

Effect of Stress-WIN, a novel polyherbal formulation on DOCA-salt-induced hypertensive Wistar rats.

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Table1Listofcommongenestweendifferentcompoundsandhypertension.

Salicylicacid	Apigenin	β-sitosterol	Piperine
ABCC1	ABCC1	ABCC1	ABCC1
ABCC8	AGER	ABO	AHR
ACE	AHR	ADIPOQ	BCL2
ADIPOQ	ALB	AGER	BRCA1
ADRB1	AR	AGTR1	CALCA
ADRB2	BCL2	AOC1	COMT
AGT	BRCA1	AOC3	CYP1A1
AGTR1	CAT	APOA1	CYP2C9
AHR	CCL2	APOE	DRD2
AIF1	CYP1A1	BCL2	FOS
ALB	ESR2	CAT	GSTP1
ALOX15	FOS	CCL2	HTR2A
ANXA1	GJA1	CD36	IL1B
APOA1	GRK2	CRP	IL6
APOE	GSTP1	ESR2	MMP9
AR	HGF	F11	MTOR
AVP	HIF1A	F12	PKD2
BCL2	HMGB1	F7	PPARA
BRCA1	HMOX1	GP1BA	RELA
CACNA1C	ICAM1	GSK3B	TNF
CAT	IL6	IL1B	UCP2
CCL2	JUN	IL6	
CRP	LEP	INS	

CXCL2	LOX	LEP	
CXCR2	LTF	LOX	
CYBB	MMP1	LPL	
CYP2C9	MMP9	MTTP	
DRD1	MTOR	MYH9	
DRD2	NFE2L2	NR3C1	
EDNRA	NOS2	PROC	
EPHX2	NPPA	PTK2B	
F12	NPY	SOD1	
FN1	OLR1	SOD2	
GBA1	PRKCD	TGM2	
GP1BA	PTEN	TNF	
GSTP1	PTGS2	VWF	
HGF	PTK2B	XDH	
HIF1A	SERPINE1		
HMGB1	SOD1		
HMOX1	STK11		
HP	TGFB1		
HRH2	TIMP1		
HSD11B1	TNF		
ICAM1	TP53		
IKBKB	TRHR		
IL1B	VDR		
IL1RN	VEGFA		
IL6	XDH		

INS			
JUN			
KNG1			
LEP			
LOX			
LTF			
MMP1			
MMP2			
MMP9			
MTOR			
MTR			
MTTP			
NFE2L2			
NOS2			
NOS3			
NPPB			
NPR1			
NQO1			
NR3C1			
OLR1			
OXT			
PLAT			
POMC			
PON1			
PPARA			

PPARG			
PPBP			
PRKAG2			
PRKCD			
PTGIS			
PTGS2			
PTH			
PTK2B			
PTPN1			
RELA			
REN			
RETN			
RPS6KB1			
SELP			
SERPINE1			
SOD1			
SOD2			
STK11			
TACR1			
TGFB1			
TH			
TIMP1			
TLR4			
TNF			
TP53			

VCAM1			
VDR			
VEGFA			
VHL			
VWF			
XDH			

Table2.EnrichmentanalysisoftargetgenesofSalicylicacid

Enrichment FDR [#]	nGenes ^{\$}	Pathway Genes*	Fold Enrichment [€]	Pathway
1.39E-12	10	49	39.91104134	Malaria
7.22E-23	19	100	37.15717949	AGE-RAGEsignalingpathwayindiabetic complications
1.47E-17	16	109	28.70665726	HIF-1signalingpathway
3.30E-11	10	69	28.34262356	Adipocytokinesignalingpathway
3.17E-20	19	138	26.92549238	Fluidshear stressandatherosclerosis
1.24E-12	12	92	25.5083612	Rheumatoidarthritis
1.86E-13	13	101	25.17161716	Chagasdisease
2.04E-11	11	89	24.17084414	Longevityregulatingpathway
3.91E-13	13	108	23.54012346	Insulinresistance
2.68E-11	11	93	23.13123794	IL-17signalingpathway
3.38E-23	24	214	21.93242272	Lipidandatherosclerosis
1.14E-11	12	112	20.9532967	TNFsignalingpathway
2.39E-11	13	155	16.40215054	Non-alcoholicfatty liverdisease
9.85E-13	16	223	14.03150512	Chemicalcarcinogenesis-reactiveoxygenspecies

