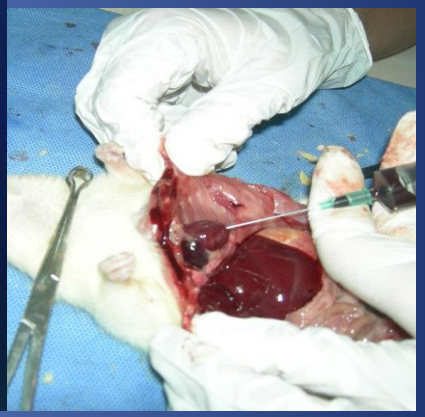
EFFICIENCY OF PROPOLIS ON EXPERIMENTAL ENDOTOXEMIC RENAL DAMAGE

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ERCİYES ÜNİVERSİTESİ 1978







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Endotoxic shock,

*is a leading life-threatening complication among critically ill patients in hospitals

*is characterized by

hypotension,

poor tissue perfusion and

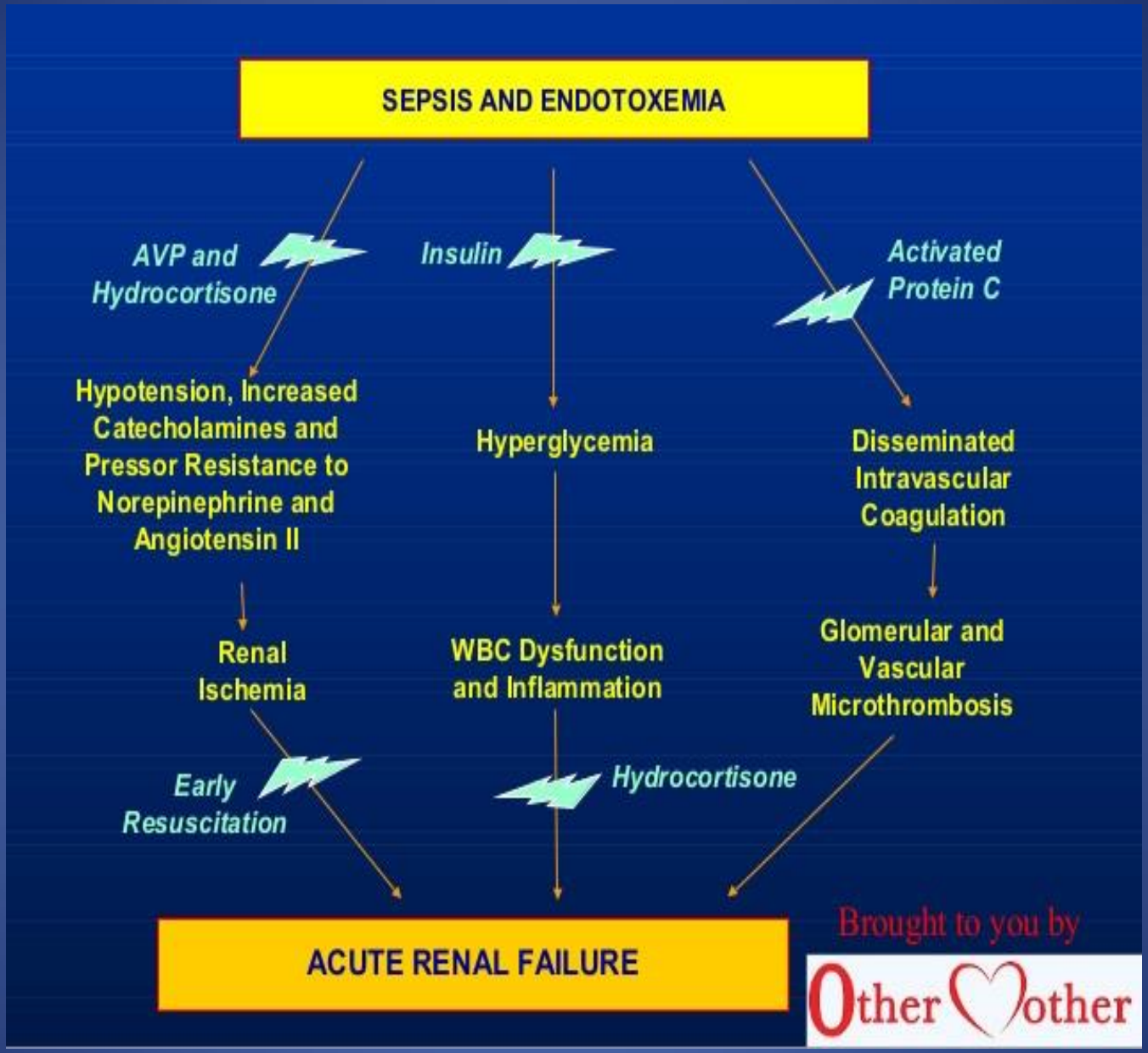
multi-organ dysfunction

Lipopolysaccharide (LPS; also known as endotoxin)

*major structural and functional component of endotoxic shock

*In Gram-negative bacteria, LPS plays a dominant role

*The outer membrane of Gram-negative bacteria is constructed of a lipid bilayer and separated from the inner cytoplasmic membrane by peptidoglycan


SEPSIS AND ENDOTOXEMIA
AVP and Hydrocortisone
Insulin
Activated Protein C
Hypotension, Increased Catecholamines and Pressor Resistance to Norepinephrine and Angiotensin II
Hyperglycemia
Disseminated Intravascular Coagulation
Renal Ischemia
WBC Dysfunction and Inflammation
Glomerular and Vascular Microthrombosis
Early Resuscitation
Hydrocortisone
ACUTE RENAL FAILURE
Brought to you by
Other Mother

