האם תתכן מעורבות של צמחי מרפא בסינדרום המטבולי -בסוס מוליקולרי

Natural and traditional herbal medicines have potential as alternative or combination (complementary) therapy for MS. Despite the long history of herbal and natural traditional medicines for the management of MS, there is still no conclusive evidence for their effectiveness or their safety profiles. Therefore, further investigation into their exact mechanisms of action are warranted and required to gather proof of efficacy and safety for possible protection against MS-related pathophysiology and disease progression.

לכן:

המטרה: מתן דוגמאות למחקר מוליקולרי בצמחי מרפא

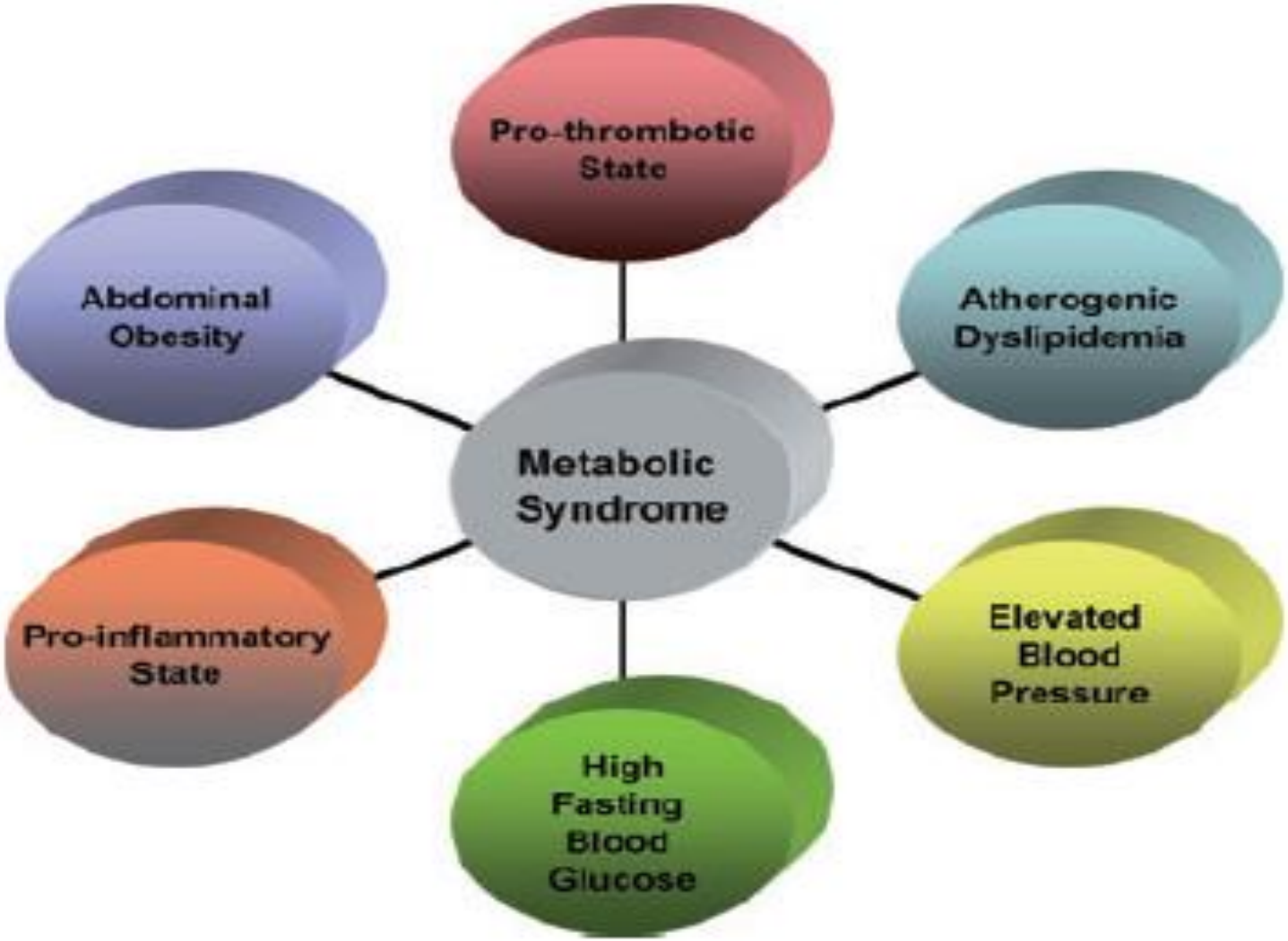
J Diabetes Res. 2014;2014:313718

Metabolic syndrome

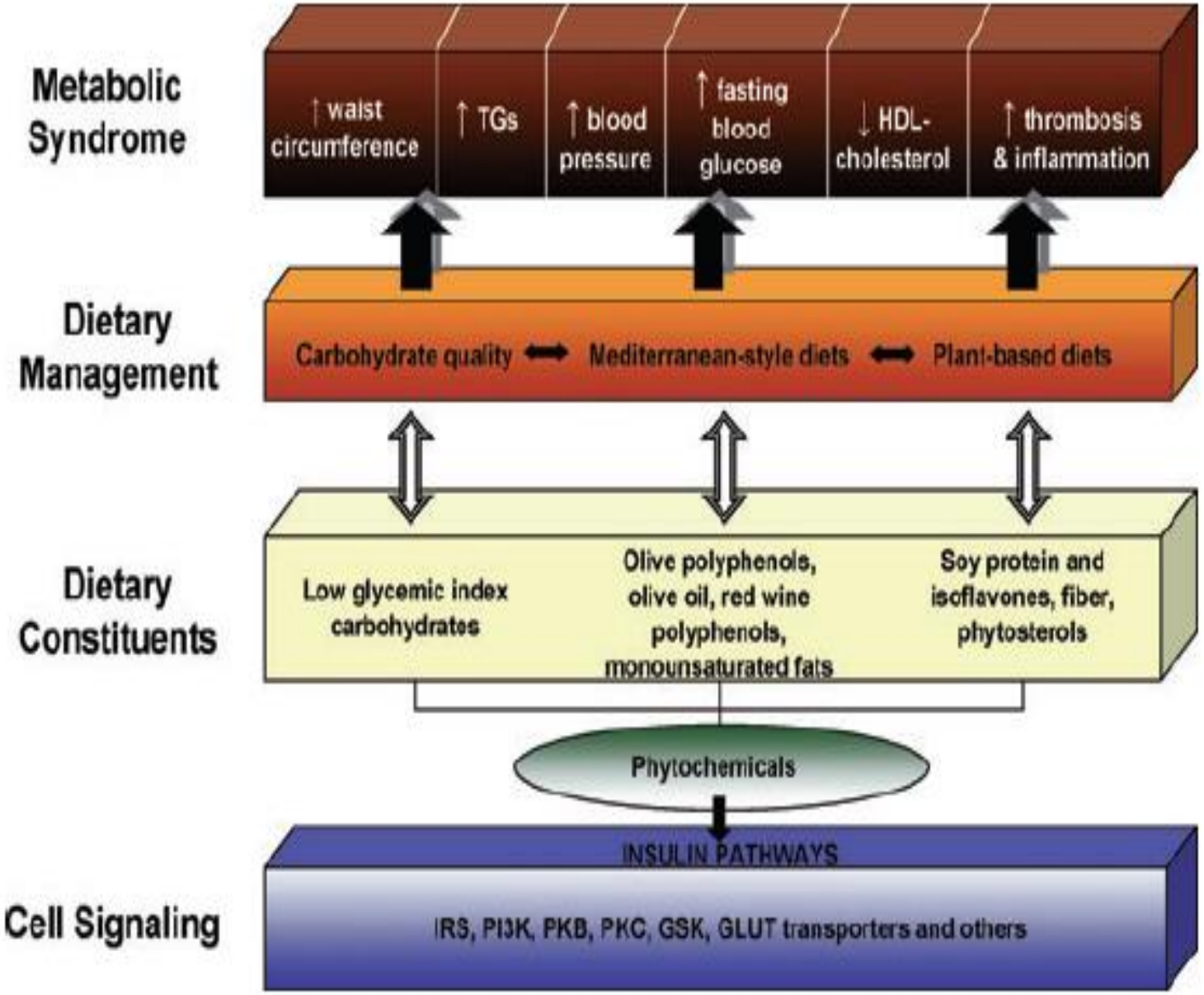
Metabolic syndrome is diagnosed when a patient has at least 3 of the following 5 conditions:

- **1. Fasting glucose ≥100 mg/dL (or receiving drug therapy for hyperglycemia)**
- **2. Blood pressure ≥130/85 mm Hg (or receiving drug therapy for hypertension)**
- **3. Triglycerides ≥150 mg/dL (or receiving drug therapy for hypertriglyceridemia)**
- **4. HDL-C < 40 mg/dL in men or < 50 mg/dL in women (or receiving drug therapy for reduced HDL-C)**
- **5. Waist circumference ≥102 cm (40 in) in men or ≥88 cm (35 in) in women; if Asian American, ≥90 cm (35 in) in men or ≥80 cm (32 in) in women**

Nutrition Reviews® Vol. 66(8):429–444



Nutrition Reviews® Vol. 66(8):429–444



המנגנון המוליקולרי

NAFLD and NASH

NAFLD is considered to cover a spectrum of disease activity. This spectrum begins as fatty accumulation in the liver (hepatic steatosis). A liver can remain fatty without disturbing liver function, but by varying mechanisms and possible insults to the liver may also progress to outright inflammation of the liver. When inflammation occurs in this setting, the condition is then called NASH. Over time up to 20 percent of patients with NASH may develop cirrhosis

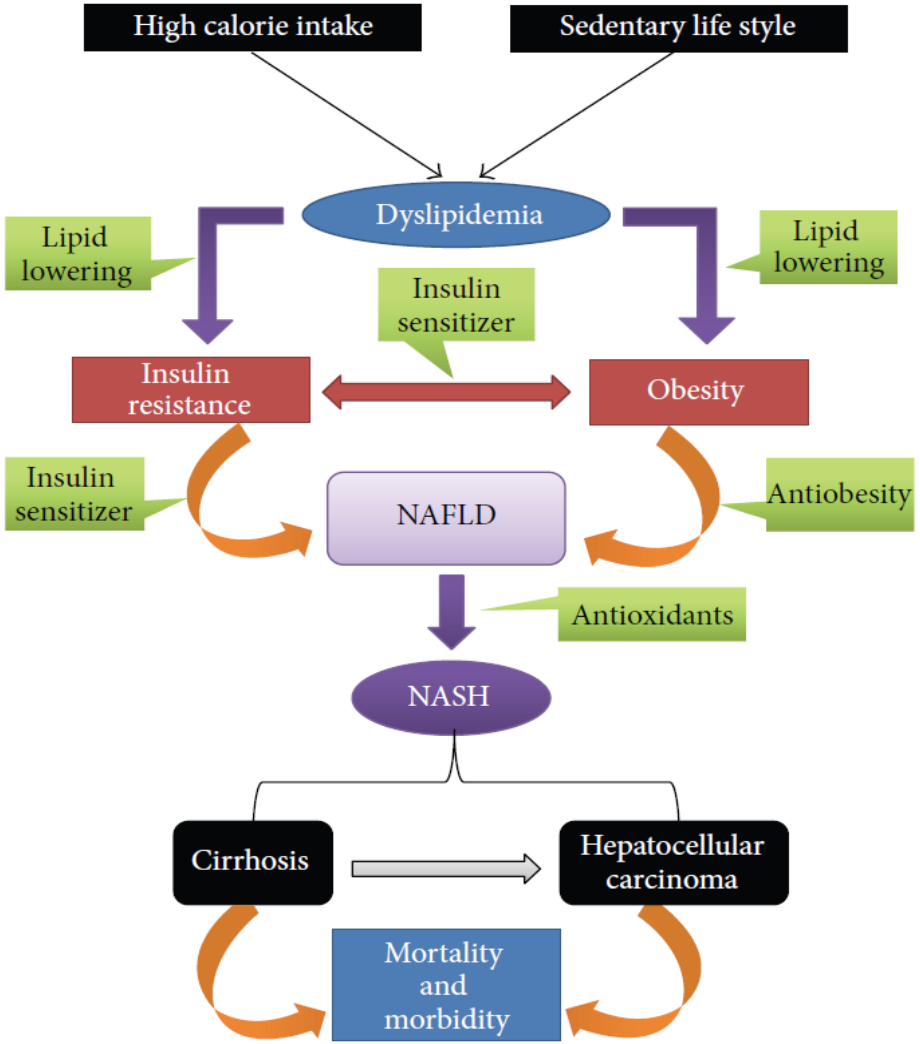


FIGURE 1: An overview of the pathogenesis of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) and potential targets for herbal therapeutic intervention.Green color graphics represent herbal property that could be beneficial against NASH.