2.68E-11	14	197	13.89795653	Chemicalcarcinogenesis-receptoractivation
3.50E-11	14	203	13.48717949	Diabeticcardiomyopathy
2.01E-10	14	232	11.80128205	Coronavirusedisease-COVID-19
3.93E-20	29	530	10.70067731	Pathwaysin cancer
4.79E-10	16	354	8.839055483	PI3K-Aktsignalingpathway
6.33E-10	16	362	8.64371724	Neuroactiveligand-receptorinteraction

#EnrichmentFalseDiscoveryRate(FDR)

\$Thenumberofgenesinthepathwaythatoverlapwithyourgene list

*Thetotalnumberofgenesinapathway.

€Fold Enrichment of a pathway is defined as the ratio of the percentage of genes inyourlist to thecorresponding percentage in the background genes.

Figure 1.¹HNMRpeaksofβ-sitosterol.

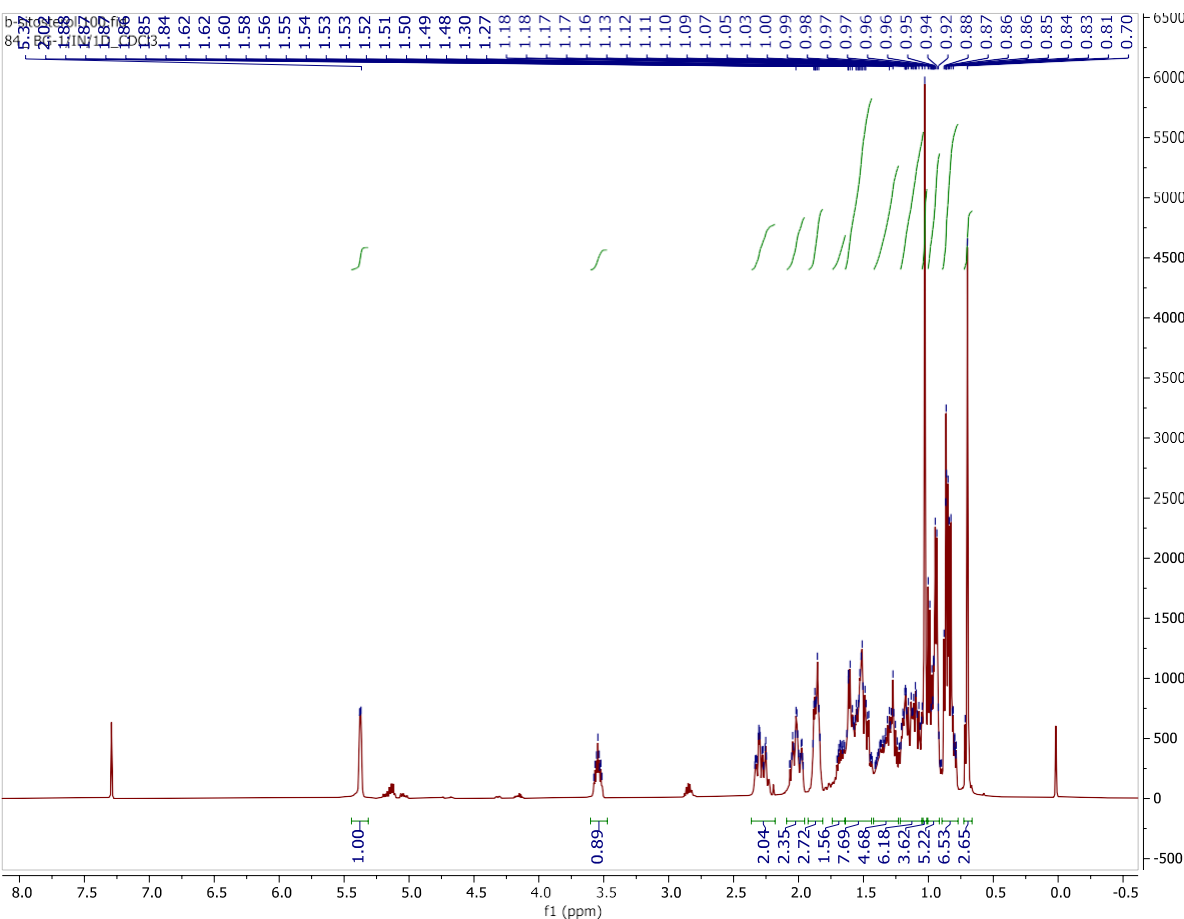
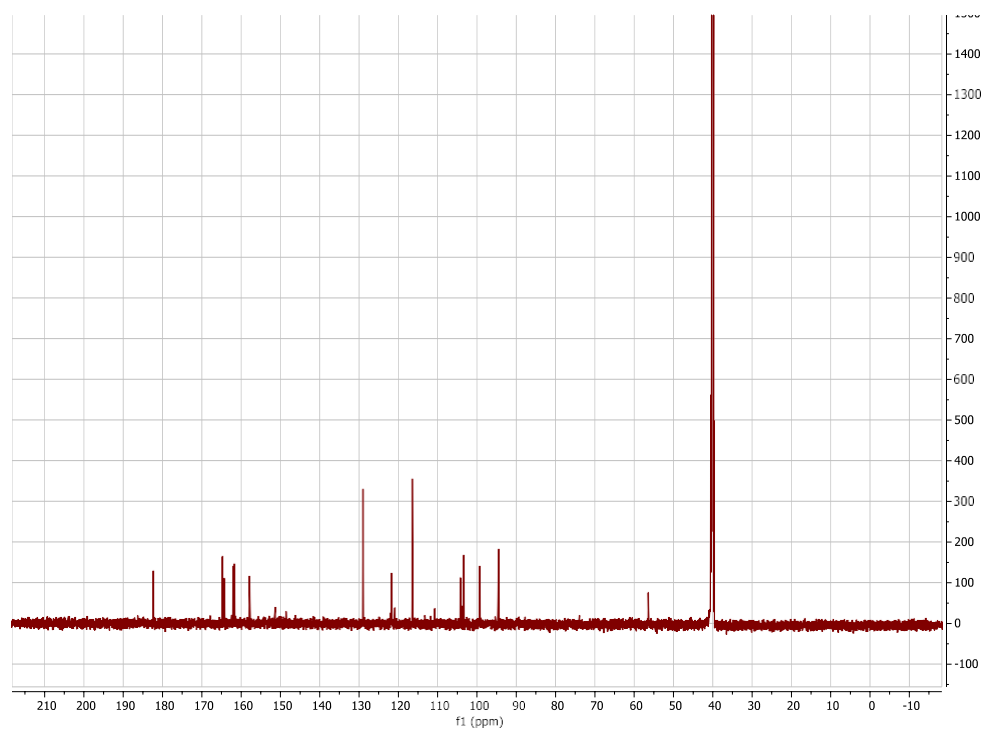
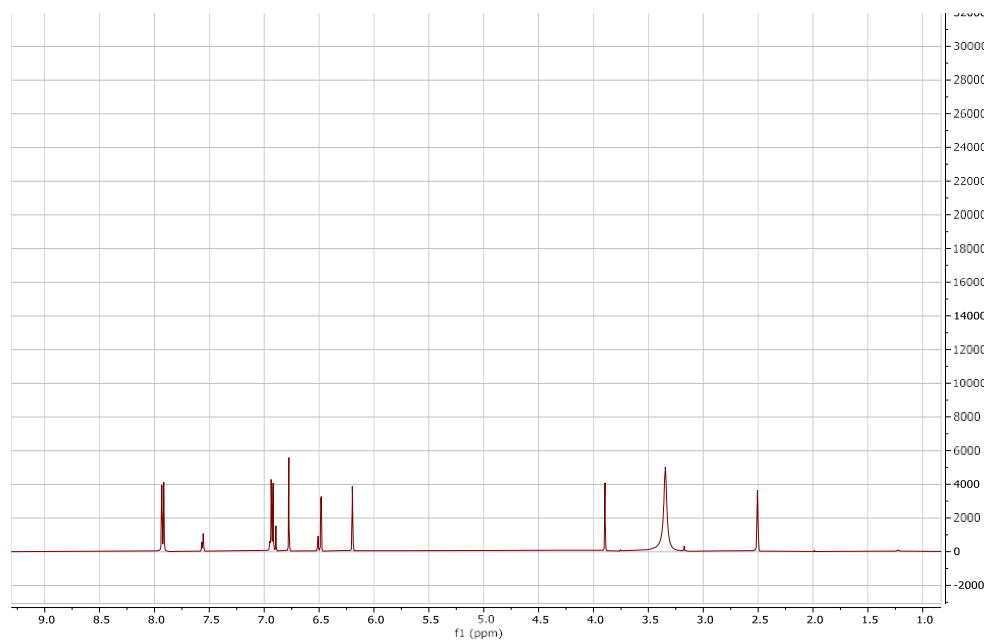