*The LPS molecule is embedded in the outer membrane and the lipid A portion of the molecule serves to anchor LPS in the bacterial cell wall

*Bacterial lipopolysaccharide (LPS), the major structural component of the outer wall of Gram-negative bacteria, is a potent activator of macrophages and activated macrophages produce a variety of inflammatory cytokines

LPS cause oxidative stress through the generation of free radicals and changes in antioxidant enzymes and oxygen-free radical scavengers. Lipid peroxidation is known to be one of the molecular mechanisms of LPS-induced toxicity

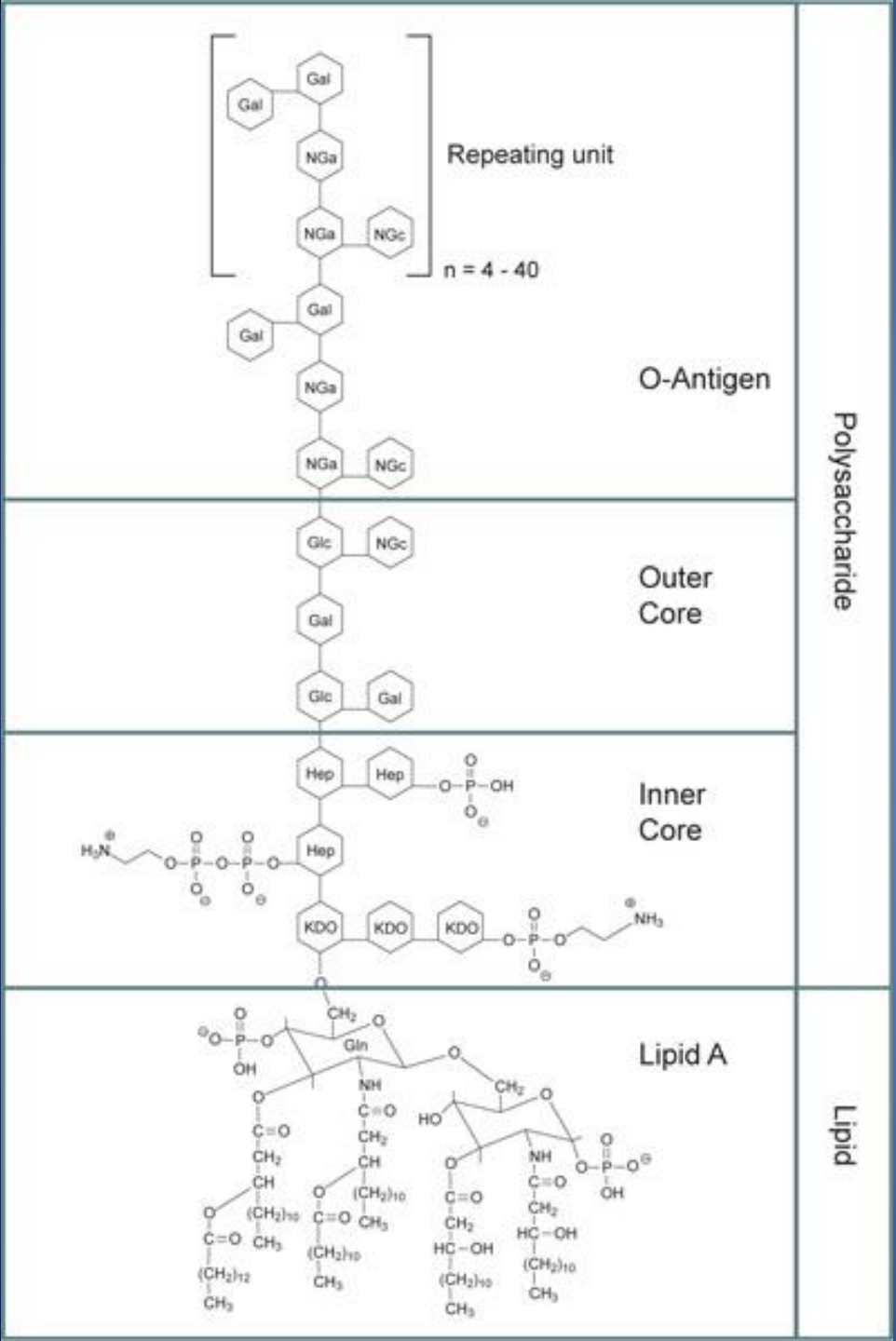
Gram negative bacteria, contributing greatly to the structural integrity of the bacteria, and protecting the membrane from certain kinds of chemical attack.

LPS also increases the negative charge of the cell membrane and helps stabilize the overall mmebrane structure

Within Gram-negative bacteria, the membrane lipopolysaccharides protect the bacterium against the action of bile salts and lipophilic antibiotics

It is crucial importance to gram-negative bacteria, whose death results if it is mutated or removed.

LPS induced a strong response from normal animal immune systems. It has also been implicated in non-pathogenic aspects of bacterial ecology, including surface adhesion, bacteriophage sensitivity, and interaction with predators such as amoebae



General structure for bacterial lipopolysaccharides. KDO: 3-deoxy-α-D-mannooctulosonic acid; Hep: Heptulose (ketoheptose); NGa: Galactosamine; NGc: NGc: Glucosamine.

