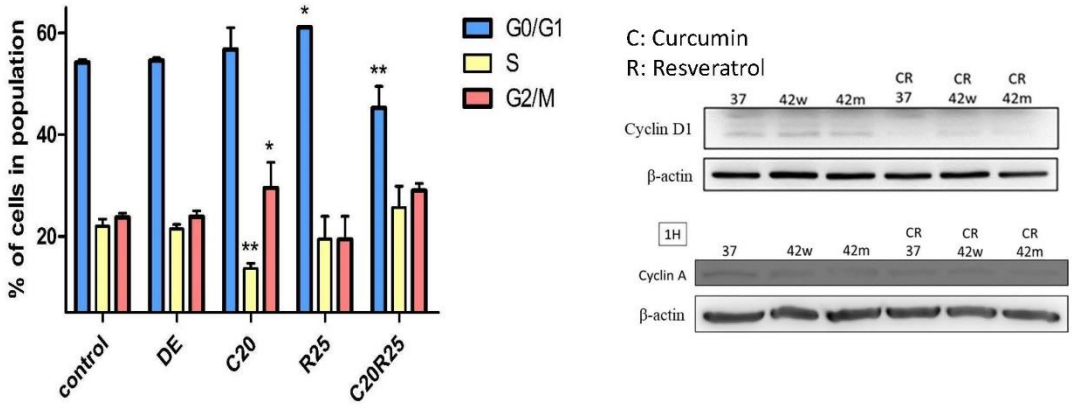
* AUC: area under the blood concentration vs time curve; C_{max}: maximum concentration; and T_{max} : time to reach C_{max}.

Sample	$AUC_{(0\text{-last})}$ (ng*hr/mL)	C_{max} (ng/mL plasma)	T_{max} (hr)
Curcumin suspension	46.3 ± 30.7	18.9 ± 20.1	2.5 ± 1.8
Curcumin nanoparticles	215 ± 46.4	37.7 ± 21.8	2.17 ± 1.44
Resveratrol suspension	1608 ± 284	522 ±152	2.67 ± 0.58
Resveratrol nanoparticles	1632 ± 286	782 ± 105	0.83 ± 1.01

Nano formulation of curcumin plus resveratrol inhibited the cell viability in CT26

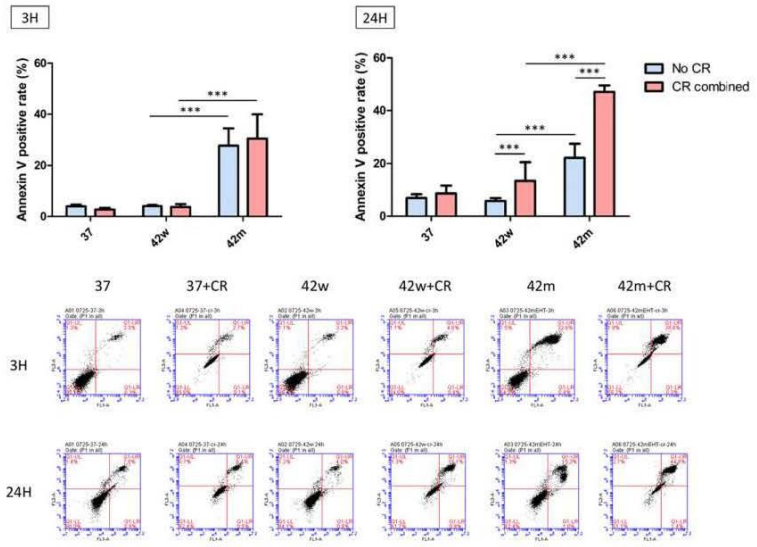


Nano formulation of curcumin plus resveratrol induced cell cycle arrest in CT26



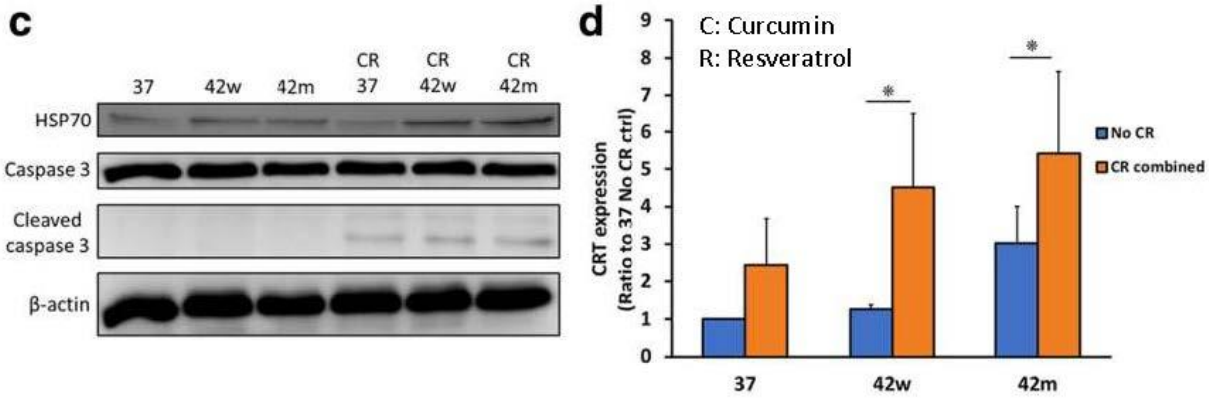
Both Cyclin D1 and Cyclin A decreased after CR treatment on CT26 to reveal decreased cell viability was partially due to their damaging cell cycle progression.