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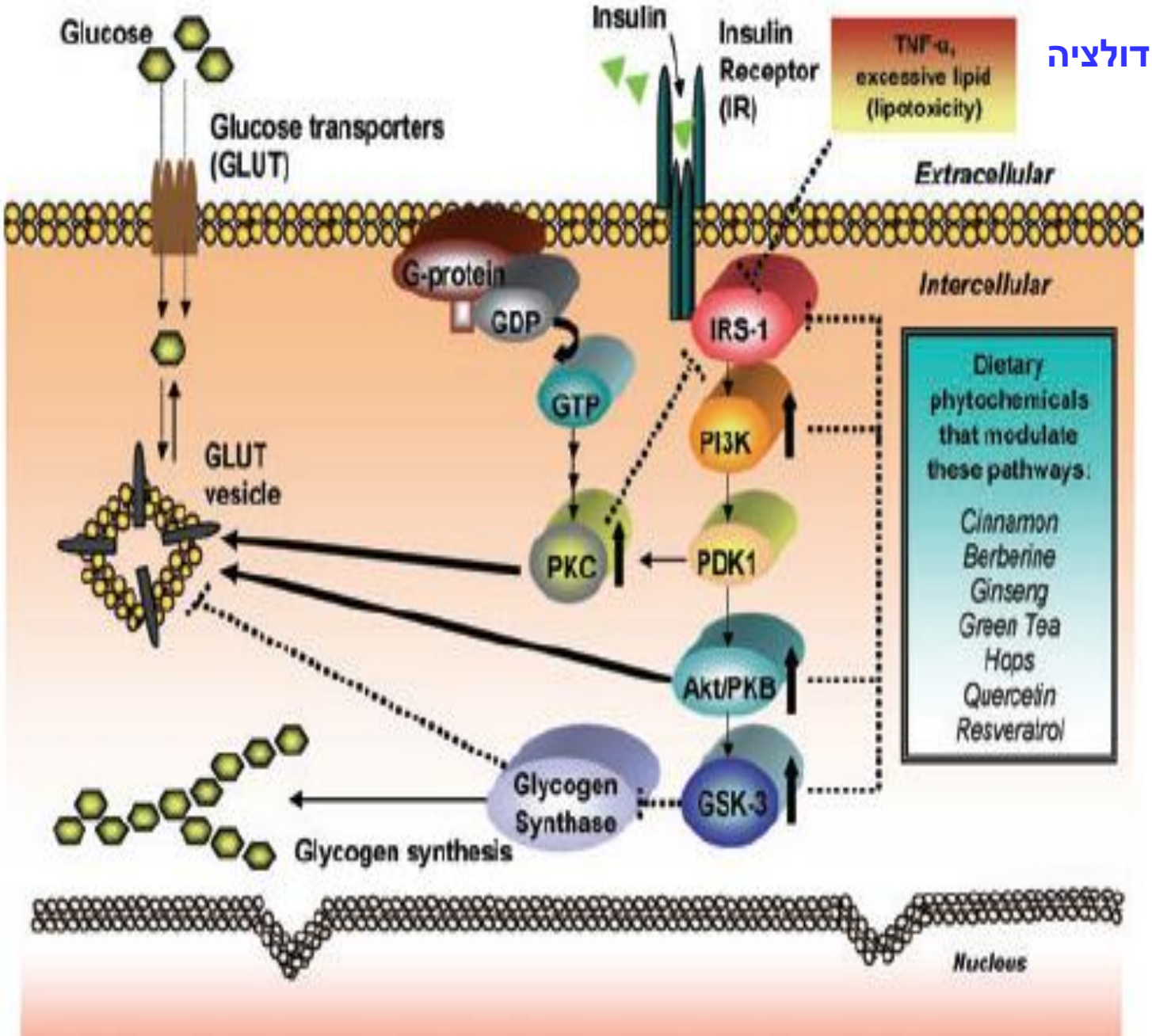


יכולה להיות מודולציה

Nutrition Reviews® Vol. 66(8):429–444

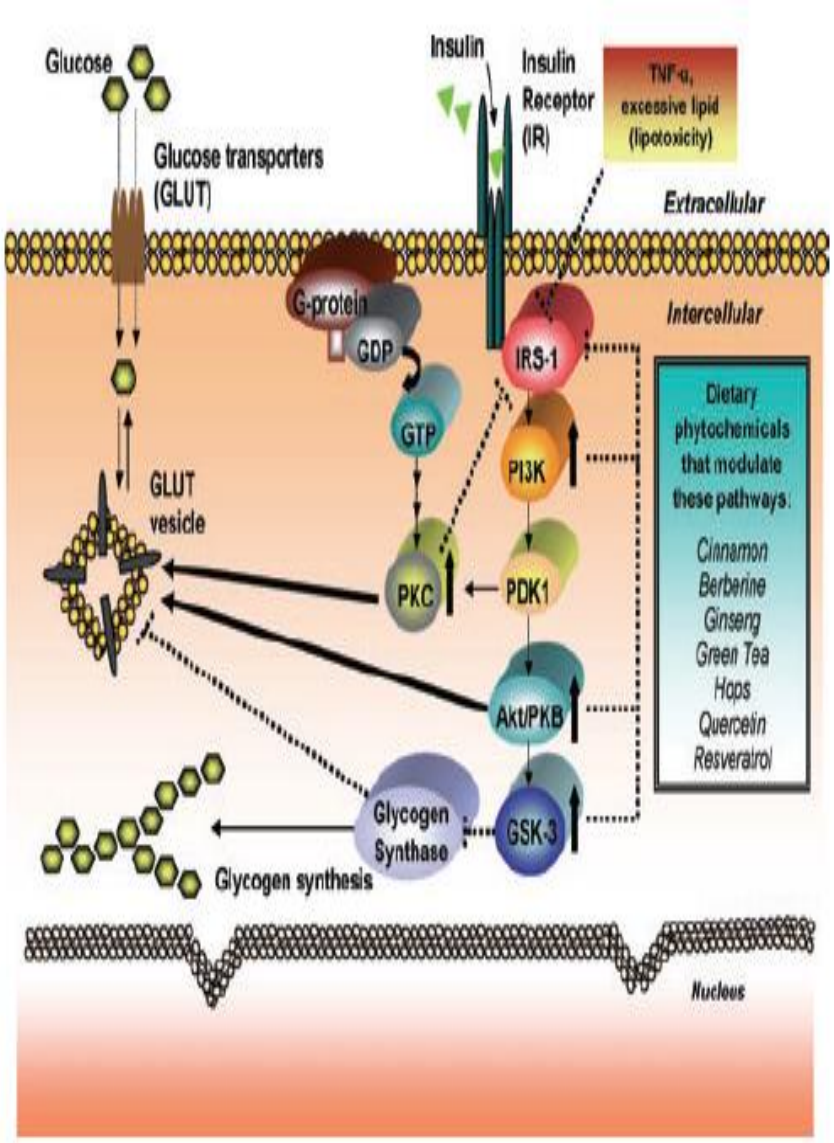
Table 1 **Modulation of the insulin pathway targets through phytochemicals.**

Phytochemical	Insulin pathway targets*				
	IR	IRS	PI3K	Akt/PKB	P
Resveratrol		X	X	X	
Quercetin			X	X	X
Cinnamon	X	X	X	X	
Green tea	X	X	X	X	
Bitter melon	X	X	X		
Berberine		X†		X†	
Ginseng	X				
Hops			X	X	X

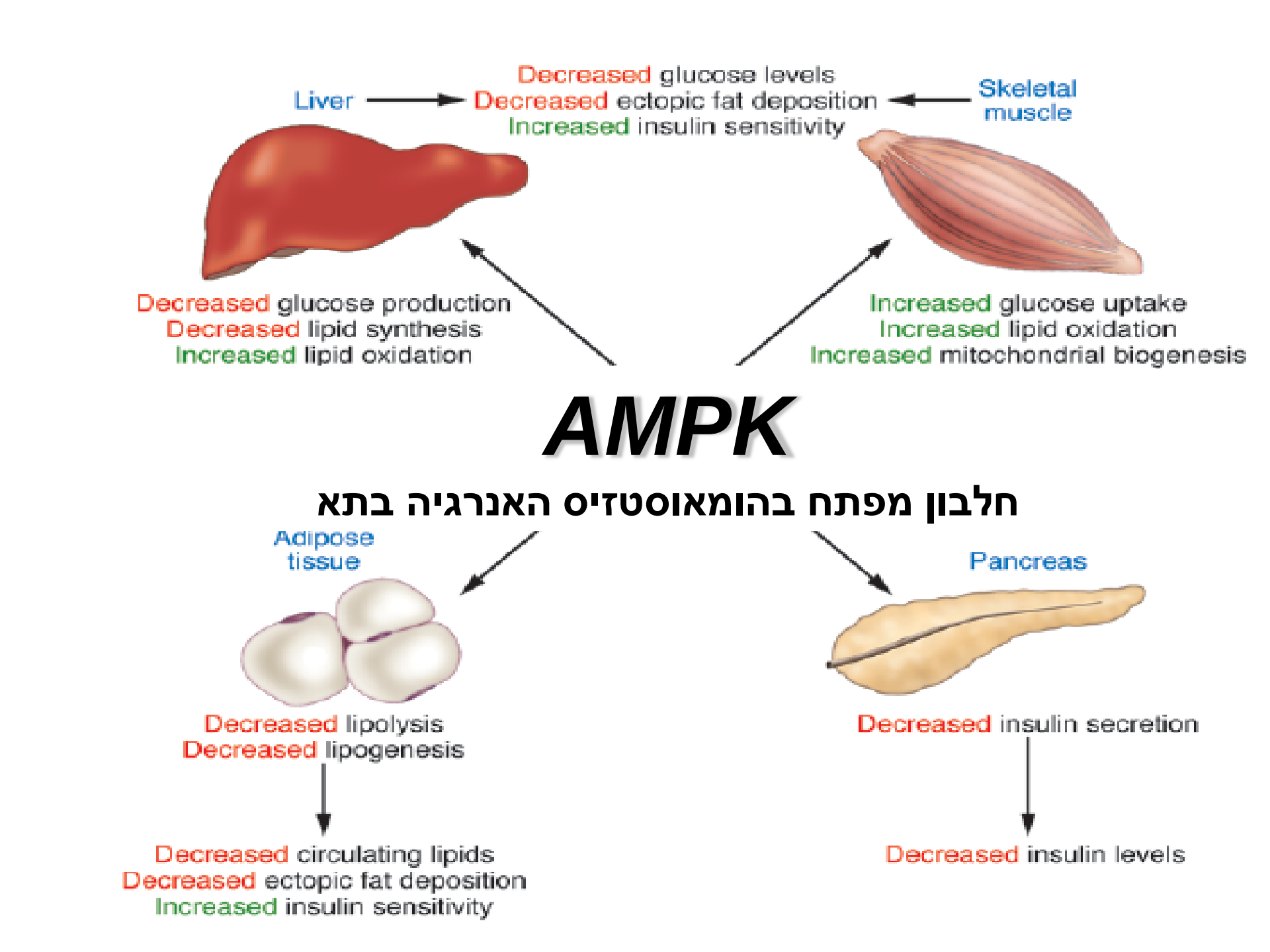
* Various phytochemicals have been shown to influence sel signaling cascade.