The lipid A core is made up of a beta-glucosamine-(1-6)-glucosamine-1-phosphate base with fatty acid esters attached to both carbohydrates

The inner polysaccharide core typically contains between 1 and 4 molecules of the KDO

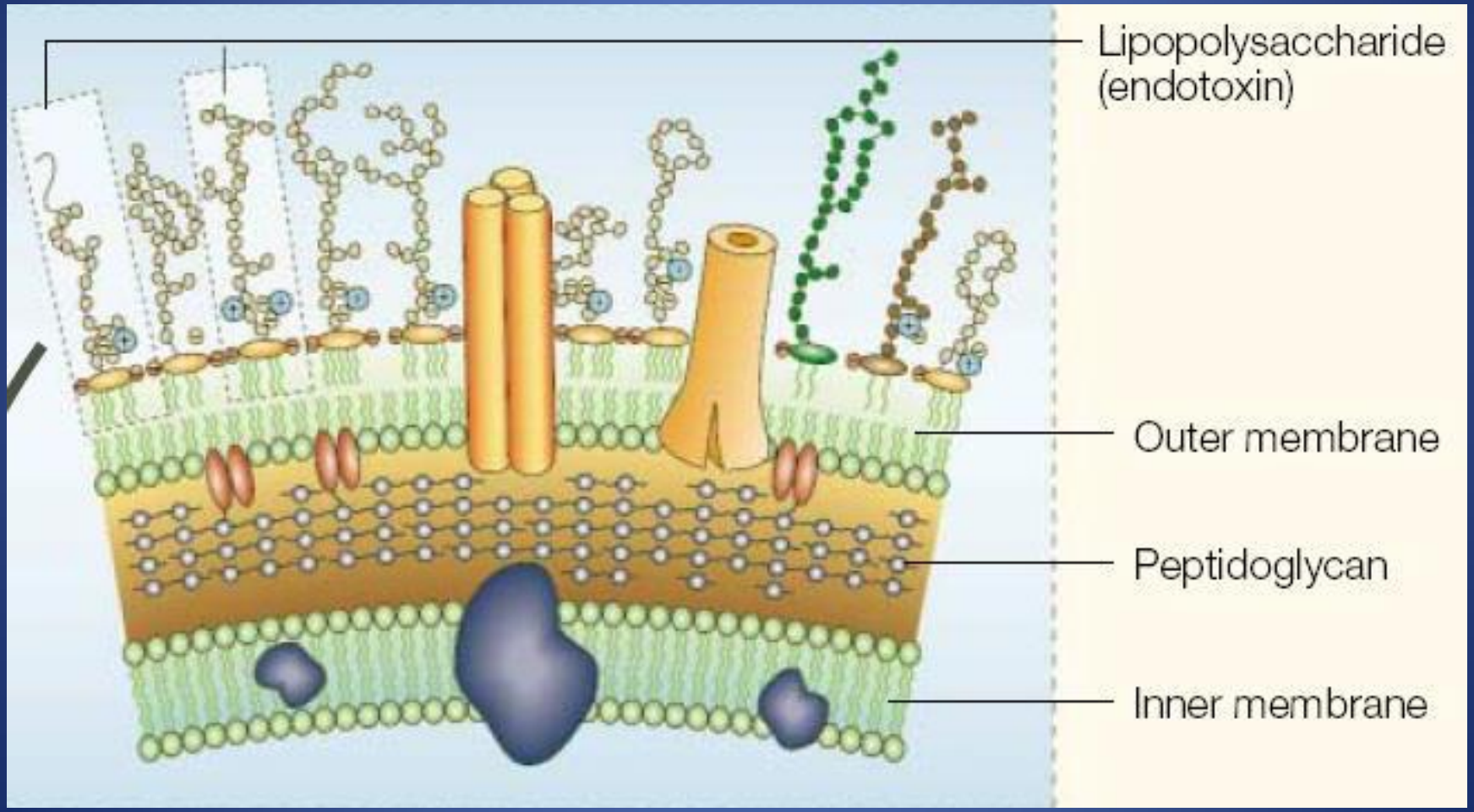
The outer core of the lipopolysaccharide contains more common hexoses, including glucose, galactose, and N-acetylglucosamine and is structurally more diverse than the inner core.

The O-antigen is a repeating oligosaccharide unit typically comprised of two to six sugars

The core section and the lipid A section of a lipopolysaccharide may have some variability in structure..

Lipopolysaccharides are heat stable endotoxins and have long been recognized as a key factor in septic shock (septicemia) in humans and, more generally, in inducing a strong immune response in normal mammalian cells.

