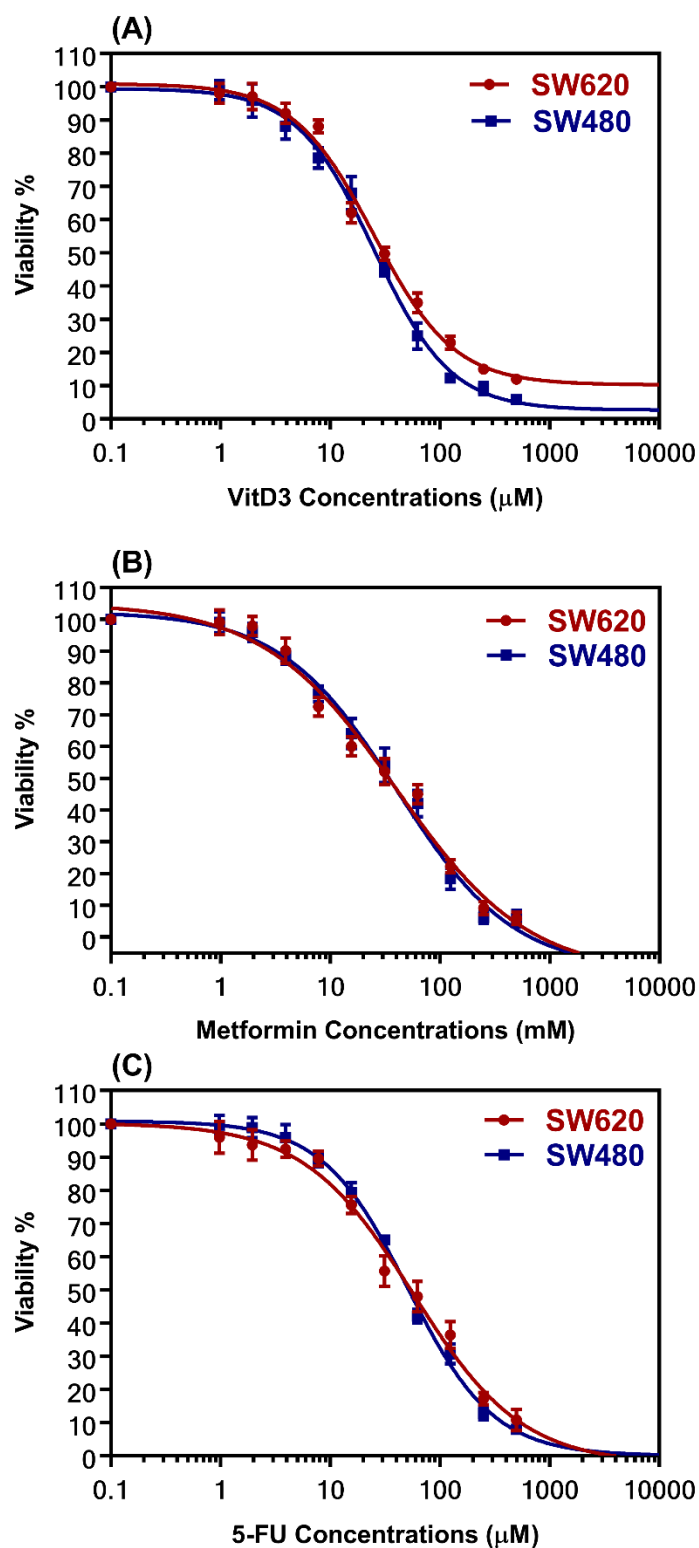


Supplementary Figure S1: Summary of *in vivo* experimental design. A total of 90 male BALB/c mice were used and CRC was induced in 80 animals by azoxymethane (AOM) intraperitoneal injections for two successive (10 mg/Kg/week). Treatments with 5-FU (50 mg/Kg/week), active VD₃ (0.07 µg/Kg/day; five times/week) and/or metformin (430 mg/Kg/day; five times/week) single, dual and triple therapies started at week-21 post AOM injections and lasted for 4 weeks.



Supplementary Figure S2: Cells were treated with different concentrations of the drugs of interest for 24h, and the IC₅₀ for each determined using the MTT cell viability assay.

Supplementary Table S1. The sequences of PCR primers used for the detection of human *GAPDH*, *PIK3CA*, *AKT1*, *mTOR*, *PTEN*, *CCND1*, *CCND3*, *CDKN1A*, *CDKN1B*, *BCL2*, *Cytochrome C*, and *Caspase-3* mRNAs in colon samples including the corresponding genes accession numbers and amplicon sizes.