† In presence of insulin.[164]

Abbreviations: Akt/PKB, Akt/protein kinase B; GLUT, cellular glycogen synthase; GSK, glycogen synthase kinase; IR, insul receptor substrate; PKC, protein kinase C; PI3K, phosphatidy



5' adenosine monophosphate-activated protein kinase (AMPK): a key regulator of energy balance in the single cell and the whole organism


Decreased glucose levels
Liver
Decreased ectopic fat deposition
Increased insulin sensitivity
Skeletal muscle
Decreased glucose production
Decreased lipid synthesis
Increased lipid oxidation
Increased glucose uptake
Increased lipid oxidation
Increased mitochondrial biogenesis
AMPK
חלבון מפתח בהומאוסטזיס האנרגיה בתא
Adipose tissue
Pancreas
Decreased lipolysis
Decreased lipogenesis
Decreased insulin secretion
Decreased circulating lipids
Decreased ectopic fat deposition
Increased insulin sensitivity
Decreased insulin levels

PPARs control the expression of genes involved in adipogenesis, lipid metabolism, inflammation and maintenance of metabolic homeostasis

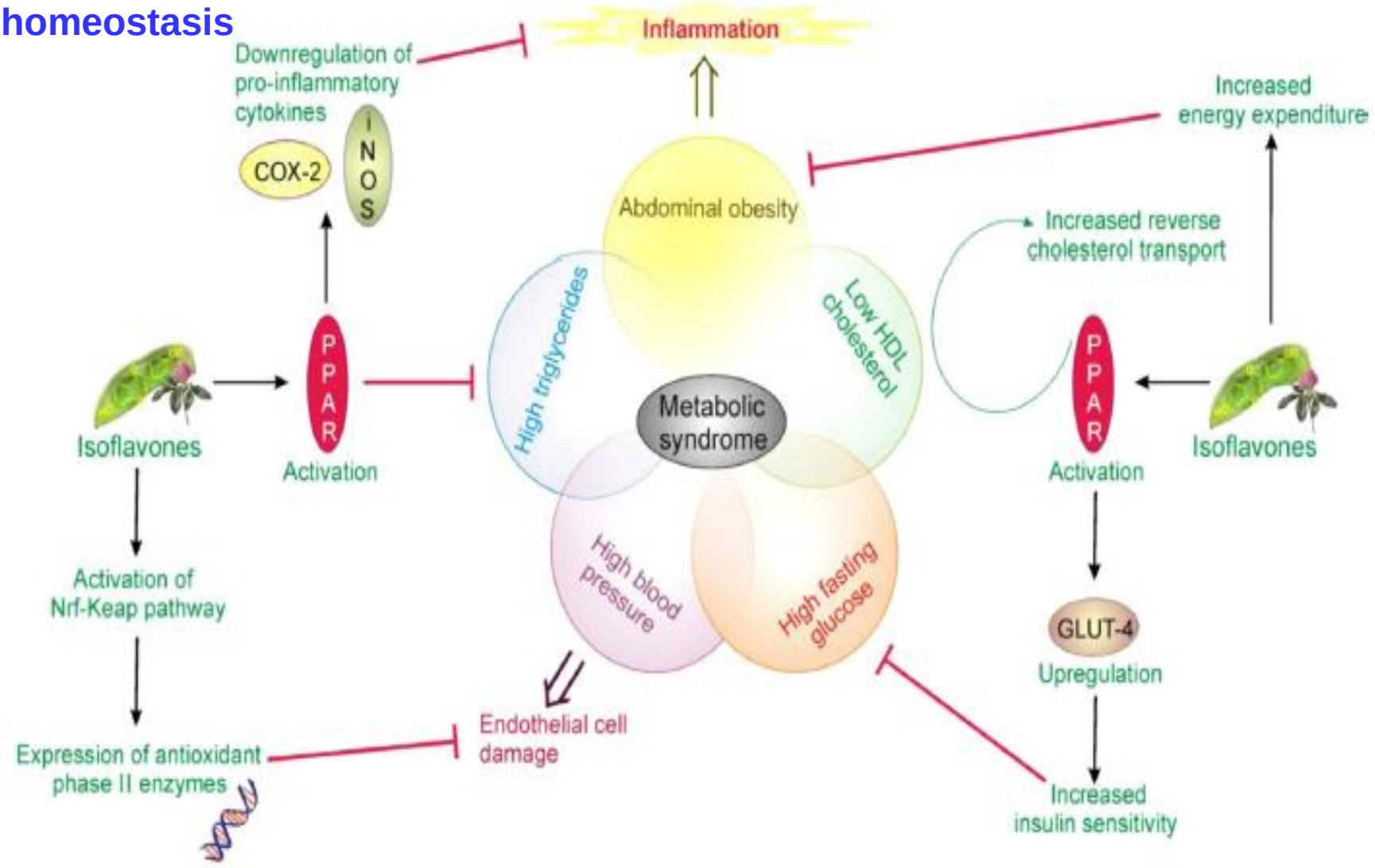
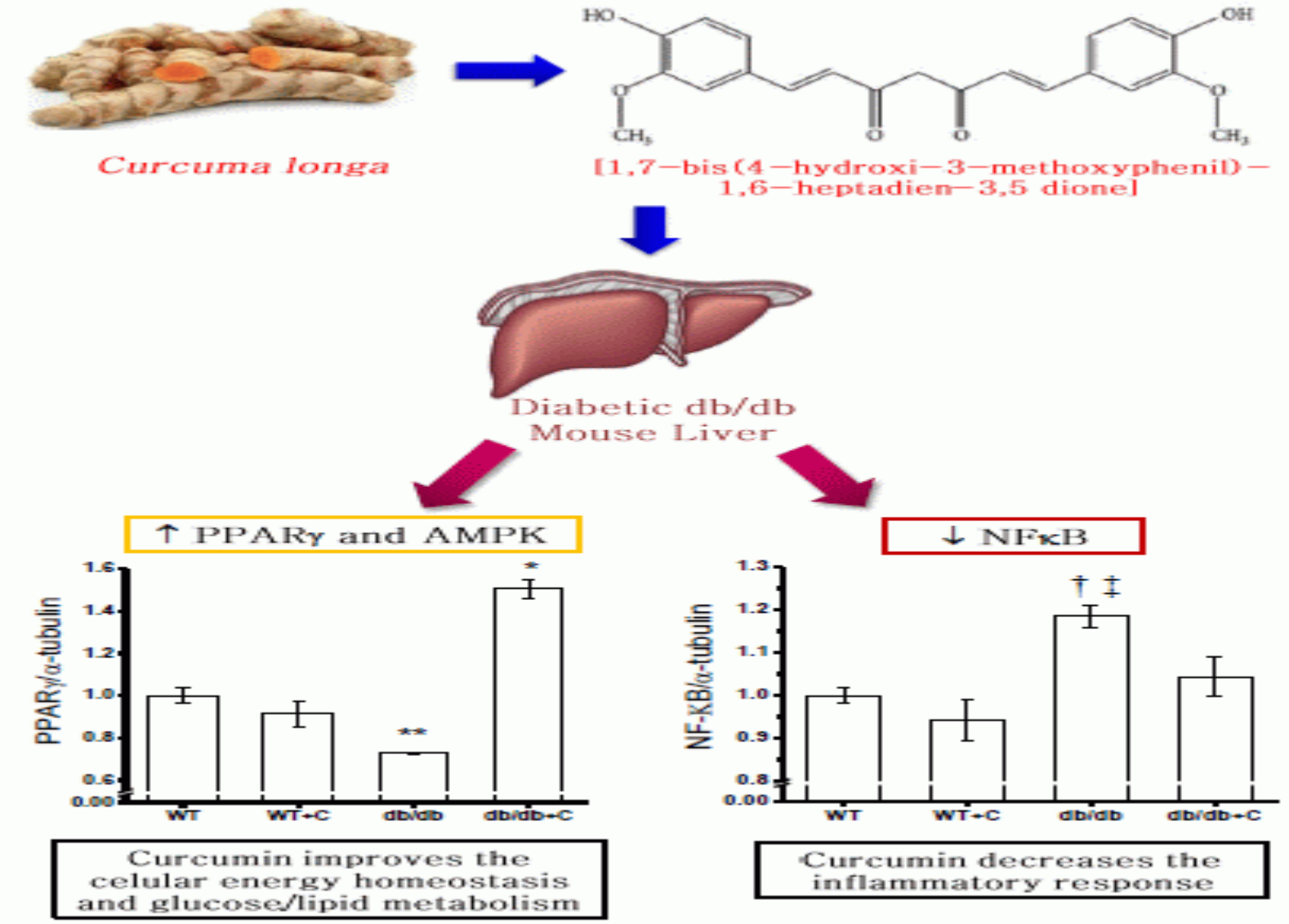
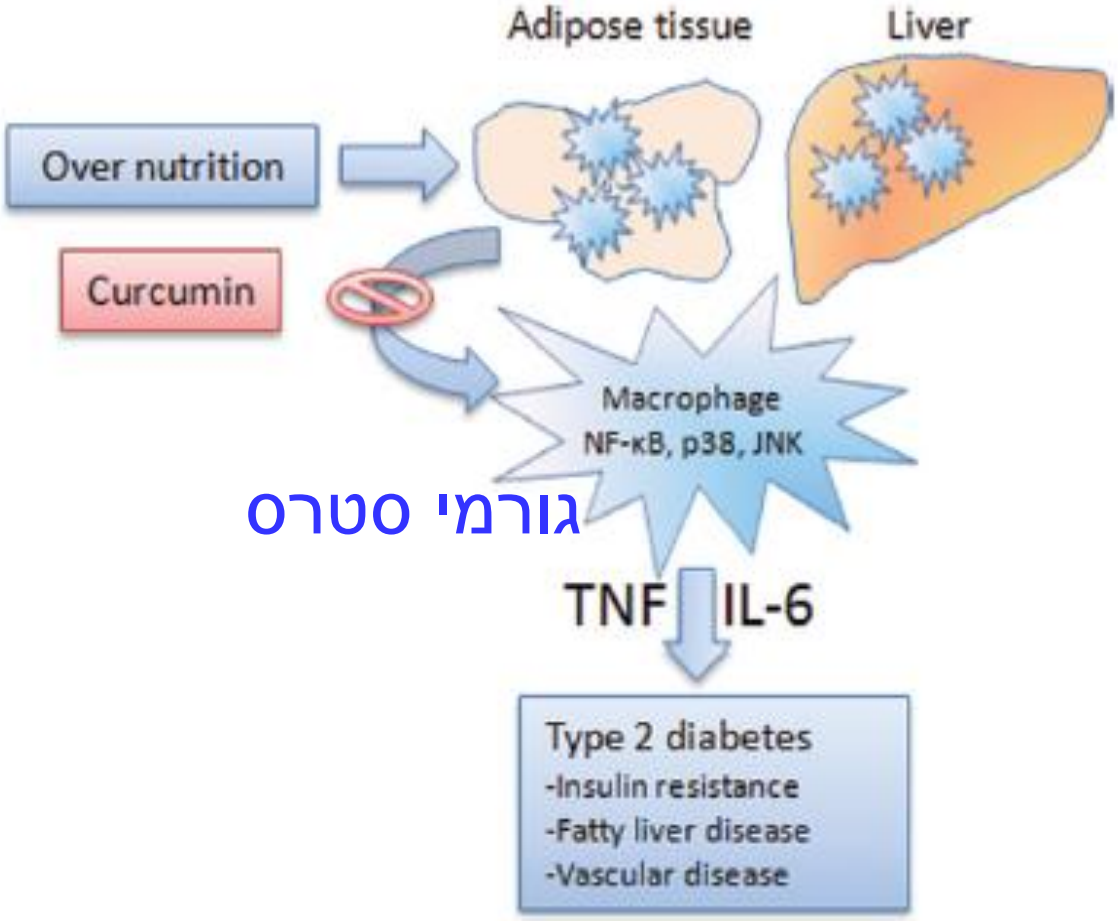


Fig. 2. Cellular/molecular mechanisms that explain the effects of phytoestrogens on the metabolic syndrome.



In conclusion, curcumin regulates the expression of AMPK, PPARγ, and NF-κB; suggesting a beneficial effect for treatment of T2DM complications. In order to observe best beneficial effects it is desirable to administer curcumin in the earlier states of T2DM. Molecules 2014, 19, 8289-8302



גורמי סטרס

Figure 1. Curcumin as a treatment for type 2 diabetes. Chronic obesity can lead to insulin resistance, fatty liver disease and vascular disease. Obesity is associated with increased numbers of pro inflammatory macrophages in metabolic tissue. Danger associated molecular patterns released from hypertrophied adipocytes or hepatocytes signal macrophages via stress activated pathways including NF-κB, p38 and c-Jun *N*-terminal kinases to produce TNF and IL-6 leading to impaired insulin signalling and insulin resistance. Curcumin prevents progression of type 2 diabetes by inhibiting stress activated pathways in macrophages and other cells leading to reduced inflammation.