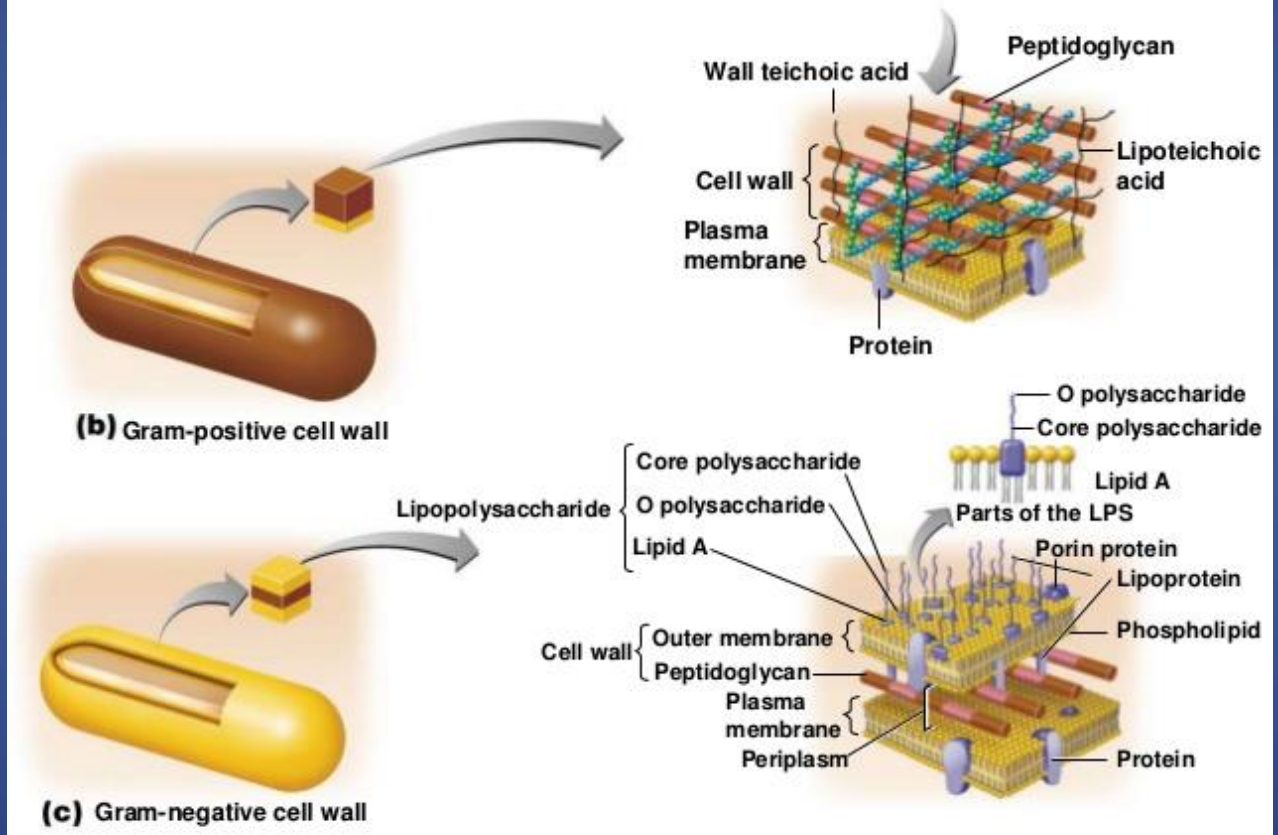
The lipid A moiety has been identified as critical to the endotoxin activity of lipopolysaccharide.


Lipopolysaccharide
(endotoxin)
Outer membrane
Peptidoglycan
Inner membrane

Lipopolysaccharide preparations have been used in research for the elucidation of LPS structure, metabolism,immunology, physiology, toxicity, and biosynthesis.

They have also been used to induce synthesis and secretion of growth promoting factors such as interleukins. Because of its connection to septicemia, lipopolysaccharide has been studied to identify possible targets for antibodies and inhibitors to LPS biosynthesis.

Figure 4.13b-c Bacterial cell walls.



Despite antibiotic therapy and intensive care management, the morbidity and mortality rates of Gram-negative septic shock remain high. Endotoxin mediates its effects through interaction with receptors on the surface of a variety of host cells. These interactions result in the production and release of numerous biochemical mediators that exert toxic effects during endotoxic shock

Lipid peroxidation is the initial step of cellular membrane damage caused by pesticides, metals, other xenobiotics, and antibiotics and considered to be a valuable indicator of oxidative damage of cellular components.. This may lead to muscle degradation, impairment of the nervous system, haemolysis, the general deterioration of cellular metabolism, and eventually cell death.

Propolis

Propolis is a resinous material collected by honey bees from exudates and bud of the plants and mixed with wax and bee enzymes.

It is a complex resinous mixture which contains approximately 50% resin and balsam, 30% wax, 10% essential and aromatic oils, 5% pollen, and 5% impurities.





Propolis is one of the most abundant sources of polyphenols, and mainly contains flavonoides, phenolic acids, and their esters

The principal flavonoids in propolis are: flavones, flavonols, and flavanones

Flavone is a class of flavonoids (chrysin, apigenin, luteolin, and rutin)

Flavonol is a class of flavonoids such as galangin, quercetin, kaempferol and rhamnazin.



Propolis sources in the world

Propolis type	*Geographic origin*	*Plant source*	*Major constituents*	*Authors*
Poplar	Europe, North America, non-tropic regions of Asia, New Zealand	*P.nigra* (most often, Aigeiros section)	Flavones,flavanones, cinnamic acids and their esters	Greenaway et al., 1988, Bankova et al. 2000
Green (alecrim) Brazilian	Brazil	Baccharis spp. predominantly B. dracunculifolia,	Prenylated p-coumaric acid, diterpenic acids	Salatino et al. 2005
Birch	Russia	*Betula verrucosa* Ehrh	Flavones and flavonols (not the same as in poplar type)	Popravko, 1978
Red propolis	Cuba, Brazil, Mexico	Dalbergia spp.	isoflavonoids (isoflavans, pterocarpans)	Campo Fernandez et al.
Mediterranean	Sicily, Greece, Crete, Malta	Cupressaceae	Diterpenes (mainly acids of labdane type)	Trusheva et al. 2003
Clusia	Cuba, Venezuella	Clusia spp.	Polyprenylated benzophenones	Trusheva et al. 2004
Pacific	Pacific region (Taiwan, Indonesia, Okinawa	*Macaranga tamarius*	c-prenyl flavanones	Kumazawa et al. 2008

