Herbal Nephrotoxicity

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Agenda

Tanacetum parthenium	بابونه گاوی
euphorbia	فرفیون
Aloe vera	آلوورا
Yohimbine	یوهیمبین

Introduction

Currently in Europe, despite the many advances in production technology of synthetic
drugs, the interest in natural preparations is increasing. According to the World Health
Organization (WHO) data, 80% of the world’s population choose traditional medicines to
meet their healthcare needs . Herbal medicines are popular in many countries. They
constitute a significant part of the drugs in various therapeutic groups, such as in

Kili´s-Pstrusi´nska, K.;Wiela-Hoje´nska, A. Nephrotoxicity of Herbal Products in Europe—A Review of an Underestimated Problem. *Int. J. Mol. Sci.* **2021**, *22*, 4132. https://doi.org/10.3390/ ijms22084132

- Among the plants that can cause nephrotoxicity particular attention has been paid to Chinese herbs. “Chinese herb nephropathy” now is appropriately termed aristolochic acid
nephropathy (AAN).
- In the early 1990s in Belgium nine similar cases of rapidly progressive fibrosing interstitial nephritis in young women were described. They were treated with herbs *Stephania tetrandra* and *Magnolia officinalis* in a weight-loss clinic in Brussels. It was later discovered that *S. tetrandra* had been inadvertently replaced by *Aristolochia fangchi* by the manufacturers of the weight-reducing formula.
- *Aristolochia fangchi* contains aristolochic acid (AA), a plant alkaloid, which is nephrotoxic and carcinogenic in humans
and animals

- .In contrast to AAN, little is known about the nephrotoxicity of plants

Mechanism of Plants Nephrotoxicity

- **Three main factors involved in increasing exposure to toxins and the risk of kidney injury:**

  - high relative proportion of blood flow through the kidneys,
  - their high metabolic activity, and
  - glomerular filtrate reabsorption by the renal tubules, which may result in high agent concentration intracellularly

mechanisms which may be involved in nephrotoxicity are:

hemodynamic alterations
glomerular epithelial cell injury(podocytopathy)
renal inflammation.

Table 1. Risk factors that increase renal susceptibility to nephrotoxins.

Factors	
Patient-specific factors	kidney disease, other diseases predisposing to kidney injury metabolic disturbances (systemic alkalosis or acidosis, alkaline or acid urine pH), electrolyte abnormalities (hypokalemia, hypomagnesemia, hypercalcemia) older age specific pharmacogenetics (gene mutations in hepatic and renal P450 system, gene mutations in renal transporters and transport proteins) hypovolemia
Kidney-specific factors	high rate of blood delivery high metabolic activity increased toxin concentration in renal medulla and interstitium biotransformation of substances to reactive oxygen species proximal tubular uptake of toxins disruption of proximal tubule polarity leading to glucose accumulation and lipotoxicity
Herbal product-specific factor	direct nephrotoxic effects of the herbal product or its compound herbal-herbal or herbal-drug interaction promoting enhanced nephrotoxicity insolubility of substances and their metabolites in urine prolonged exposure at high doses