Figure 2. ^1H NMR and ^{13}C NMR peaks of Apigenin.



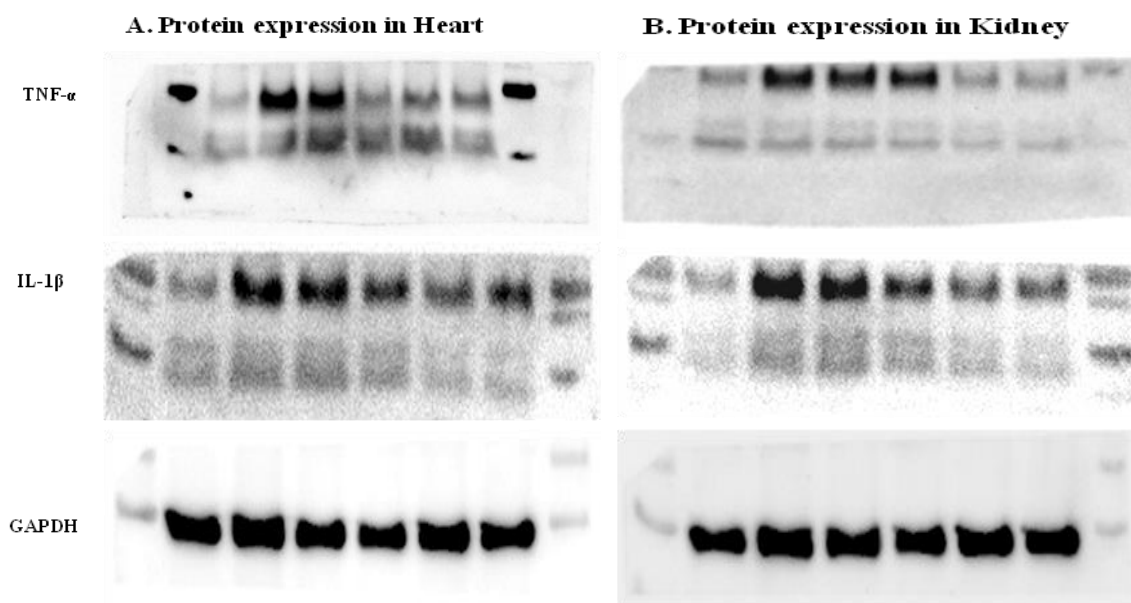


Figure 3. Effect of *Stress-WIN* on DOCA-salt induced inflammation in heart and kidney of rats (A): TNF- α & IL-1 β blots (heart): Representative blots of TNF- α & IL-1 β protein expressions in heart of rats.

Table3.EnrichmentanalysisoftargetgenesofApigenin

Enrichment FDR	nGenes	Pathway Genes	Fold Enrichment	Pathway
6.18E-08	6	49	44.47230321	Malaria
1.71E-13	11	100	39.95095238	AGE-RAGEsignalingpathwayindiabetic complications
1.11E-10	9	92	35.52950311	Rheumatoidarthritis
1.45E-11	10	109	33.32022717	HIF-1signalingpathway
1.71E-13	12	138	31.58178054	Fluidshear stressandatherosclerosis
3.76E-09	8	93	31.2421915	IL-17signalingpathway
6.67E-09	8	101	28.76756247	Chagasdisease
1.04E-07	7	95	26.76140351	Endocrineresistance
1.13E-07	7	97	26.20962199	Prostatecancer
1.30E-08	8	112	25.94217687	TNFsignalingpathway
6.79E-14	14	214	23.76012461	Lipidandatherosclerosis
2.14E-07	7	108	23.54012346	Th17celldifferentiation