Genes	Forward	Reverse	Amplicon size
<i>GAPDH</i> (NCBI: NM_002046.5)	5' CAC ATG GCC TCC AAG GAG TAA 3'	5' TGA GGG TCT CTC TCT TCC TCT TGT 3'	74 bp
<i>PIK3CA</i> (NCBI: NM_006218.4)	5' GGA CCC GAT GCG GTT AGA G 3'	5' ATC AAG TGG ATG CCC CAC AG 3'	168 bp
<i>AKT1</i> (NCBI: NM_001382431.1)	5' CTC AGT GTC GTC AGA GCC C 3'	5' ATG GAA AGC AGG CCA GAC TC 3'	100 bp
<i>mTOR</i> (NCBI: NM_004958.4)	5' GAC GAG AGA TCA TCC GCC AG 3'	5' ACA AGG GAC CGC ACC ATA AG 3'	97 bp
<i>PTEN</i> (NCBI: NM_000314.8)	5' CTC AGC CGT TAC CTG TGT GT 3'	5' AGG TTT CCT CTG GTC CTG GT 3'	129 bp
<i>CCND1</i> (NCBI: NM_053056.2)	5' TGA CCC CGC ACG ATT TCA TT 3'	5' CAT GGA GGG CGG ATT GGA AA 3'	143 bp
<i>CCND3</i> (NCBI: NM_001136017.3)	5' GGT GCA ATC CTC TCC TCG C 3'	5' TAG TTC ATG GCC AGG GGG AA 3'	183 bp
<i>CDKN1A</i> (NCBI: NM_000389.4)	5' AGT CAG TTC CTT GTG GAG CC 3'	5' GCA TGG GTT CTG ACG GAC AT 3'	109 bp
<i>CDKN1B</i> (NCBI: NM_004064.4)	5' CTG GCC TCA GAA GAC GTC AAA 3'	5' AGG ATG TCC ATT CCA TGA AGT CAG 3'	147 bp
<i>BCL2</i> (NCBI: NM_000633.3)	5' CTT TGA GTT CGG TGG GGT CA 3'	5' GGG CCG TAC AGT TCC ACA AA 3'	162 bp
<i>Cytochrome C</i> (NCBI: NM_018947.6)	5' CGT TGT GCC AGC GAC TAA AA 3'	5' TGG CAC TGG GAA CAC TTC AT 3'	88 bp
<i>BAX</i> (NCBI: NM_001291428.1)	5' TCG CCC TTT TCT ACT TTG CCA 3'	5' GTC CTG GAG ACA GGG ACA TCA 3'	195 bp
<i>CASP3</i> (NCBI: NM_004346.3)	5' CTC TGG TTT TCG GTG GGT GT 3'	5' CCA CTG AGT TTT CAG TGT TCT CC 3'	90 bp

Supplementary Table S2: Serum concentrations (mean \pm SD) of liver enzymes, total protein, albumin, creatinine, and urea in the different study groups.

	NC group	PC group	5-FU group	VD3 group	Met group	VF group	MF group	VMF Group
ALT (IU/L)	58.7 \pm 5.1	61.02 \pm 4.6	63.3 \pm 5.1	57.9 \pm 6.4	58.3 \pm 5.7	57.8 \pm 4.7	59.1 \pm 4.4	60.2 \pm 5.5
AST (IU/L)	51.3 \pm 6.3	53.2 \pm 4.7	56.1 \pm 7.2	52.9 \pm 5.9	52.5 \pm 6.6	54.8 \pm 5.6	52.7 \pm 6.6	51.8 \pm 4.7
ALP (IU/L)	108.1 \pm 12.9	105.2 \pm 10.3	111.4 \pm 17.6	107.9 \pm 11.2	105.8 \pm 10.3	101.5 \pm 13.2	107.8 \pm 9.9	105 \pm 13.3
Total bilirubin (mg/dL)	0.45 \pm 0.2	0.48 \pm 0.3	0.47 \pm 0.3	0.45 \pm 0.3	0.46 \pm 0.1	0.49 \pm 0.3	0.46 \pm 0.1	0.46 \pm 0.09
Total protein (g/dL)	7.5 \pm 0.6	7.4 \pm 0.4	7.1 \pm 0.7	7.6 \pm 0.5	7.2 \pm 0.3	7.4 \pm 0.6	7.8 \pm 0.7	7.5 \pm 0.6
Albumin (g/dL)	4.1 \pm 0.33	3.7 \pm 0.41	4.0 \pm 0.45	4.4 \pm 0.57	4.2 \pm 0.44	3.8 \pm 0.41	4.2 \pm 0.34	4.3 \pm 0.46
Creatinine (mg/dL)	0.47 \pm 0.08	0.51 \pm 0.12	0.48 \pm 0.11	0.48 \pm 0.14	0.53 \pm 0.15	0.46 \pm 0.21	0.53 \pm 0.24	0.50 \pm 0.16
Urea (mg/dL)	41.2 \pm 6.8	41.3 \pm 5.7	43.2 \pm 5.4	43.4 \pm 6.1	40.4 \pm 7.3	42.7 \pm 6.6	40.8 \pm 6.9	43.3 \pm 6.1