Medicine Science 2012;1(4):292-300
Original Investigation
Propolis and thyroid cancer
doi: 10.5455/medscience.2012.01.8029

Antitumor Activity of Propolis on Differentiated Cancer Cell Lines

Neşe Ersöz Gülçelik[1], Dilara Zeybek[2], Figen Kaymaz[2], Ömür Gencay[3], Bekir Salih[4], Esin Asan[2], Kadriye Sorkun[3], Aydan Usman[1]

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Phytomedicine 12 (2005) 742–747

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The anticarcinogenic effect of propolis in human lymphocytes culture

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Immunomodulatory effects of Turkish propolis: Changes in neopterin release and tryptophan degradation

Gozde Girgin[a,b,1], Terken Baydar[b], Maximilian Ledochowski[c], Harald Schennach[d], Duygu Nur Bolukbasi[e], Kadriye Sorkun[e], Bekir Salih[f], Gonul Sahin[b,*], Dietmar Fuchs[a]

Effects of diets containing different concentrations of propolis on hematological and immunological variables in laying hens

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Pesticide Biochemistry and Physiology 88 (2007) 273–283
PESTICIDE
Biochemistry & Physiology
www.elsevier.com/locate/ypest

Evaluation of propolis effects on some biochemical parameters in rats treated with sodium fluoride

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Available online at www.sciencedirect.com
ScienceDirect
Ecotoxicology and Environmental Safety 72 (2009) 909–915
Ecotoxicology and Environmental Safety
www.elsevier.com/locate/ecoenv

Antioxidant effect of propolis against exposure to propetamphos in rats

Murat Kanbur[a], Gokhan Eraslan[a,*], Sibel Silici[b]

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Available online 11 March 2008

Propolis harvesting





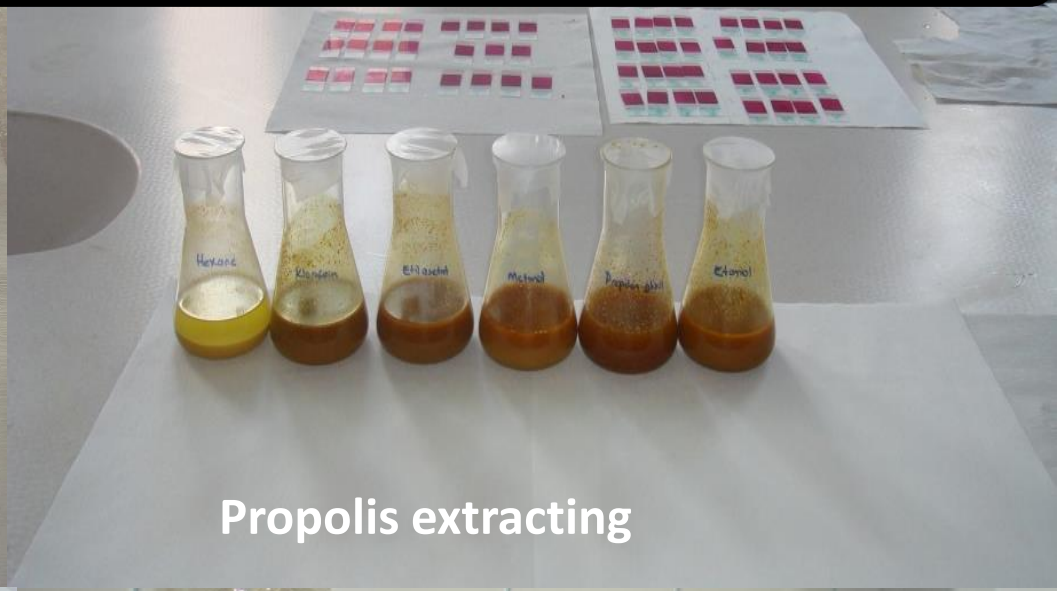




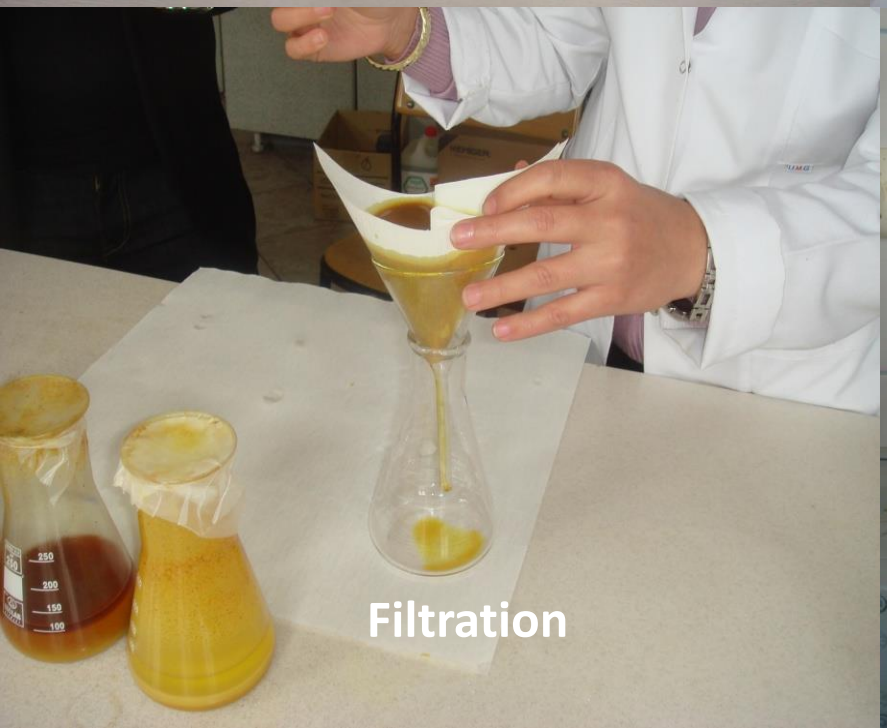
Erciyes Uni. Biotechnology Lab.