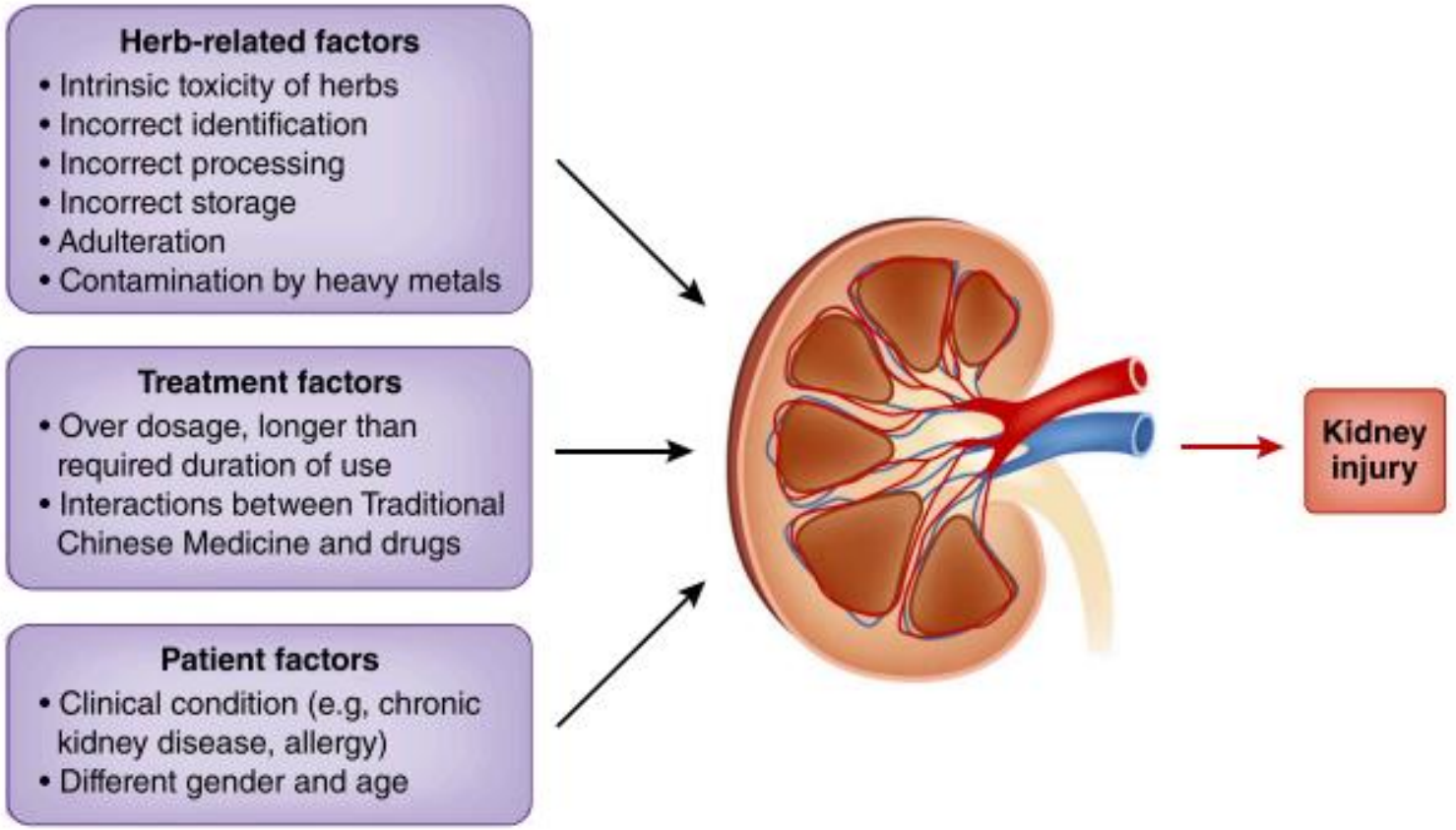


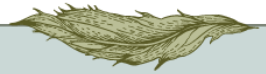
Figure 3. | Factors influencing the development of kidney disease associated with herbal medicine. The figure shows herb-related, treatment, and patient factors which may contribute to nephrotoxicity of hebal medicine.

Clin J Am Soc Nephrol 13: 1605–1611, 2018. doi: https://doi.org/10.2215/CJN.11571017

Tanacetum parthenium

بابونه گاوی

بابونه گاوی feverfew



- *Tanacetum parthenium* commonly known as Feverfew, Featherfew or Midsummer Daisy, has been cultivated for centuries as a medicinal and ornamental plant.

- A member of the Asteraceae (or Compositae) family that includes Chamomile, Echinacea, and Marigold, Feverfew has been used in traditional and folk medicine as an alternative to conventional medications in the treatment of fevers (emphasizing plant's name), headaches, vertigo, arthritis, menstrual disorders, toothache, stomach ache and insect bites

- Feverfew gained attention for its apparent effectiveness in reducing migraine headaches.
  Several placebocontrolled clinical trials have since shown Feverfew to be an affective oral agent in reducing the frequency and severity of migraine headaches

Inflammopharmacology 17 (2009) 42–49
0925-4692/09/010042-8
DOI 10.1007/s10787-008-8040-9

بابونه گاوی feverfew

- The mechanism of action for the anti-migraine benefits of Feverfew has been believed to be associated with the anti-inflammatory properties of the plant.