5.54E-10	10	161	22.55841467	MicroRNAsincancer
1.46E-12	13	223	21.17253897	Chemicalcarcinogenesis-reactiveoxygenspecies
1.08E-08	9	162	20.17724868	HepatitisB
6.63E-07	7	129	19.70801034	Relaxinsignalingpathway
3.62E-09	10	197	18.43606478	Chemicalcarcinogenesis-receptoractivation
2.14E-07	8	167	17.39834616	Hepatocellularcarcinoma
4.56E-08	9	194	16.84904271	Kaposisarcoma-associatedherpesvirusinfection
1.58E-15	20	530	13.70530099	Pathwaysincancer

Table4.Enrichmentanalysisoftargetgenesof β -sitosterol

Enrichment FDR	nGenes	Pathway Genes	Fold Enrichment	Pathway
1.93E-05	4	30	58.66923077	Antifolateresistance
3.20E-05	4	37	47.56964657	Africantrypanosomiasis
3.81E-06	5	49	44.89992151	Malaria
7.29E-05	4	51	34.51131222	Cholesterolmetabolism
2.42E-07	7	100	30.80134615	AGE-RAGEsignalingpathwayindiabetic complications
0.000129753	4	62	28.38833747	Longevityregulatingpathway-multiplespecies
3.20E-05	5	85	25.88348416	Complementandcoagulationcascades
4.00E-05	5	93	23.65694789	IL-17signalingpathway
4.76E-05	5	99	22.22319347	Hematopoieticcelllineage
0.000331297	4	82	21.46435272	Peroxisome
8.06E-09	10	214	20.5616463	Lipidandatherosclerosis
6.70E-05	5	108	20.37126068	Insulinresistance
3.41E-06	7	155	19.87183623	Non-alcoholicfatty liverdisease
0.000434234	4	89	19.7761452	Longevityregulatingpathway

1.93E-05	6	137	19.27091522	Yersinia infection
0.000163766	5	141	15.60351882	Alcoholic liver disease
0.000129753	6	224	11.7862294	Human cytomegalovirus infection
0.000142909	6	232	11.37980769	Coronavirus disease-COVID-19
4.00E-05	8	384	9.167067308	Alzheimer disease
0.000129753	8	476	7.395281189	Pathways of neurodegeneration-multiple diseases

Table 5. Enrichment analysis of target genes of piperine

Enrichment FDR	nGenes	Pathway Genes	Fold Enrichment	Pathway
1.98E-08	5	30	131.5	Antifolate resistance
7.32E-06	4	57	55.36842105	Legionellosis
7.50E-07	5	76	51.90789474	Pertussis
7.21E-08	6	93	50.90322581	IL-17 signaling pathway
1.19E-07	6	108	43.83333333	Th17 cell differentiation
1.27E-07	6	112	42.26785714	TNF signaling pathway
2.10E-06	5	97	40.67010309	Prostate cancer
1.98E-08	7	138	40.02173913	Fluid shear stress and atherosclerosis
2.18E-06	5	100	39.45	AGE-RAGE signaling pathway in diabetic complications
2.18E-06	5	101	39.05940594	Chagas disease
2.23E-06	5	103	38.30097087	Toll-like receptor signaling pathway
2.64E-06	5	108	36.52777778	Insulin resistance
6.74E-10	9	214	33.18224299	Lipid and atherosclerosis
7.50E-07	6	155	30.54193548	Non-alcoholic fatty liver disease
8.15E-07	6	162	29.22222222	Hepatitis B
7.32E-06	5	137	28.79562044	Yersinia infection

7.32E-06	5	139	28.38129496	Measles
1.19E-07	7	197	28.03553299	Chemicalcarcinogenesis-receptoractivation
7.46E-06	5	141	27.9787234	Alcoholicliverdisease
6.44E-06	6	249	19.01204819	Salmonellainfection