Pounding



Propolis extracting



Filtration



Evaporation


Koc et al. 2005, Mycoses

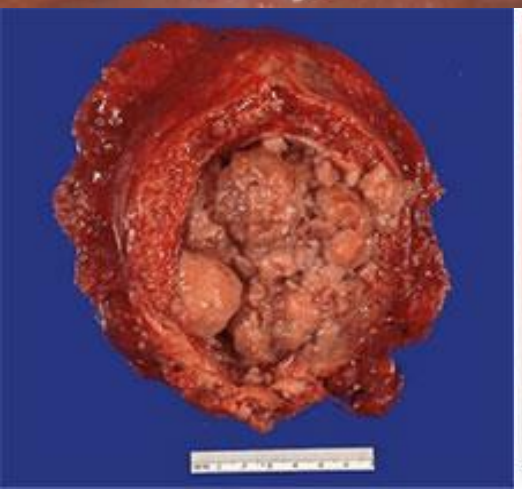

Silici et al.,2005 J Pharm.Sci




Arslan et al 2012, Lasers Med Sci


Artan et al 2012, Saudi Med J


Kaynar et al 2012, Afr J Tradit




Koc et al 2011, J Med Food


Silici and Koc 2011, Let Apl Mic

*Antioxidant agents improve renal damage when used immediately after bacterial inoculation. For example

treatment by thymoquinone before or during *Escherichia coli* inoculation prevented oxidative damage in acute pyelonephritis in an ascending obstructive rat model

LPS-induced NO generation resulted in peroxynitrite formation and oxidant stress in the kidney and that inhibitors of iNOS may offer protection against LPS-induced renal toxicity

*the protective effect of chelating agent, N-(2-hydroxy ethyl ethylene diamine triacetic acid, HEDTA) with and without propolis against aluminum (Al) induced toxicity in rats.

*combined treatment of HEDTA and propolis preserved histological features, mitigated oxidative stress and improved liver, kidney and brain functions more profoundly

*the biochemical changes in cobalt-exposed rats and investigated the potential role of Tunisian propolis against the cobalt-induced renal damage

Caffeic acid phenethyl ester (CAPE), a bioactive component of propolis extract, exhibits antioxidant and anti-inflammatory properties.

protective effect of CAPE on carbon tetrachloride (CCl_4)-induced renal damage.

Study groups

- Group 1 (Control): 0.1ml of normal saline (NS), ie. 0.9 % NaCl solution i.p. 30 minutes apart as twice; (n=10)
- Group 2 (LPS): 30 mg/kg of LPS i.p., 30 minutes after NS administration (n=10)
- Group 3 (Propolis): 250 mg/kg of propolis orally, 30 minutes after NS administration (n=10)
- Group 4 (Propolis + LPS): 250 mg/kg of propolis orally, 60 minutes before LPS administration (n=10),
- Group 5 (LPS + Propolis): 250mg/kg of propolis orally, 60 minutes after LPS administration (n=10),

R.T.	Compounds	% TIC
Phenolic compounds		
27.93	4,5 dimethoxy-(2-propenyl) 2-phenol	1.25
31.06	Pinocembrin	14.75
34.12	Chrysin	7.67
34.84	Galangin	4.90
Organic and fatty acids		
9.03	Decanoic acid	0.23
13.31	4-pentenoic acid	1.74
20.30	Cinnamic acid	0.29
20.73	3-hydroxy-4-methoxycinnamic acid	1.82
16.74	2-propenoic acid	2.70
20.91	3,4-dimethoxycinnamic acid	3.40
22.93	Coumaric acid	0.19
25.12	9-Octadecanoic acid	2.05
25.49	Octadecanoic acid	0.21
Alcohol, ketone and terpenes		
8.02	2-propen-1-ol	0.21
34.38	5-3,3-dimethyl-cyclohexanone	1.36
24.49	2-Nonadecanone	0.66
15.22	Gamma-eudesmol	0.37
15.66	Beta-eudesmol	0.38
15.71	Alpha-eudesmol	0.59
16.26	Alpha-bisabolol	0.17
29.72	2-propen-1-one	15.30

Results (biochemical changes)