- At a phytochemical level, **parthenolide**, a sesquiterpene lactone isolated from Feverfew plant extracts has been shown to be a potent inhibitor of the transcription factor NF-κB, which results in the decreased release of the cytokines TNF-α, IL-1, IL-2, IL-6, and IL-8 *(Bork et al.,1997; Humar et al., 2003).*
- In another study, the flavonoid **taxifolin** found in Feverfew was shown to inhibit the interferon ©γ-induction of mRNA for intercellular adhesion molecule-1 (ICAM-1) in human primary keratinocytes and in a reconstituted human skin equivalent (*Bito et al., 2002*).

- Feverfew appears to be an inhibitor of prostaglandin synthesis. Extracts of the above ground portions of the plant suppress prostaglandin production; leaf extracts inhibit prostaglandin production to a lesser extent.

- Inhibition was irreversible and the effect was not caused by cytotoxicity

- Whether or not these extracts block the synthesis of thromboxane, a prostaglandin involved in platelet aggregation, is controversial. Results suggest that feverfew's inhibition of prostaglandin synthesis differs in mechanism from that of the salicylates

- Are feverfew and chamomile the same?

chamomile

feverfew

فرفیون *Euphorbia*

فرفیون، شیرشیرک یا شیرسگ نام یک سرده از تیره فرفیونیان است.

فرفیون دارای شیره شیری رنگ و بسیار سمی است. در صورت تماس با پوست احتمال سرطان پوست بالاست. در صورت تماس با چشم باعث کوری و یا ضعف بینایی میشود.

برای ساخت داروی طب سنتی جامع رضا مورد استفاده قرار میگیرد.

نام محلی گونه بومی ایران در بندرعباس و اطراف آن **پِرِخ** و **پَره** است. در منطقه تربت حیدریه به این گیاه "شیروک" گفته میشود.

- Euphorbia paralias, the sea spurge, is a species of Euphorbia, native to Europe, northern Africa, and western Asia.
- The extracts and secondary metabolites from Euphorbia plants may act as active principles of medicines for the treatment of many human ailments, mainly inflammation, cancer, and microbial infections. However, the herb may be nephrotoxic

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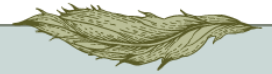
Boubaker et al. described a man with acute renal failure following the ingestion of Euphorbia paralias, which was used for treating edema. Acute kidney injury was due to severe tubular necrosis confirmed by kidney biopsy. The exact mechanism of the plant toxicity is not known. However, Euphorbiaceae plants are well known to contain irritant, cytotoxic, and tumor-promoting constituents.

Saudi J Kidney Dis Transpl 2013;24(3):571-575

Aloe vera

Aloe vera



- The Aloe plant is employed as a dietary supplement in a variety of foods and as an ingredient in cosmetic products.
- Chemical analysis revealed that the Aloe plant contains various polysaccharides and phenolic chemicals, notably anthraquinones.
- Aloe emodin is a naturally anthraquinone derivative and an active ingredient of some herbs, such as Rheum palmatum L. and Aloe vera

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- Emerging evidence suggests that aloe-emodin exhibits many pharmacological effects, including anticancer, antivirus, anti-inflammatory, antibacterial, antiparasitic, neuroprotective, and hepatoprotective activities.

- These pharmacological properties lay the foundation for the treatment of various diseases, including influenza virus, inflammation, sepsis, Alzheimer's disease, glaucoma, malaria, liver fibrosis, psoriasis, type 2 diabetes, growth disorders, and several types of cancers.