Nano formulation of curcumin plus resveratrol with mEHT increased significant apoptosis in CT26



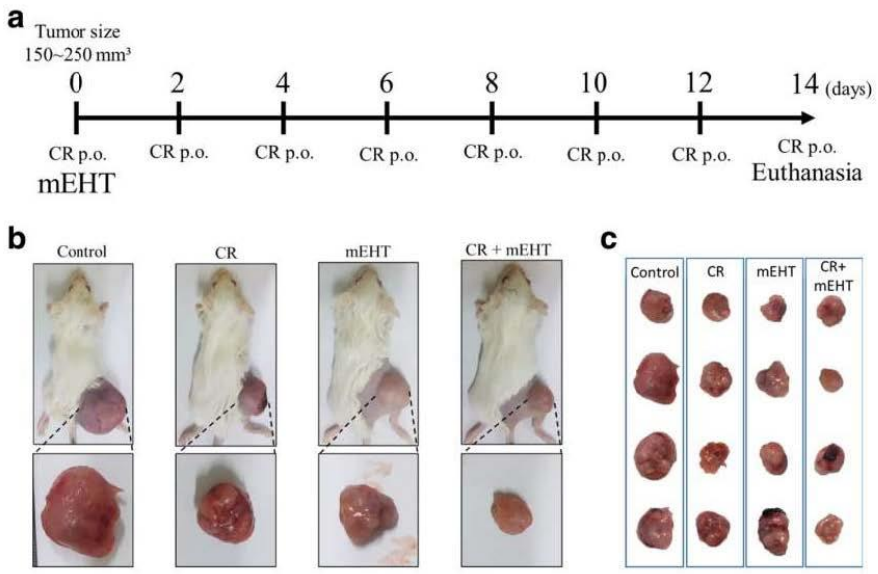
C: Curcumin
R: Resveratrol

Nano formulation of curcumin plus resveratrol with mEHT increased significant apoptosis in CT26



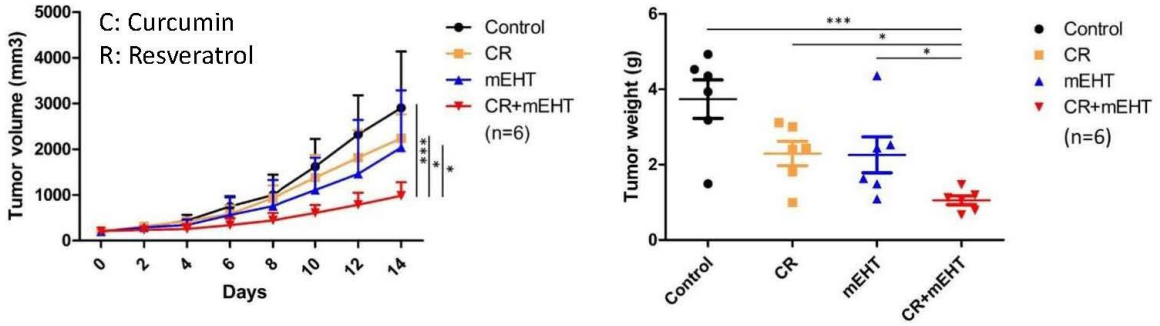
These results showed mEHT combined with curcumin and resveratrol induce cell apoptosis and immunogenic cell death to trigger further immune response.