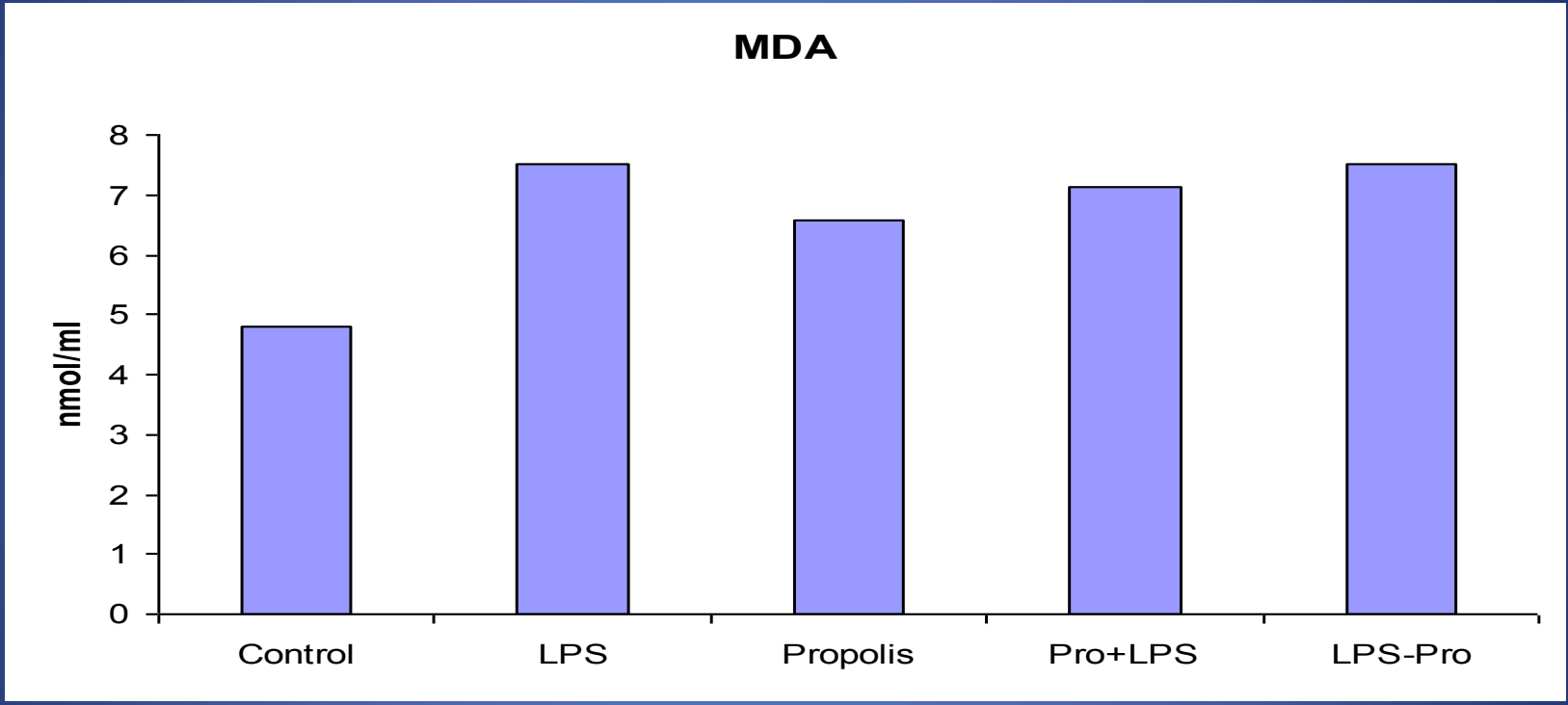
Compared with the control group the MDA levels increased in the group administered LPS only

In the group administered propolis only, the MDA levels increased compared with the control group while decreased compared with the group administered LPS only.

In the group administered propolis before LPS, the MDA levels increased compared with the control group while decreased compared with the group administered LPS only.

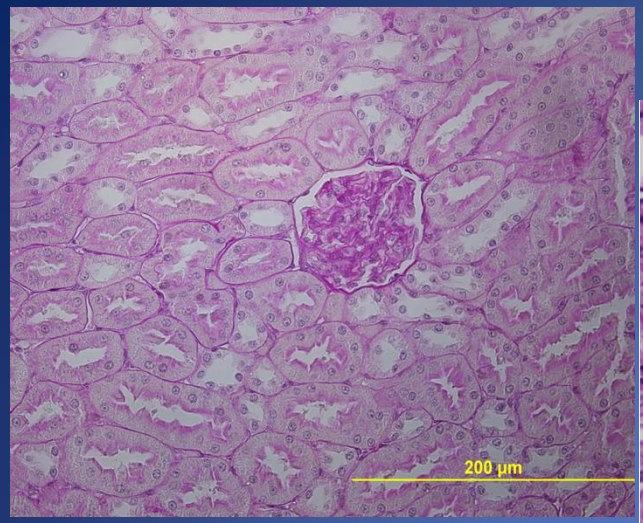
In the group administered propolis after LPS, the MDA levels increased compared with the control group

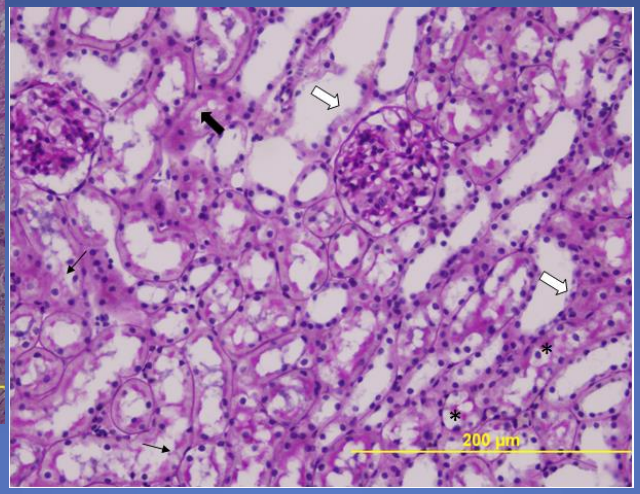
The MDA levels increased in the group administered LPS only and decreased in the groups pre-treated, posttreated and simultaneously treated with propolis. The group that was administered propolis only showed no statistically significant difference from the control group.