- However, ingestion of Aloe preparations may be associated with diarrhea, hypokalemia, and kidney failure

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Toxicity of Aloe emodin

- Phototoxicity
  - the exposure of human
    skin fibroblasts to aloe-emodin and ultraviolet radiation elicited significant phototoxicity

    Vath et al., 2002
- hepatotoxicity
- nephrotoxicity.
  - in vivo studies have showed that
    aloe-emodin may be the primary chemical component in R. palmatum L. that causes hepatic and renal toxicity (Wang et al., 2009)
  - aloe-emodin inhibited cell proliferation and induced cell-cycle arrest and apoptosis in HepaRG and HL-7702 cells, most probably through a mechanism involving both Fas death pathway and the mitochondrial pathway by generation of ROS (Dong et al.,2017; Dong, Fu, Yin, Yang, & Ni, 2017)

Toxicity of Aloe emodin

- aloe-emodin could induce primary damage to DNA in the liver and kidney of mouse in vivo comet assay (Nesslany, Simar-Meintières, Ficheux, & Marzin, 2009).

- Zhu et al. (2012) was the first to show that aloe-emodin suppressed HK-2 cell proliferation and induced apoptosis with the involvement of ER stress-triggered signaling pathway.

Overall, the implications of the toxic effects of aloe-emodin for clinical use are unclear and these findings underscore the need for risk assessment of human exposure to aloe-emodin.

Yuhimbine

- **Yohimbine**, indole alkaloid is either the active ingredient obtained from the bark of the tree Pausinystalia yohimbe or from the root of Rauwolfia which has been known as an aphrodisiac compound since before the last century.

- The plant is native to the tropical rain forest of West Africa.

- The dried stem bark is widely used in North Eastern Nigeria for the treatment of erectile dysfunction and as an aphrodisiac

- Several pharmacological and physiological properties of yohimbine have been described
- The best documented activity of yohimbine was the antagonism of the α- adrenoreceptor .
- Current hypothesis on the beneficial mechanism of the action of yohimbine on sexual activities mainly points to a central mechanism of action

Biology and Medicine, 2 (1): 30-36, 2010

Research Article *Biology and Medicine, 2 (1): 30-36, 2010*

eISSN: 09748369, www.biolmedonline.com

The histological effects of mixed diet containing *Pausinystalia yohimbe* ground stem bark on the kidney of adult Wistar rats (*Rattus norvegicus*)

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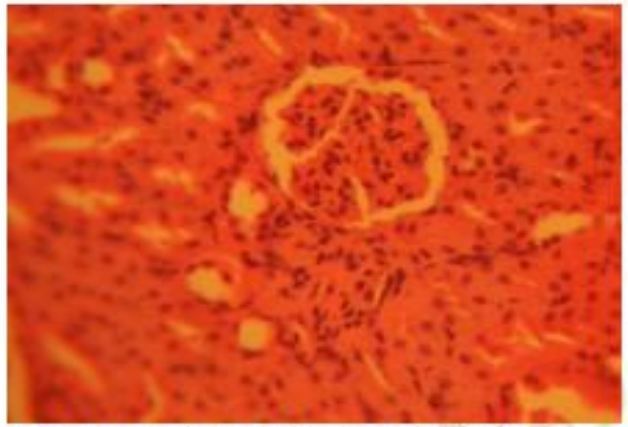

FIGURE 1: Control section of kidney: this shows cortical parenchyma to consist of dense rounded structures, the glomeruli, surrounded by narrow Bowman's capsular spaces. (Mag. X200)

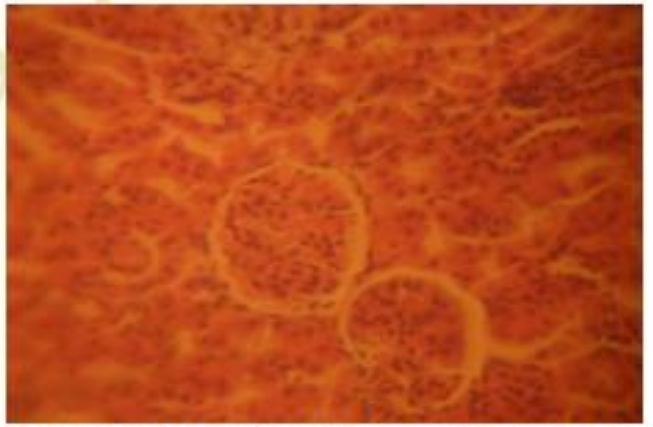

FIGURE 2: Photomicrograph of treatment section of the kidney of rats that received 30g of the ground stem bark of *Pausinystalia yohimbe* (Mag. x200)