CT26 tumors were inhibited by nano formulation of curcumin plus resveratrol combined with mEHT treatment



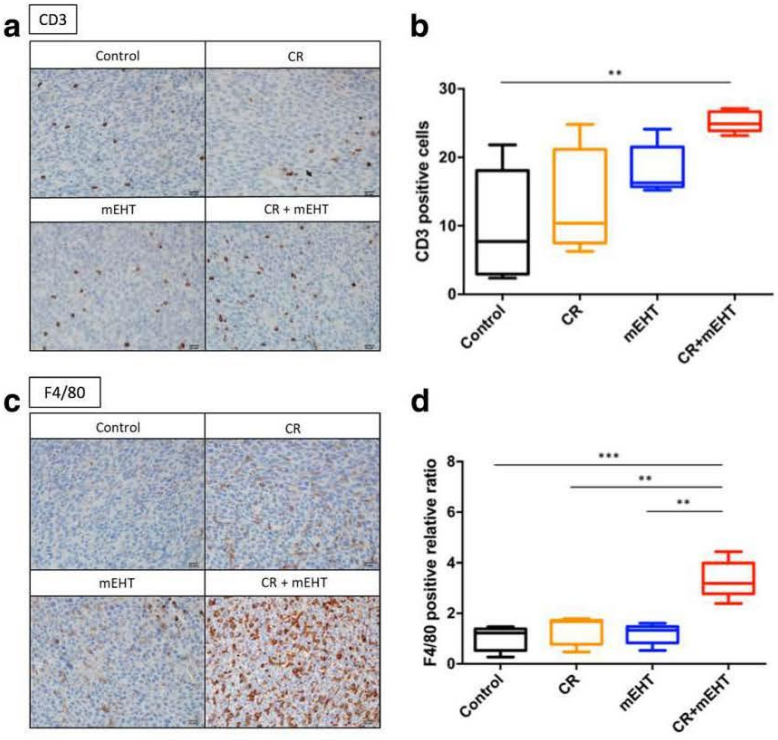
C: Curcumin
R: Resveratrol

CT26 tumors were inhibited by nano formulation of curcumin plus resveratrol combined with mEHT treatment



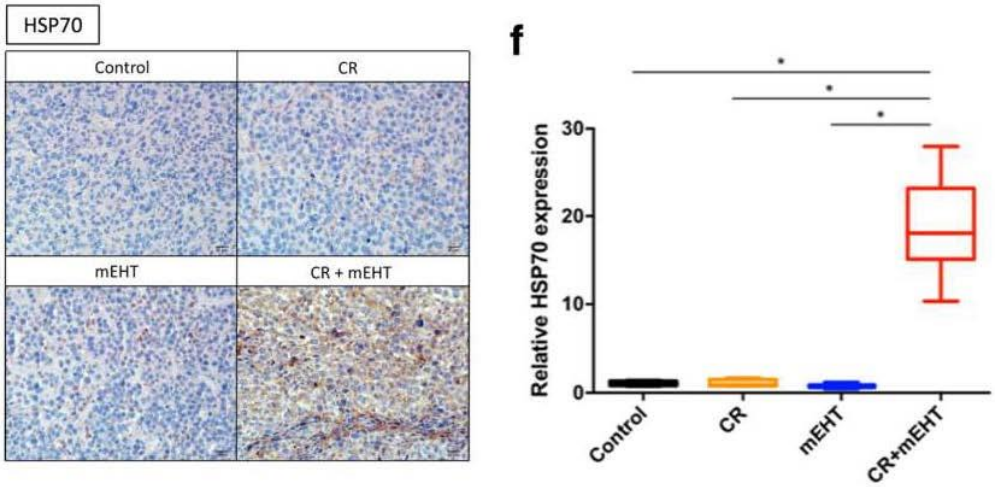
These results were in concordance with our *in vitro* findings and indicated that curcumin and resveratrol oral administration combined mEHT treatment could significantly suppress tumor growth.

Increased infiltration of macrophages and T-lymphocytes were observed in tumors treated by CR and mEHT combination



This indicates that in addition to reduced tumor cell viability, combined treatment of CR and mEHT could also trigger host immunity by recruiting T-cells and macrophages.

Increased of Hsp70 expression was observed in tumors treated by CR and mEHT combination



This results support our hypothesis that potential immune activation was induced by CR treatment and mEHT for CT26 tumor eradication.

Conclusions

- This study indicates that nano-formulated curcumin plus resveratrol compound shows enhanced bioavailability when combined with mEHT, synergistically increasing HSP-release and immune response, leading to enhanced anti-tumor efficacy in CT26 tumors.
- Further clinical studies are needed to confirm the safety and effectiveness of nano-formulated curcumin and resveratrol when combined with mEHT.

Kuo *et al. BMC Cancer* (2020) 20:603
https://doi.org/10.1186/s12885-020-07072-0

BMC Cancer

RESEARCH ARTICLE Open Access

Potential enhancement of host immunity and anti-tumor efficacy of nanoscale curcumin and resveratrol in colorectal cancers by modulated electro-hyperthermia

I-Ming Kuo[1†], Jih-Jong Lee[2†], Yu-Shan Wang[3,4], Hsin-Chien Chiang[4], Cheng-Chung Huang[4], Pei-Jong Hsieh[4], Winston Han[4], Chiao-Hsu Ke[1], Albert T. C. Liao[1] and Chen-Si Lin[1*]