Codonopsis lanceolata has been used as a complementary herbal medicine as an anti-oxidant, anti-inflammation, anti-adipogenesis, and anti-cancer agent in the Asia-Pacific region

כינוי: חלב עז, חלב ג'ינסנג, נקבה תפוח אדמה, הר קונכייה

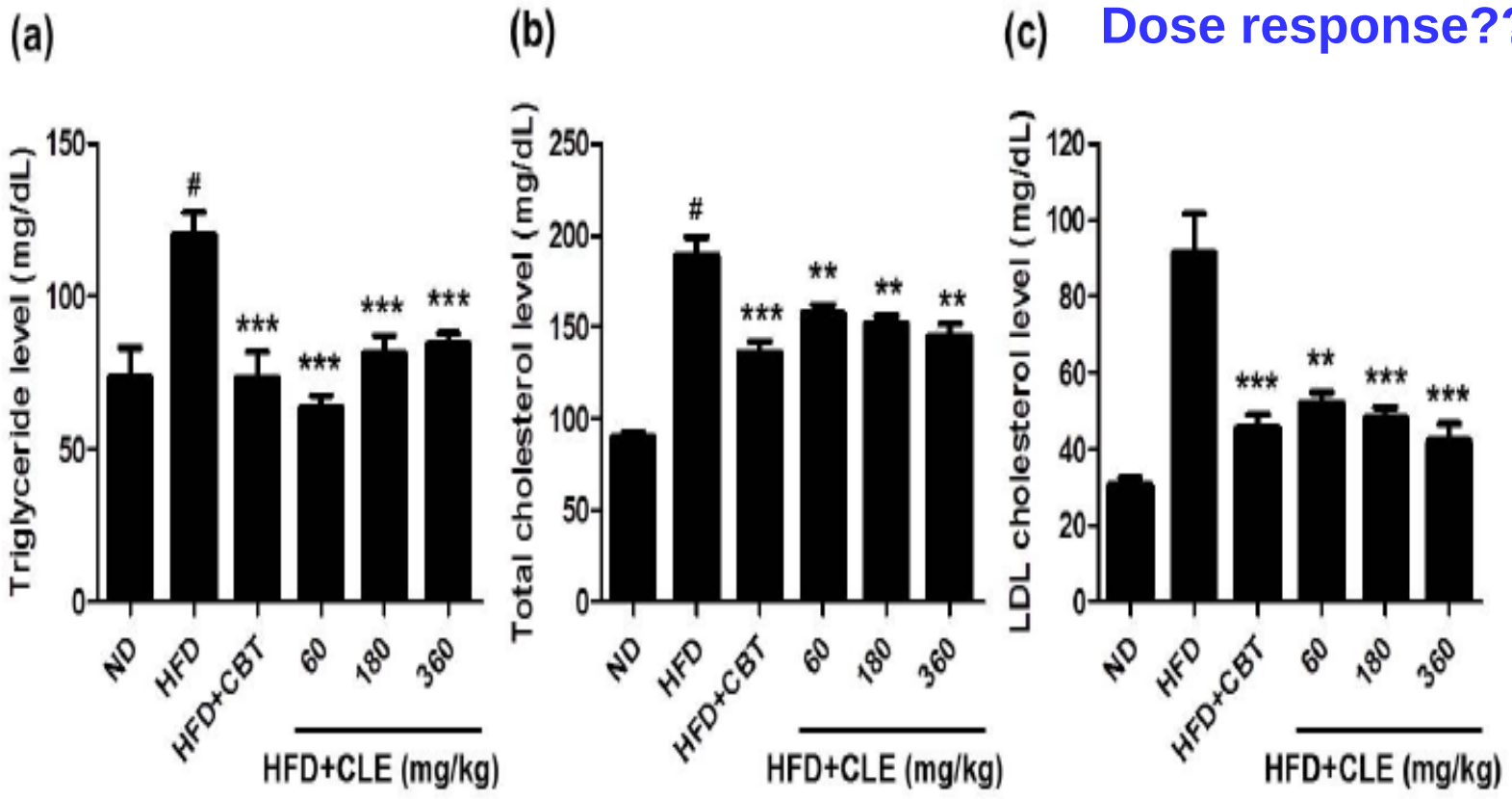
Recently, it has been reported that Codonopsis lanceolata regulates HFD-induced obesity in rats and also improves alcoholic-induced hepatic steatosis in rats

The current study was performed to determine whether dietary supplementation with C. lanceolata root extract (CLE) attenuates the development of obesity in C57BL/6 mice fed a HFD.

Codonopsis lanceolata

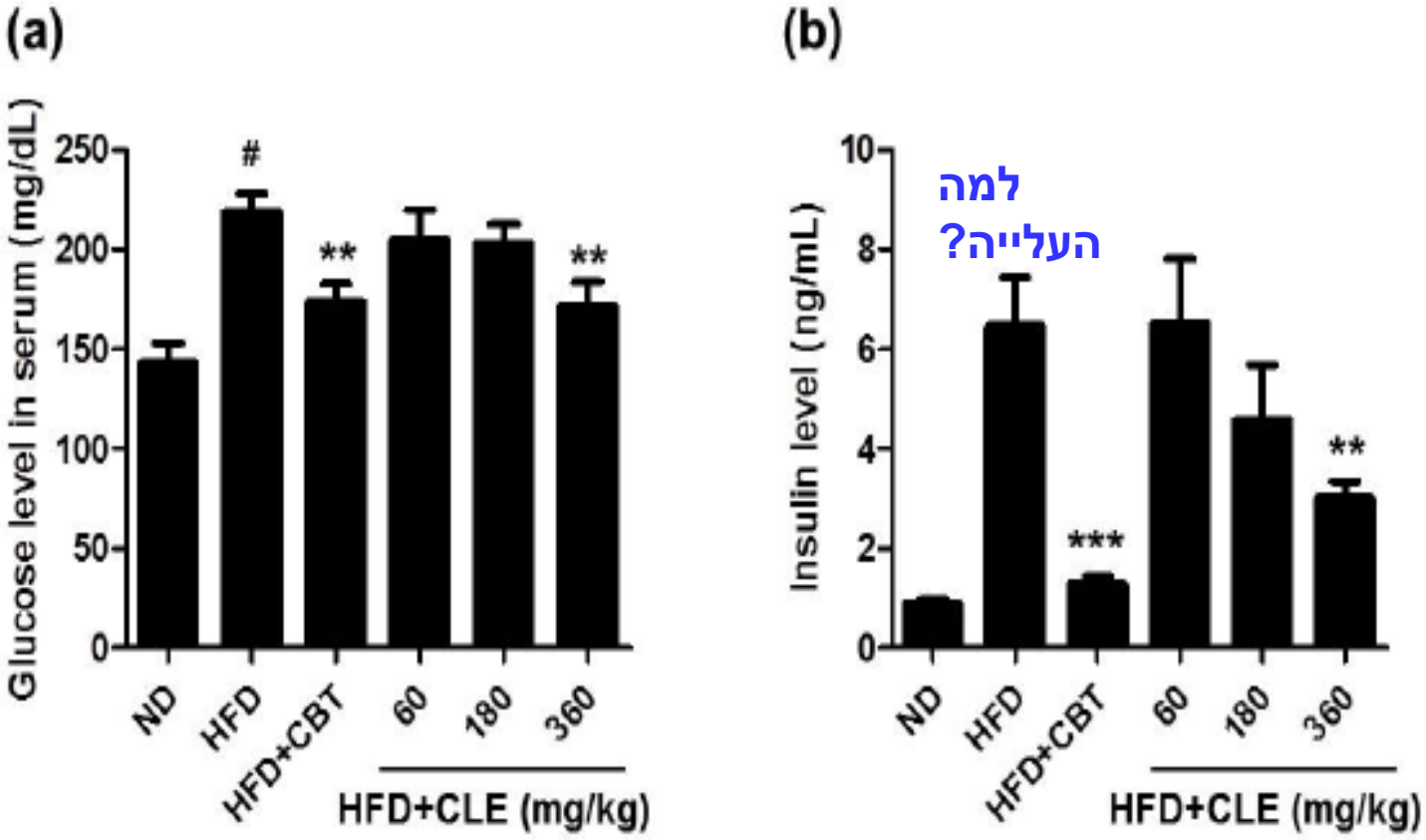
Figure 4. Effect of CLE on serum cholesterol levels of mice fed a HFD. (**a**) Serum triglyceride. (**b**) Serum total cholesterol. (**c**) Serum LDL cholesterol. The serum biochemical parameters were assessed in mice fed a ND, a HFD, a HFD with reductil (2 mg/kg), and a HFD with CLE (60, 180 and 360 mg/kg). Values are the mean ± SEM ($n = 10$), # $p < 0.05$ *vs.* ND-fed mice, ** $p < 0.01$, *** $p < 0.001$ *vs.* HFD-fed mice.

Dose response???

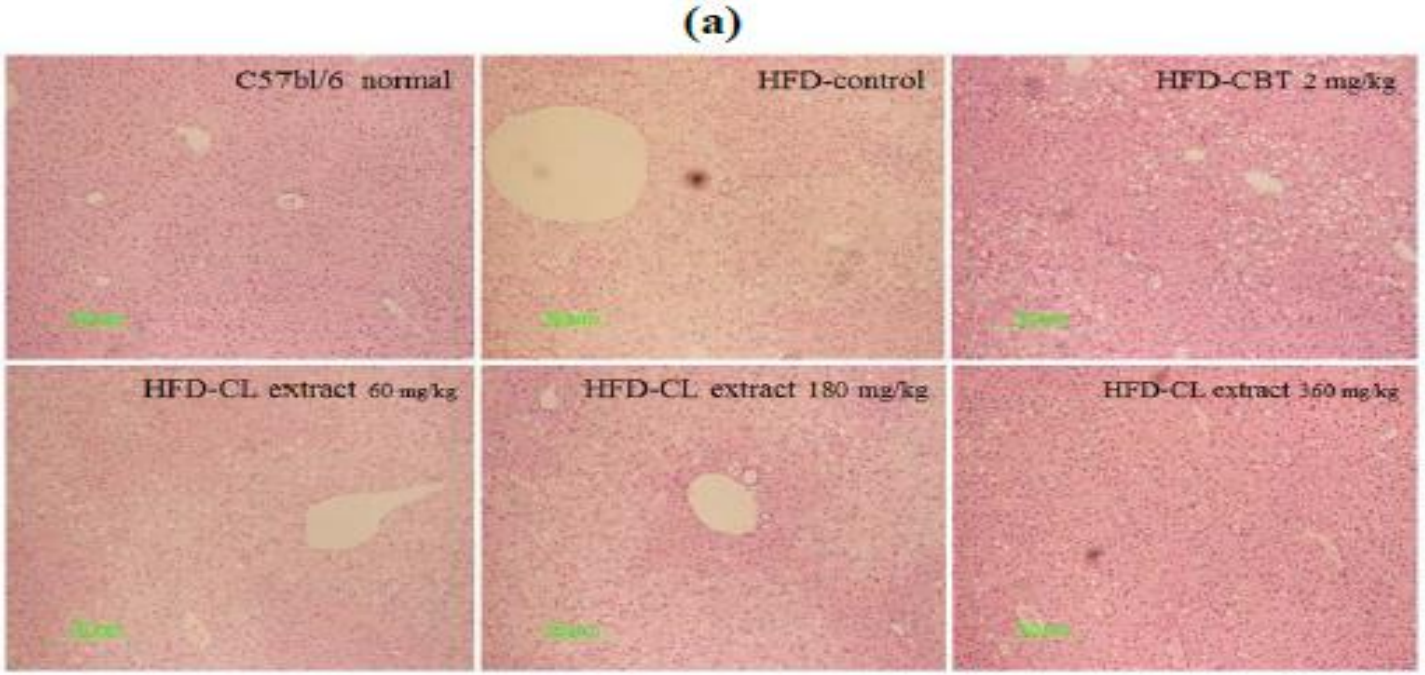


Codonopsis lanceolata

Figure 5. Effect of CLE on serum glucose and insulin levels of mice fed a HFD. (**a**) Serum glucose. (**b**) Serum insulin. Values are the mean ± SEM ($n = 10$), # $p < 0.05$ *vs.* ND-fed mice, ** $p < 0.01$, *** $p < 0.001$ *vs.* HFD-fed mice. ND: normal chow diet, HFD: 60% high fat diet + vehicle, HFD + CBT: 60% high fat diet + reductil (CBT, 2 mg/kg), HFD + CLE: 60% high fat diet + CLE (60, 180 and 360 mg/kg, respectively).