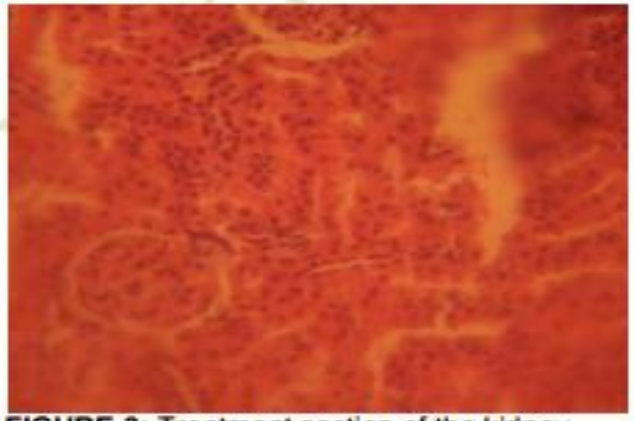

FIGURE 3: Treatment section of the kidney of rats that received 50g of the ground stem bark of *Pausinystalia yohimbe* (Mag. x200)

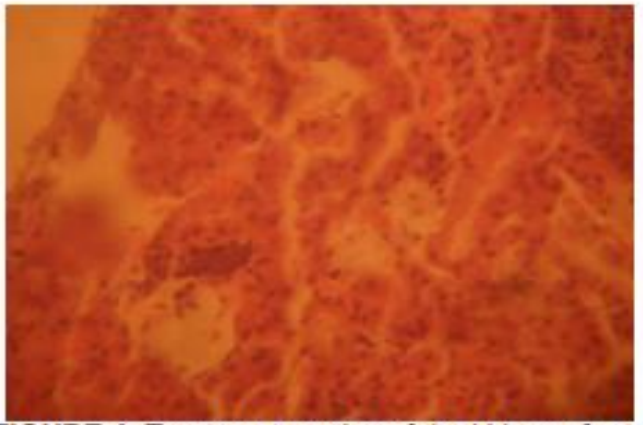

FIGURE 4: Treatment section of the kidney of rats that received 70g of the ground stem bark of *Pausinystalia yohimbe* (Mag. x200)

Mechanism of nephrotoxicity of yuhimbine

- It may be inferred from the present results that higher doses of Pausinystalia yohimbe resulted in degenerative and atrophic changes observed in the renal corpuscle.

- The necrosis observed is probably due to the high concentration of the Pausinystalia yohimbe
on the kidney.

- Pathological or accidental cell death is regarded as necrotic and could result from extrinsic insults to the cell as osmotic thermal, toxic and traumatic effect.

YOHIMBINE-INDUCED CUTANEOUS DRUG ERUPTION, PROGRESSIVE RENAL FAILURE, AND LUPUS-LIKE SYNDROME

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ABSTRACT—Yohimbine is an indole alkaloid obtained from the yohimbe tree, a common tree in West Africa. We describe a forty-two-year-old black man in whom a generalized erythrodermic skin eruption, progressive renal failure, and lupus-like syndrome developed following treatment with the drug, yohimbine. A literature review failed to reveal any reported association of these side effects. We review current information on yohimbine's use in male impotence, reported side effects, and its role as a drug allergen.

Zingiber officinale

- Ginger is a flowering plant that originated in Southeast Asia. It’s among the healthiest (and most delicious) spices on the planet.
- The rhizome is the part commonly used as a spice. It’s often called ginger root or, simply, ginger.

- Zingerone also known as vanillyl acetone is a pharmacologically active compound present usually in dry ginger.

- More than 400 chemical substances have been isolated and identified in ginger rhizomes extracts, and new ones are still being discovered (Charles, Garg, & Kumar, 2000; Jolad, Lantz, Solyom, &
Chen, 2004; Ma, Jin, Yang, & Liu, 2004). At present, only a few of them have been evaluated for their pharmacological properties (Grzanna et al., 2005).