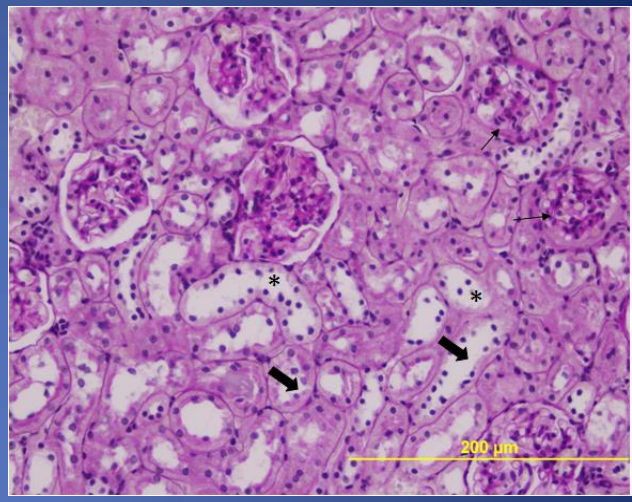

MDA
nmol/ml
8
7
6
5
4
3
2
1
0
Control
LPS
Propolis
Pro+LPS
LPS-Pro

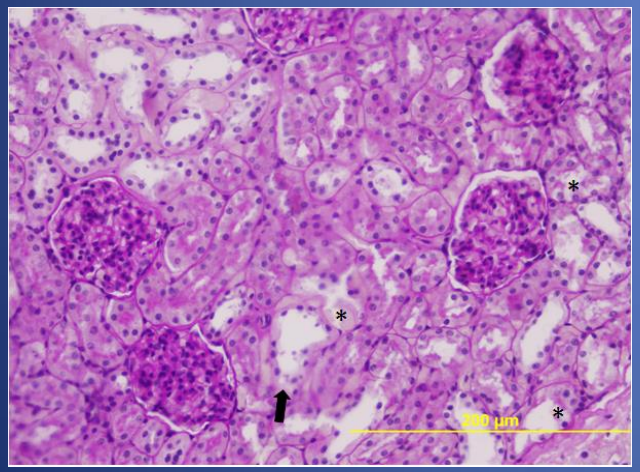
All sections were collected in slides and then stained with PAS. Histopathological examination of kidney sections from Group 1 (control animals) revealed normal structures (Figure1A). Compared with normal kidney tissues from the control group, Group 2 (NS+LPS) kidney sections of rats treated with only LPS demonstrated slight tubular damage, mild ischemic injury, ischemic damage in the form of vacuolization, tubule epithelial vacuolization, vascular congestion and glomerular atrophy (Figure 1B).

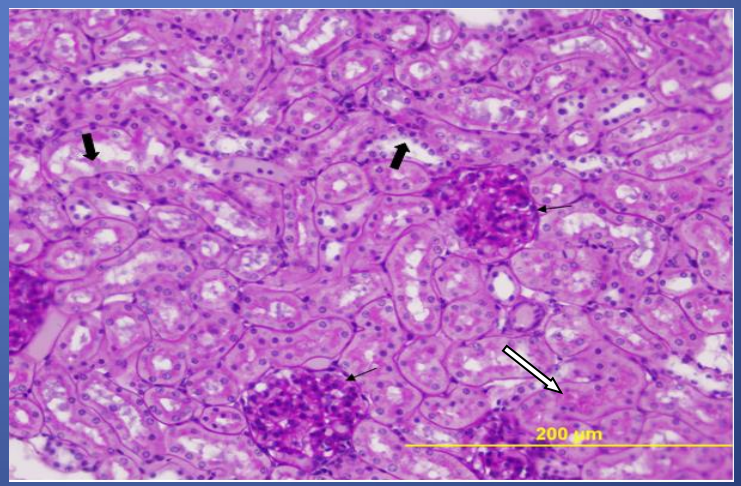
Group 3 (NS+Propolis) kidney sections of rats treated with only propolis showed mild ischemic injury (Figure 1C). While in Group 4 (propolis+LPS) kidney sections of rats treated with propolis prior to LPS challenge showed mild ischemic injury (Figure 1D), in Group 5 (LPS+propolis) sections of rats treated with propolis after LPS challenge showed mild ischemic injury, tubule epithelial vacuolization, vascular congestion and glomerular atrophy (Figure 1E).


200 µm


200 µm


200 µm


200 µm


200 µm

Discussion

It is known that pharmacological properties of propolis are due to the high polyphenolic contents. Flavonoids are polyphenolic compounds that are present in plants. They have been shown to possess a variety of biological activities. For example, chrysin is present in honey and propolis and in low concentrations in fruits, vegetables, and certain beverages.

It has been reported that chrysin has potent anti-inflammatory, anti-cancer, and antioxidant properties. The flavanone pinocembrin has strong antifeedant, anti-inflammatory, and antioxidant activities . Results from in vitro and in vivo studies indicate that galangin, with its antioxidant and radical scavenging activities, is capable of modulating enzyme activities and suppressing the genotoxicity of chemicals.

In the present study, it was demonstrated that compared with the normal kidney tissues from the control group, kidney sections of rats treated with only LPS demonstrated slight tubular damage, ischemic injury, ischemic damage in the form of vacuolization, tubule epithelial vacuolization, vascular congestion and glomerular atrophy.

In comparison with the kidney sections of rats treated with only LPS, administration of propolis showed a mild but not a significant effect against LPS-induced renal damage. In addition, in the present study the increase in serum MDA levels in the group that was administered LPS only demonstrates lipid peroxidation to have developed.