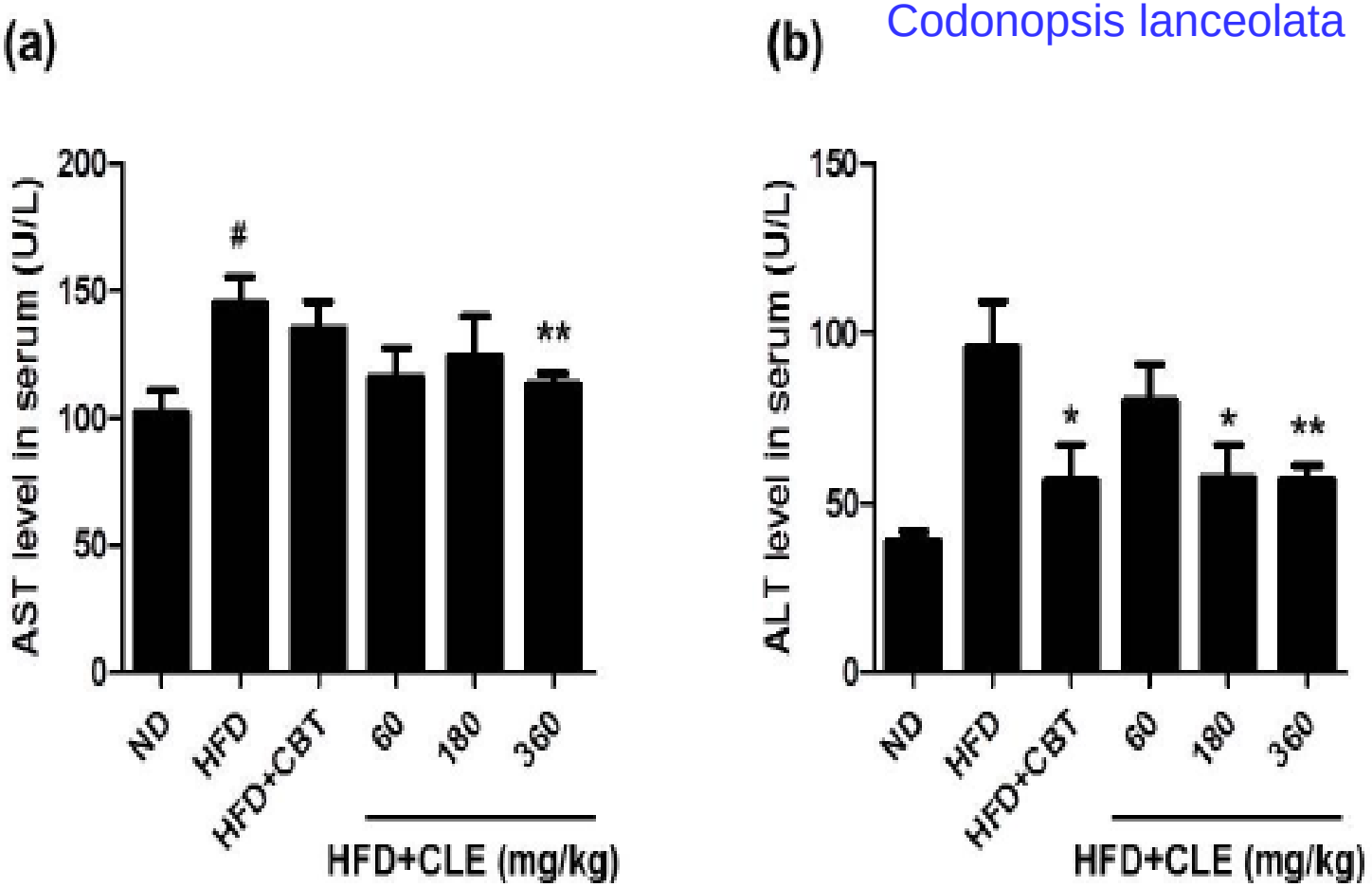
in HFD-fed mice. Values are the mean ± SEM (n = 10), * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ *vs.* HFD-fed mice.



Codonopsis lanceolata

Figure 7. Effect of CLE on serum AST and ALT levels of mice fed a HFD. (**a**) Serum AS
(**b**) Serum ALT. Values are the mean ± SEM ($n = 10$), # $p < 0.05$ *vs.* ND-fed mice, * $p < 0.$
** $p < 0.01$ *vs.* HFD-fed mice. ND: normal chow diet, HFD: 60% high fat diet + vehic
HFD + CBT: 60% high fat diet + reductil (CBT, 2 mg/kg), HFD + CLE: 60% high
diet + CLE (60, 180, and 360 mg/kg, respectively).

Codonopsis lanceolata



C57BL/6 mice fed with HFD for 12 weeks increased fatty liver, hyperglycemia, hyperinsulinemia, hypercholesterolemia, and high levels of serum AST and ALT as opposed to the normal control ND group. CLE supplementation reduced serum TG, TC, glucose, and insulin levels in HDF-fed mice. Altogether, CLE had marked effects on inhibiting the development of obesity and hyperlipidemia in obese C57BL/6 mice fed HFD.

DOSE RESPONSE:מסרון

These findings suggest that Codonopsis lanceolata as a complementary herbal medicine may attenuate some of the physiological changes that occur in obesity induced by HFD.

Red clover is a legume, which like soy contains "phytoestrogens" (plant-based chemicals that are similar to estrogen and may act in the body like estrogen or may actually block the effects of estrogen).

Isofavone derived from Red clover

היתרון של הפרסום

European Journal of Clinical Nutrition (2014), 1–9

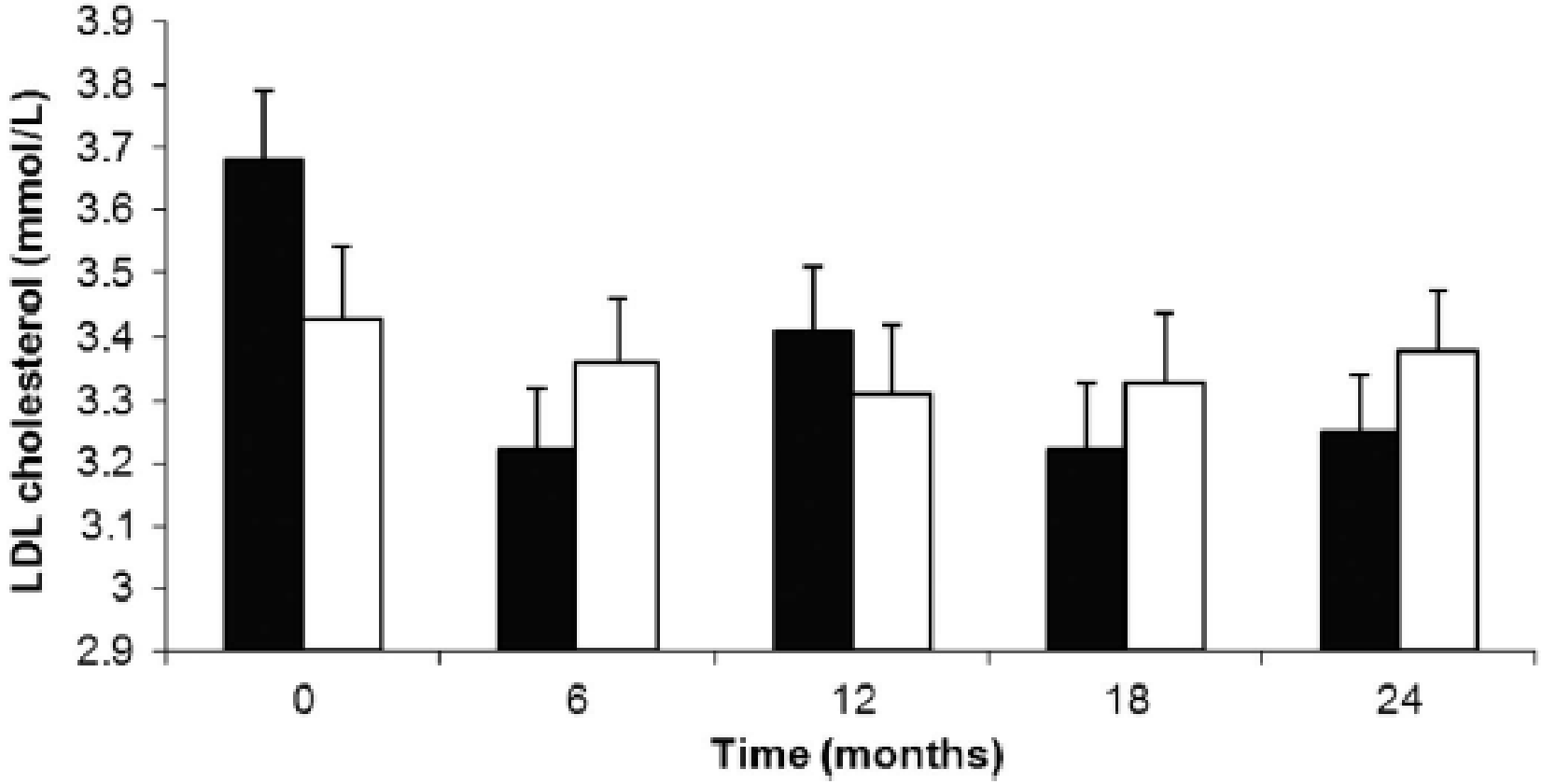
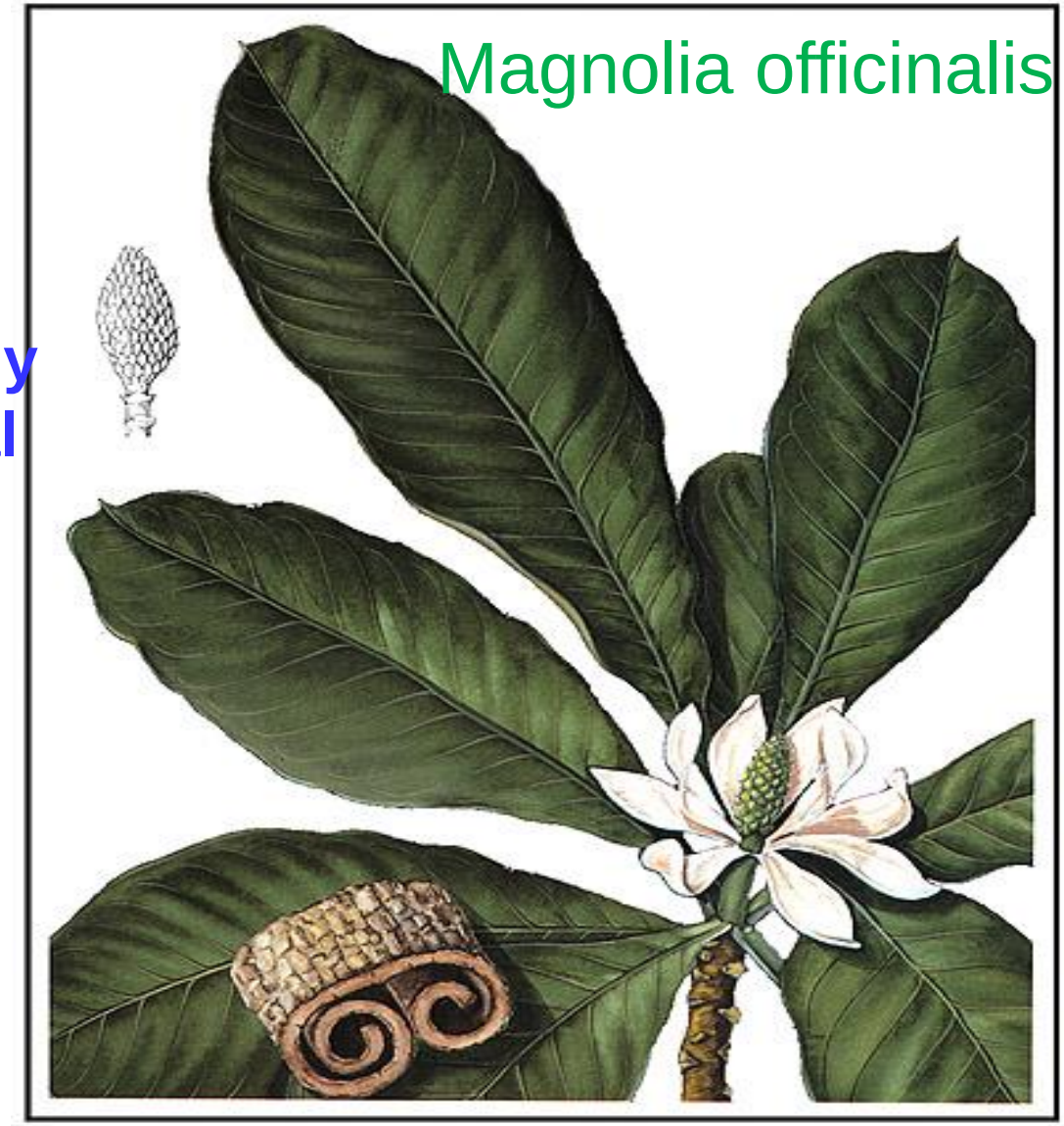


Figure 2. LDL cholesterol measurements by time in the active treatment group (closed bars) and the placebo group (open bars). Using a linear mixed-effects model, there was significant evidence of a difference between treatments in the within-patient change observed over time ($P = 0.005$).