- The treatment with zingerone markedly abrogated ROS levels, inhibited the NF-κB activation and considerably reduced level of other downstream inflammatory molecules (TNF-α, IL-6, IL-1β).

- zingerone treatment improved renal functioning by significantly decreasing the levels of kidney toxicity markers KIM-1, BUN, creatinine, and LDH and suppressed TGF-β.

Arch Physiol Biochem
. 2019 Jul;125(3):201-209. doi:
10.1080/13813455.2018.1448422.
Epub 2018 Mar 14

Ginger analgesic effects

- Inhibition of prostaglandins via COX and LOX pathways
- Antioxidant activity on free radical scavenging cascade
- Inhibition of the transcription factor, nuclear NF-kB
- Vanilloid nociceptor agonist

Phytotherapy Research. 2020;34:2843–2856

› Arch Physiol Biochem. 2019 Jul;125(3):201-209. doi: 10.1080/13813455.2018.1448422.
Epub 2018 Mar 14.

Zingerone (4-(4-hydroxy-3-methylphenyl)butan-2-one) ameliorates renal function via controlling oxidative burst and inflammation in experimental diabetic nephropathy

Muneeb U Rehman [1], Shahzada Mudasir Rashid [1], Saiema Rasool [2], Sheeba Shakeel [3], Bilal Ahmad [1], Sheikh Bilal Ahmad [1], Hassan Madkhali [4], Majid Ahmad Ganaie [4], Sabiya Majid [5], Showkat Ahmad Bhat [5]

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PMID: 29537332 DOI: 10.1080/13813455.2018.1448422

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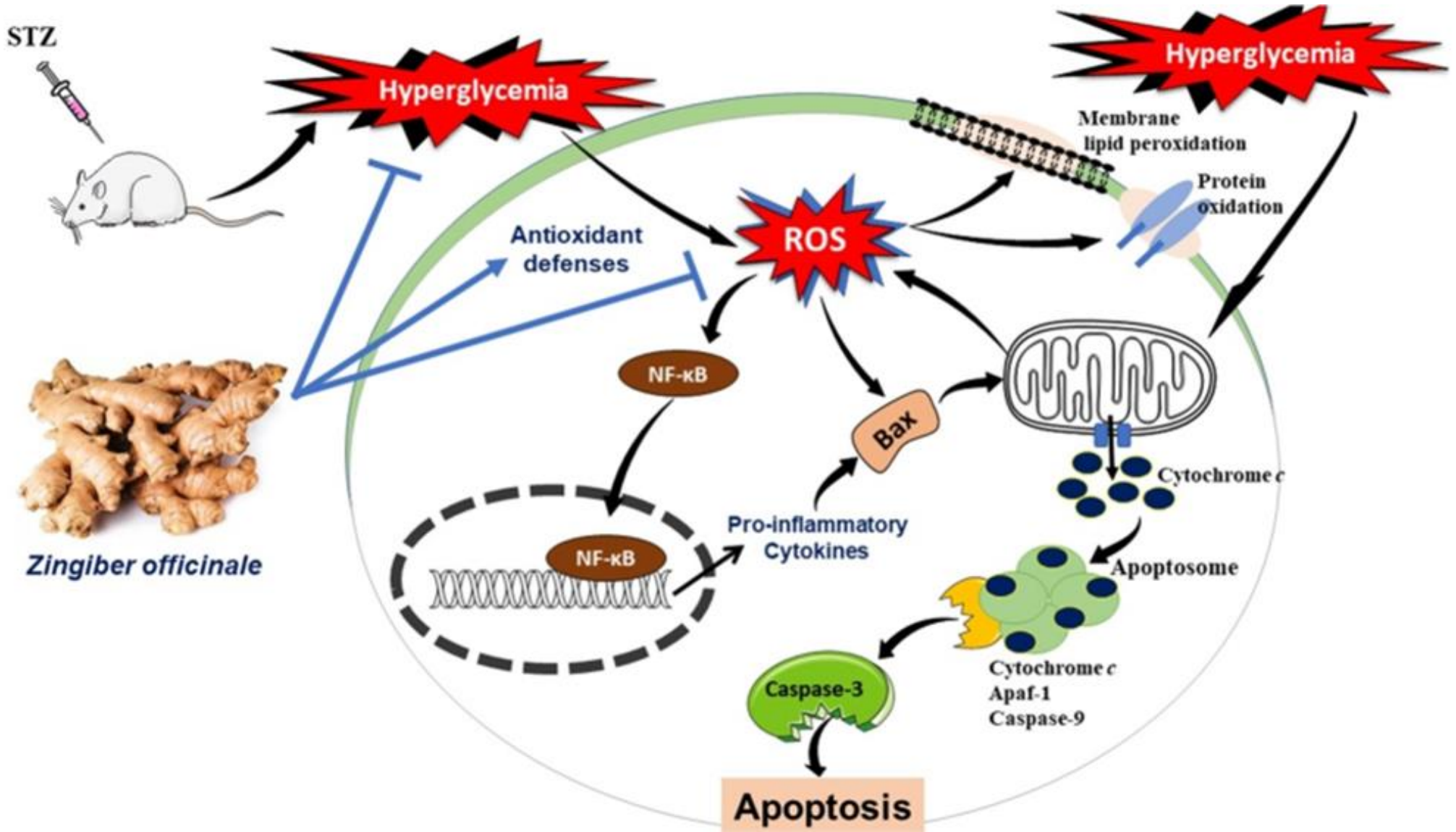
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Hyperglycemia
Membrane
lipid peroxidation
Protein
oxidation
Antioxidant
defenses
ROS
NF-κB
Bax
Cytochrome c
Pro-inflammatory
Cytokines
NF-κB
Apoptosome
Zingiber officinale
Caspase-3
Cytochrome c
Apaf-1
Caspase-9
Apoptosis