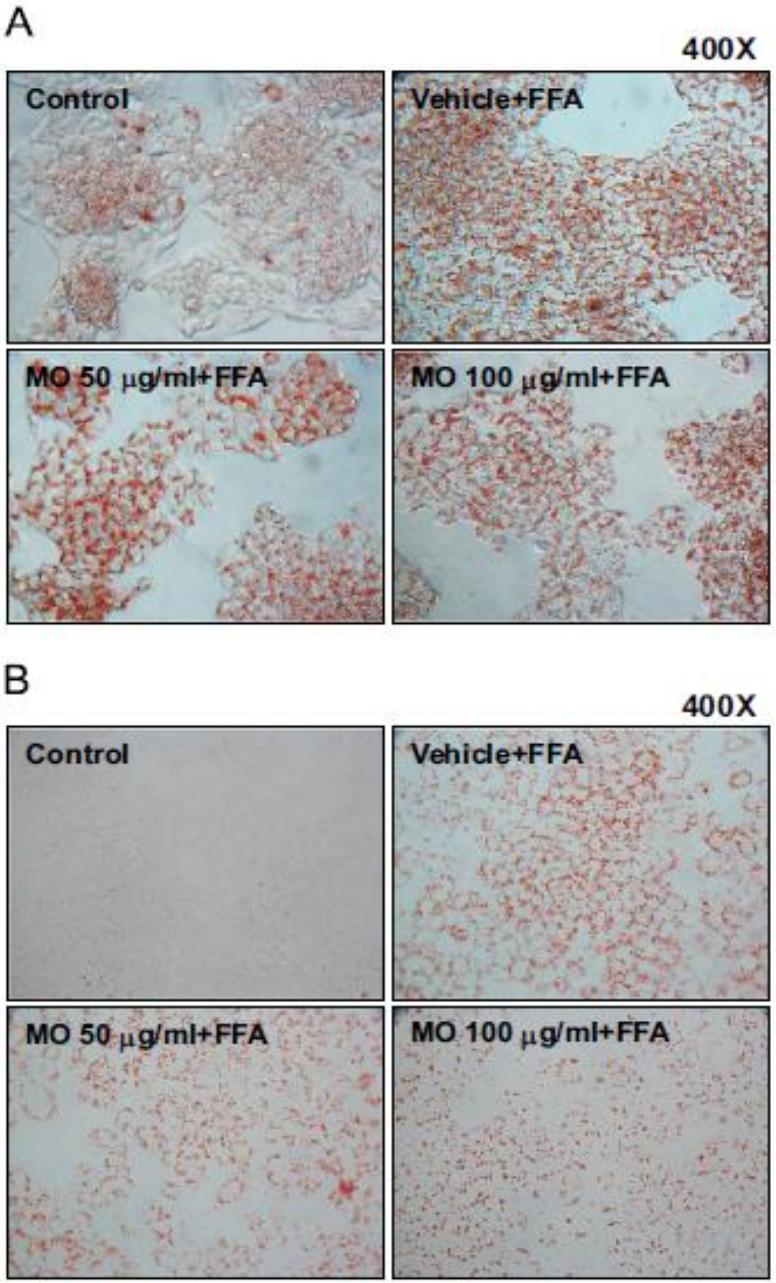
Magnolia bark is a highly aromatic herbal material obtained from Magnolia officinalis of the Family Magnoliaceae

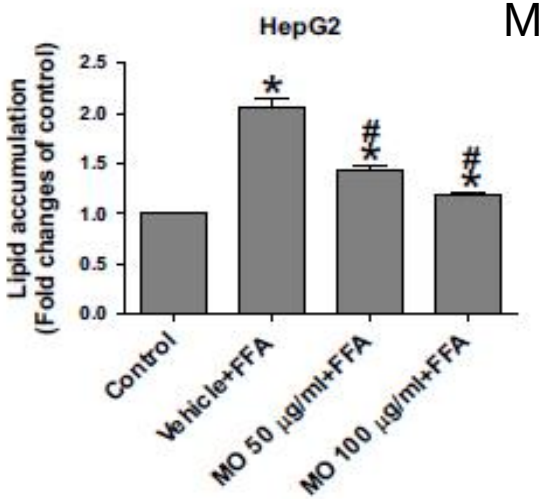


ניצול קוי תאים למחקר של צמחי מרפא

Journal of Ethnopharmacology 157 (2014) 140–148

Magnolia bark





DOSE RESPONSE?

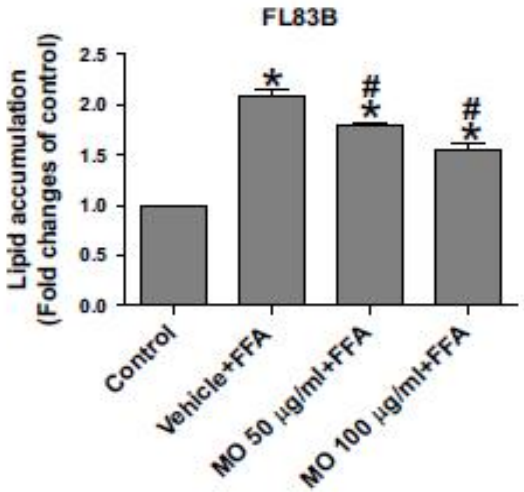
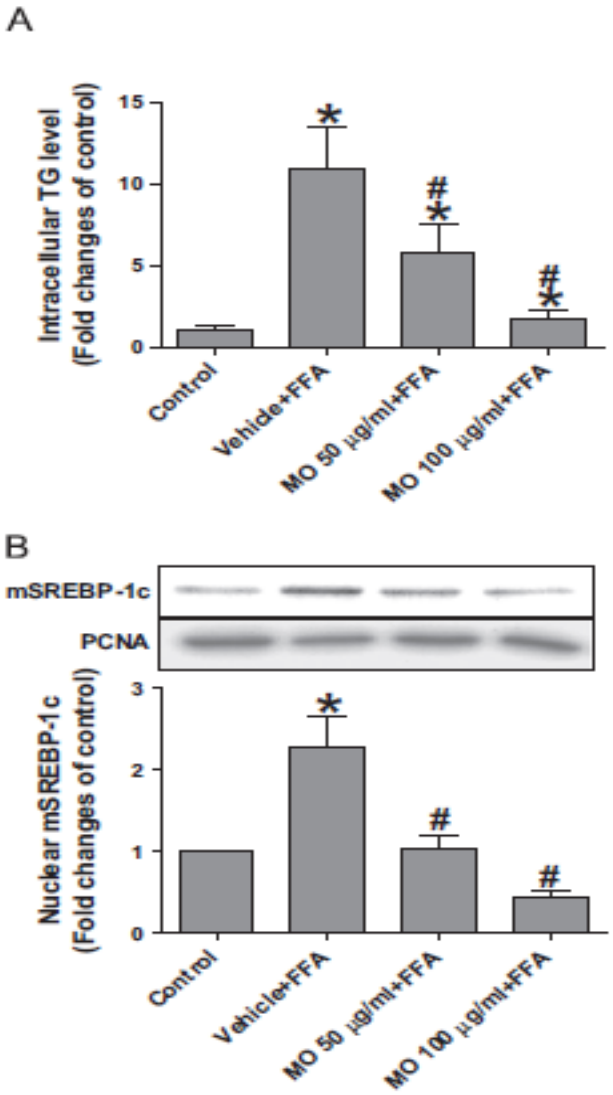
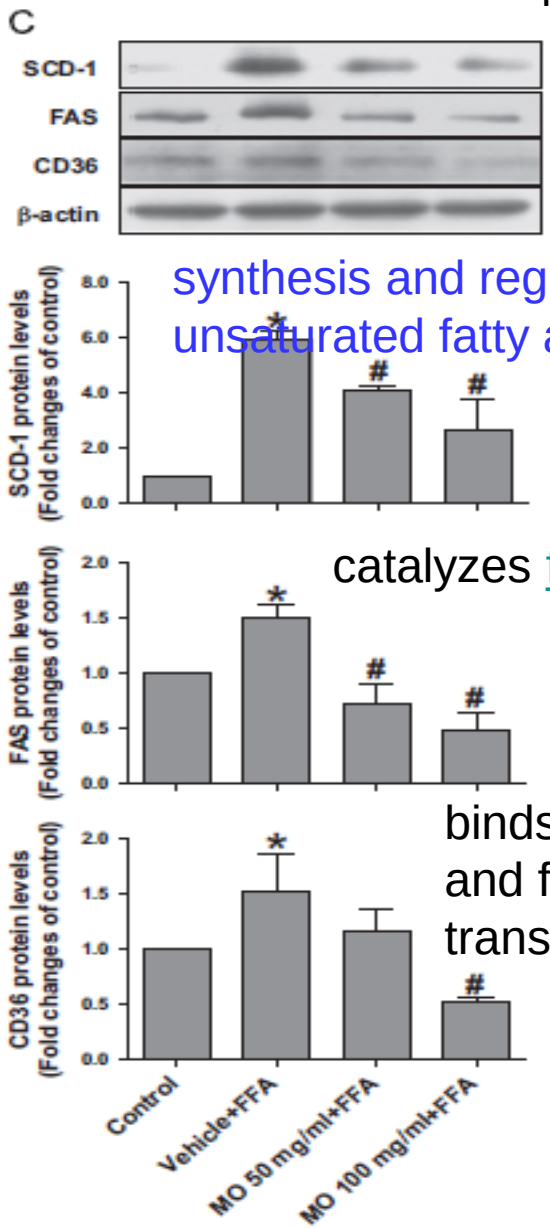


Fig. 3. MO inhibits the lipid accumulation in HepG2 (A) and FL83B (B) cells treated with FFA mixture. Both HepG2 and FL83B cells were treated with 0.5 mM FFA mixture for 24 h and MO (50 or 100 μg/ml) was pretreated 1 h prior to FFA mixture treatment. Control cells were treated with 1% BSA. Cells were stained with Oil Red O and analyzed using spectrometer at 545 nm. Photographs (magnification 400×) are representative images of 3 independent experiments. Data are presented as the mean ± SEM. $^{*}P < 0.05$ vs. control cells, $^{\#}P < 0.05$ vs. vehicle + FFA-treated cells.

Magnolia bark





synthesis and regulation of unsaturated fatty acids

catalyzes fatty acid synthes

binds long-chain fatty and facilitates their transport into cells

key regulator of lipid homeostasis

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Fig. 4. MO inhibits the increase in intracellular TG level (A), the nuclear expression of SREBP-1c (B), and the protein expressions of SCD-1, FAS, and CD36 (C). HepG2 cells were treated with 0.5 mM FFA mixture for 24 h and MO (50 or 100 μg/ml) was pretreated 1 h prior to FFA mixture treatment. Control cells were treated with 1% BSA. Data are presented as the mean ± SEM. *$P < 0.05$ vs. control cells, #$P < 0.05$ vs. vehicle+ FFA-treated cells.

Magnolia bark

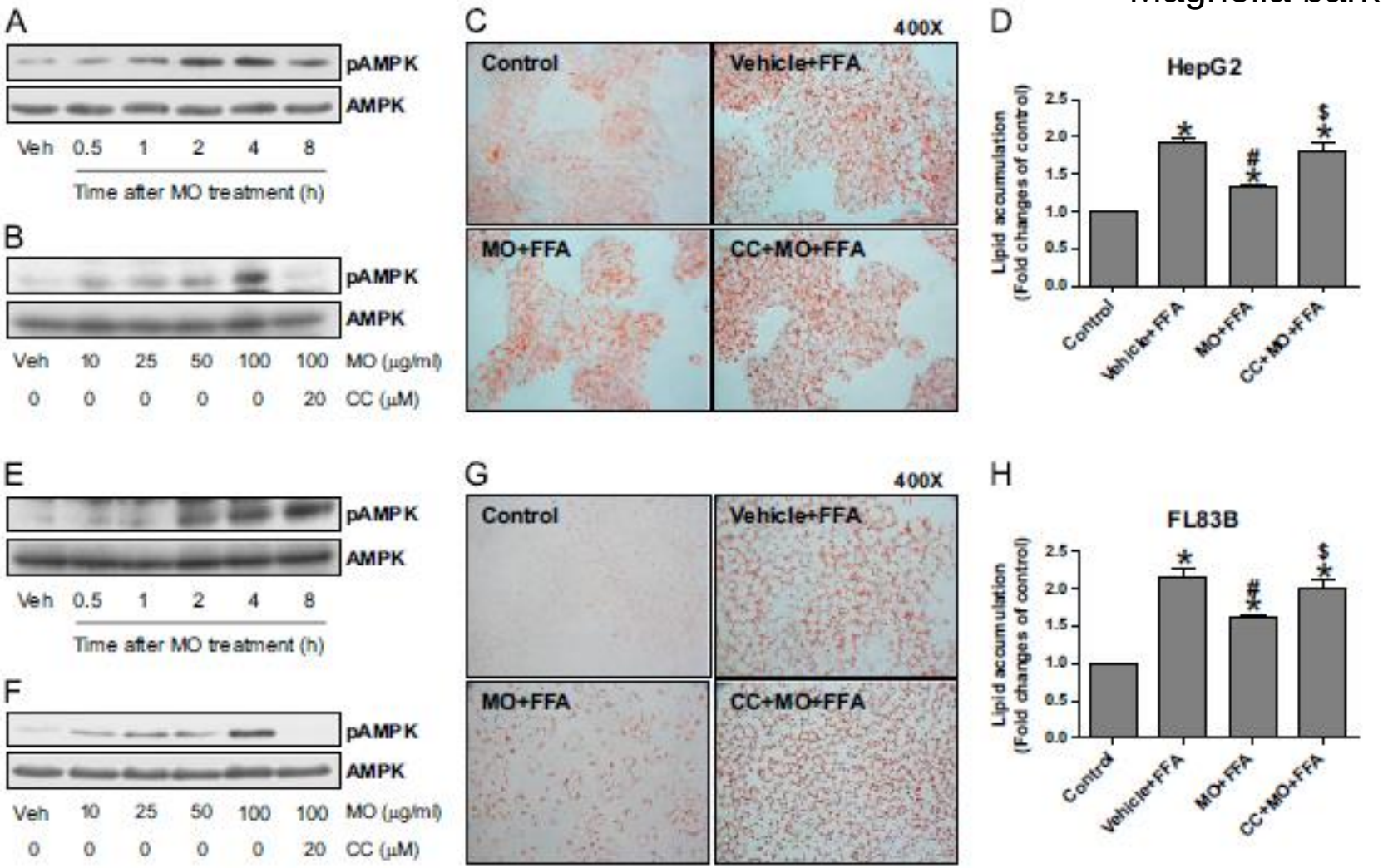

Fig. 5. AMPK mediates the inhibitory effect of MO on lipid accumulation in HepG2 (A–D) and Fl83B (E–H) cells treated with FFA mixture. (A and E) Cellular extracts were collected at the indicated times after treatment of MO (100 μg/ml). (B and F) Cellular extracts were collected at 4 h after MO treatment (10–100 μg/ml). pAMPK and AMPK levels were determined by western blot analysis. (C, D, G, and H) The cells were treated with 0.5 mM FFA mixture for 24 h and MO (100 μg/ml) was treated 1 h prior to FFA mixture exposure. The cells were stained with Oil Red O and analyzed using a spectrometer at 545 nm. 0.1% DMSO was treated as a vehicle for MO, and control cells were treated only with 1% BSA. Compound C (CC) was pretreated 30 min prior to MO treatment. Photographs (magnification 400X) are representative images of 3 independent experiments. Data are presented as the mean ± SEM. *$P < 0.05$ vs. control cells, #$P < 0.05$ vs. vehicle+FFA-treated cells, $$P < 0.05$ vs. MO+FFA-treated cells.

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Magnolia bark

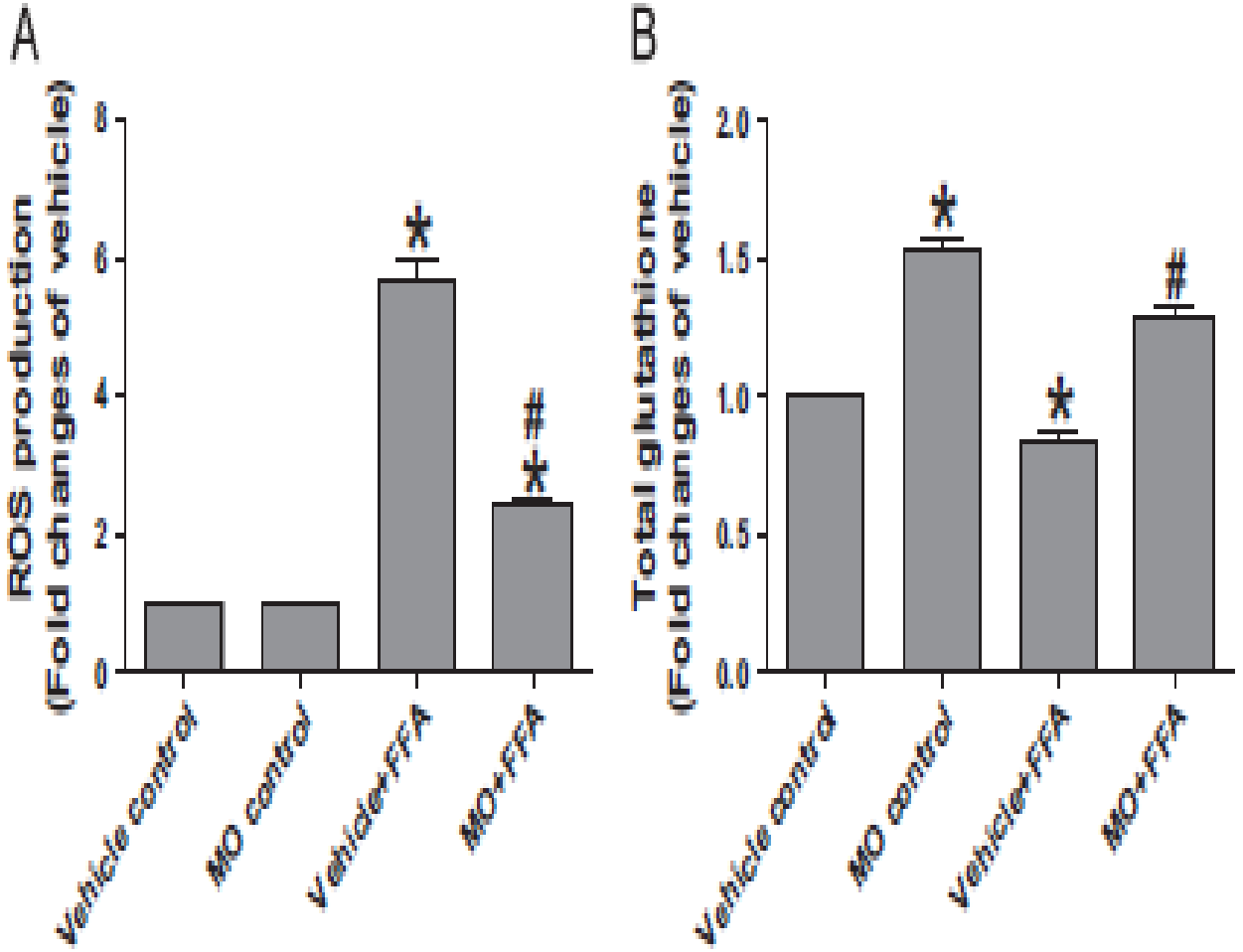

Fig. 7. Effect of MO on ROS production (A) and total glutathione level (B) in HepG2 cells treated with FFA mixture. HepG2 cells were treated with 0.5 mM FFA mixture for 24 h and MO (100 μg/ml) was treated 1 h prior to FFA mixture exposure. Data are presented as the mean ± SEM. *$P < 0.05$ vs. vehicle control cells, #$P < 0.05$ vs. vehicle + FFA cells.

הבסיס המוליקולרי

Magnolia bark triglyceride biosynthesis and accumulation induced by FFAs in hepatocytes, suggesting its pharmacological potential for the prevention of nonalcoholic fatty liver disease. These effects may be mediated by the inhibition of SREBP-1c via AMPK phosphorylation

סה"כ נסויים עם רסברטרול

man		
ainen, 2010 [128]	Randomized, double-blinded, placebo-controlled trial. Healthy obese men (n = 24). Groups including placebo group or RSV group for 4 weeks.	— Blood pressure, resting energy expenditure, oxidation rates of lipid, ectopic or visceral fat content or inflammatory and metabolic biomarkers
mmers, 2011 [124]	Randomized, placebo-controlled, double-blinded crossover study. Healthy, obese men subjects (n = 11). Groups including placebo group or RSV group (150 mg/day) for 30 days.	↓ Sleeping and resting metabolic rate ↓ Glucose, insulin, HOMA-IR, leptin ↑ Muscle mitochondrial respiration (↑ AMPK, SIRT1 and PGC-1α protein levels in muscle) ↑ Intramyocellular lipid levels ↓ Adipose tissue lipolysis, plasma FA and TG, intrahepatic lipid content, ALT ↑ Citrate synthase activity ↓ Inflammation markers (TNF-α, leukocytes, ALAT)
me-Carneiro, 2012 [125]	Triple-blinded, randomized, parallel, dose–response, placebo-controlled, 6-month follow-up trial. Patients (n = 75) on statin and at high CVD risk status. Groups including placebo, RSV (RSV-rich grape supplement; 8 mg RSV) or grape supplement group (lacking RSV) for 6 months.	— Hepatic, thyroid and renal function. ↓ LDL-cholesterol, ApoB, LDLox and LDLox/ApoB ↑ non-HDLc/ApoB
me-Carneiro, 2013 [126]	Triple-blinded, randomized, parallel, dose–response, placebo-controlled, 1-year follow-up trial. Patients (n = 75) on statin and at high CVD risk status. Groups including placebo, RSV (RSV-rich grape supplement; 8 mg RSV) or grape supplement group (lacking RSV) for the first 6 months and a double dose for the next 6 months.	↓ Inflammatory and fibrinolytic biomarkers (↓ PAI-1) ↑ Serum adiponectin ↑ Inflammation-related transcription factor (↑ KLF2) ↓ Inflammation-related transcription factor (↓ NF-κB, Ap-1, JUN, ATF-2, CREBBP) ↓ 27 extracellular-space acting genes involved in inflammation, cell migration and T-cell interaction signals in PBMCs
me-Carneiro, 2013 [127]	Triple-blinded, randomized, parallel, dose–response, placebo-controlled, 1-year follow-up trial. Patients (n = 75) on statin and at high CVD risk status. Groups including placebo, RSV (RSV-rich grape supplement; 8 mg RSV) or grape supplement group (lacking RSV) for the first 6 months and a double dose for the next 6 months.	↓ Inflammation (↓ hs-CRP, TNF-α, PAI-1, IL-6/IL-10 ratio, sICAM-1) ↑ Anti-inflammation (↑ IL-10) ↑ Adiponectin