J Food Biochem. 2021 Mar;45(3):e13241. doi: 10.1111/jfbc.13241. Epub 2020 Jun 9.

Zingerone prevents lead-induced toxicity in liver and kidney tissues by regulating the oxidative damage in Wistar rats

Insha Amin [1], Ishraq Hussain [1], Muneeb U Rehman [1 2], Bilal Ahmad Mir [1], Showkat Ahmad Ganaie [3], Sheikh Bilal Ahmad [1], Manzoor Ur Rahman Mir [1], Syed Shanaz [4], Showkeen Muzamil [1], Azher Arafah [2], Parvaiz Ahmad [5]

Affiliations + expand

PMID: 32515504 DOI: 10.1111/jfbc.13241

Biomed Pharmacother. 2018 Sep;105:981-991. doi: 10.1016/j.biopha.2018.06.048. Epub 2018 Jun 19.

Therapeutic efficacy of zingerone against vancomycin-induced oxidative stress, inflammation, apoptosis and aquaporin 1 permeability in rat kidney

Fatih Mehmet Kandemir [1], Serkan Yildirim [2], Sefa Kucukler [1], Cuneyt Caglayan [3], Amdia Mahamadu [1], Muhammet Bahaeddin Dortbudak [2]

Affiliations + expand

PMID: 30021393 DOI: 10.1016/j.biopha.2018.06.048

3 Biotech. 2022 May;12(5):112. doi: 10.1007/s13205-022-03170-x. Epub 2022 Apr 11.

Kidney injury and oxidative damage alleviation by *Zingiber officinale*: pharmacokinetics and protective approach in a combined murine model of osteoporosis

Nourhene Zammel [1], Olfa Jedli [1], Tarek Rebai [1], Walid S Hamadou [2], Salem Elkahoui [2], Arshad Jamal [2], Jahoor M Alam [2], Mohd Adnan [2], Arif J Siddiqui [2], Mousa M Alreshidi [2], Houcine Naïli [3], Riadh Badraoui [2 4]

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PMID: 35462952 PMCID: PMC8995235 (available on 2023-05-01)

DOI: 10.1007/s13205-022-03170-x

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