מתוך 20 נסויים בבני אדם עם תה

Table 3 (continued)

First author, year [ref]	Experimental design and treatments	Results
Nagao, 2005	Double-blinded study.	↓ BW, BMI, body FM, subcutaneous fat area, waist
[73]	Normal to overweight male (n = 17–18, 24–46 years) in Japan.	circumference
	Groups including control group (22 mg GTC/day) or GTC group (690 mg GTC/day)	↑ Skin total chlorophyll
	for 12 weeks.	↓ MDA-modified LDL
Nagao, 2007	Randomized double-blinded controlled parallel multicenter trial.	↓ BW, BMI, body fat ratio, body FM, waist and hip
[72]	Obese subjects (n = 240, 25–65 years) in Japan.	circumference, visceral fat area and subcutaneous fat area
	Groups including control group (96 mg catechins/day) or catechin group	↓ SBP
	(583 mg catechins/day) for 12 weeks.	↓ LDL-C
Sutherland, 2012	Prospective, randomized, double-blind design.	↓ BMI, waist circumference, glucose
[74]	Obese subjects (n = 46, 30–40 years) in Poland.	— SBP, DBP, HDL-C, glucose
	Groups including placebo group or GT group (379 mg GTE, 208 mg EGCG daily)	— Serum Fe, Cu, Cr, mg
	for 3 months.	↓ TC, LDL-C, TG
		↑ Total antioxidant level (↑ serum Zn)
Thielecke, 2010	Randomized, double-blinded crossover study.	— Energy expenditure
[75]	Healthy overweight/obese men (n = 10, 20–40 years) in Germany.	↓ RQ
	Groups including placebo group, low EGCG group (300 mg daily), high EGCG group	↑ Postprandial fat oxidation rate (EGCG/caffeine group only)
	(600 mg daily), caffeine group (200 mg daily) or EGCG/caffeine group	↓ Carbohydrate oxidation rate (EGCG/caffeine group only)
	(300 mg/200 mg daily) for 3 days.	
Wang, 2010	Randomized, placebo-controlled trial.	↓ Total body fat and fat % in a dose-dependent manner
[76]	Moderately overweight Chinese subjects (n = 182, 18–55 years).	↓ Intra-abdominal fat area, waist circumference in GTD group
	Groups including control group (30 mg catechins, 10 mg caffeine/day), GTI group	
	(458 mg catechins, 106 mg caffeine/day), GTD group (468 mg catechins, 126 mg	

כורכום

Human		
Poulsen, 2013 [120]	Randomized, double-blinded, placebo-controlled trial. Healthy obese men (n = 24). Groups including placebo group or RSV group for 4 weeks.	— Blood pressure, resting energy expenditure, oxidation rates of lipid, acetate or vitamin E concentrations or inflammatory and metabolic biomarkers
Timmers, 2011 [124]	Randomized, placebo-controlled, double-blinded crossover study. Healthy, obese men subjects (n = 11). Groups including placebo group or RSV group (150 mg/day) for 30 days.	↓ Sleeping and resting metabolic rate ↓ Glucose, insulin, HOMA-IR, leptin ↑ Muscle mitochondrial respiration (↑ AMPK, SIRT1 and PGC-1α protein levels in muscle) ↑ Intramyocellular lipid levels ↓ Adipose tissue lipolysis, plasma FA and TG, intrahepatic lipid content, ALT ↑ Citrate synthase activity ↓ Inflammation markers (TNF-α, leukocytes, ALAT)
Torres-Carneiro, 2012 [125]	Triple-blinded, randomized, parallel, dose–response, placebo-controlled, 6-month follow-up trial. Patients (n = 75) on statin and at high CVD risk status. Groups including placebo, RSV (RSV-rich grape supplement, 8 mg RSV) or grape supplement group (lacking RSV) for 6 months.	— Hepatic, thyroid and renal function. ↓ LDL-cholesterol, ApoB, LDLox and LDLox/ApoB ↑ non-HDLc/ApoB
Torres-Carneiro, 2013 [126]	Triple-blinded, randomized, parallel, dose–response, placebo-controlled, 1-year follow-up trial. Patients (n = 75) on statin and at high CVD risk status. Groups including placebo, RSV (RSV-rich grape supplement, 8 mg RSV) or grape supplement group (lacking RSV) for the first 6 months and a double dose for the next 6 months.	↓ Inflammatory and fibrinolytic biomarkers (↓ PAI-1) ↑ Serum adiponectin ↑ Inflammation-related transcription factor (↑ KLF2) ↓ Inflammation-related transcription factor (↓ NF-κB, Ap-1, JUN, ATF-2, CEBPBP) ↓ 27 extracellular-space acting genes involved in inflammation, cell migration and T-cell interaction signals in PBMCs
Torres-Carneiro, 2013 [127]	Triple-blinded, randomized, parallel, dose–response, placebo-controlled, 1-year follow-up trial. Patients (n = 75) on statin and at high CVD risk status. Groups including placebo, RSV (RSV-rich grape supplement, 8 mg RSV) or grape supplement group (lacking RSV) for the first 6 months and a double dose for the next 6 months.	↓ Inflammation (↓ hs-CRP, TNF-α, PAI-1, IL-6/IL-10 ratio, sICAM-1) ↑ Anti-inflammation (↑ IL-10) ↑ Adiponectin

Liver Injury From Herbals and Dietary Supplements in the U.S. Drug-Induced Liver Injury Network

Conclusions: The proportion of liver injury cases attributed to HDS in DILIN has increased significantly. Liver injury from nonbodybuilding HDS is more severe than from bodybuilding HDS or medications, as evidenced by differences in unfavorable outcomes (death and transplantation). (HEPATOLOGY 2014;00:000-000)

Table 1 Criteria as set out by the different associations for MetS definition and for MetS diagnosis

WHO	EGIR	NCEP-ATPIII	AACE	IDF
High insulin level	High fasting insulin concentrations – insulin resistance	*Any three of the following:*	Impaired glucose tolerance	Central obesity = WC (ethnicity and gender specific)
+	+		+	+
Two of the following:	*Two of the following:*		*Two of the following:*	*Two of the following:*
1. Abdominal obesity WC > 37", BMI > 30 kg m^{-2}	1. WC > 94 cm (male) >80 cm (female)	1. WC > 40" (male) >35" (female)	1. Triglycerides > 150 mg dL^{-1} Cholesterol – HDL <40 mg dL^{-1} (male) <50 mg dL^{-1} (female)	1. Triglycerides > 150 mg dL^{-1} Cholesterol – HDL <40 mg dL^{-1} (male) <50 mg dL^{-1} (female)
2. Triglycerides > 150 mg dL^{-1} Cholesterol – HDL <35 mg dL^{-1} (male) <39 mg dL^{-1} (female)	2. Triglycerides >2 mmol L^{-1} Cholesterol – HDL <1 mg dL^{-1}	2. Triglycerides > 150 mg dL^{-1} Cholesterol – HDL <40 mg dL^{-1} (male) <50 mg dL^{-1} (female)	2. BP ≥ 130/85 mm Hg	2. BP ≥ 130/85 mm Hg
3. BP ≥ 140/90 mm Hg	3. BP ≥ 140/90 mm Hg or hypertensive medication	3. BP 130/85 mm Hg		3. Fasting plasma glucose ≥5.6 mmol L^{-1} or T2DM
4. Microalbuminuria >20 mg g^{-1}	4. Fasting glucose ≥6.1 mmol L^{-1}	4. Fasting plasma glucose ≥ 110 mg dL^{-1}		

Criteria set out for the diagnosis of MetS according to a number of influential associations.

AACE, American Association of Clinical Endocrinology; BMI, body mass index; BP, blood pressure; EGIR, European Group for the Study of Insulin Resistance; HDL, high-density lipoprotein; IDF, International Diabetes Federation; MetS, metabolic syndrome; NCEP-ATPIII, National Cholesterol Education Program – Third Adult Treatment Panel; T2DM, type 2 diabetes mellitus; WC, waist circumference; WHO, World Health Organization.

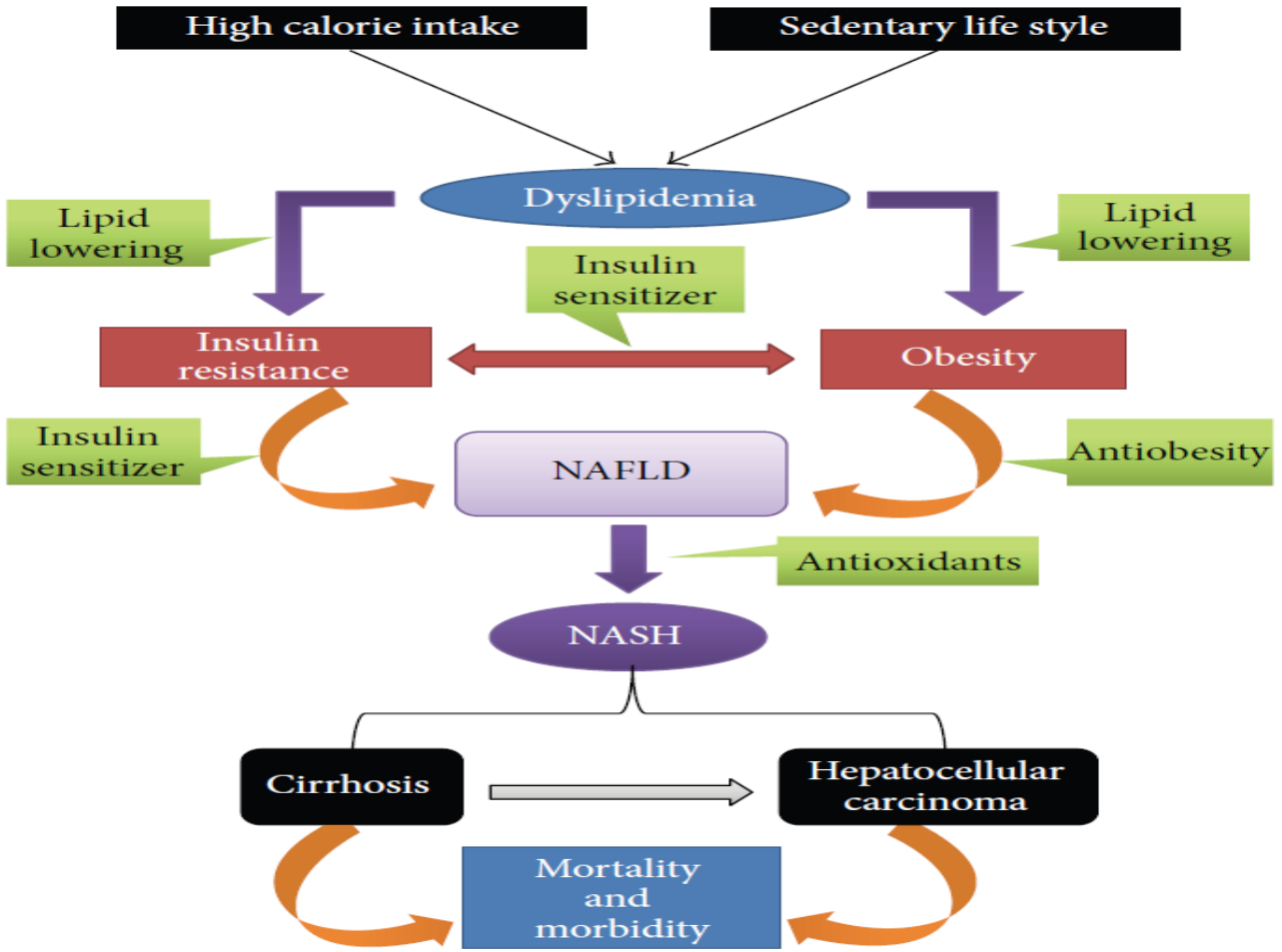

FIGURE 1: An overview of the pathogenesis of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) and potential targets for herbal therapeutic intervention.Green color graphics represent herbal property that could be beneficial against NASH.