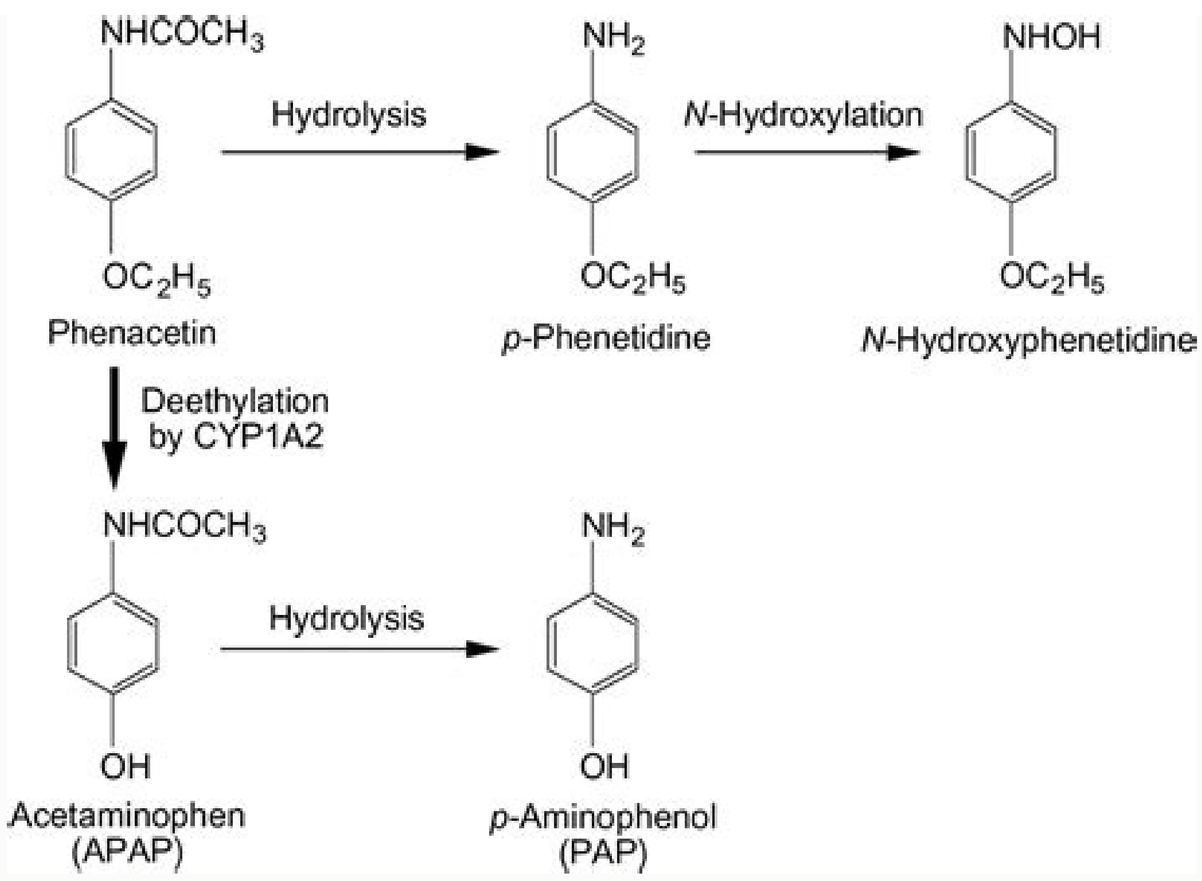
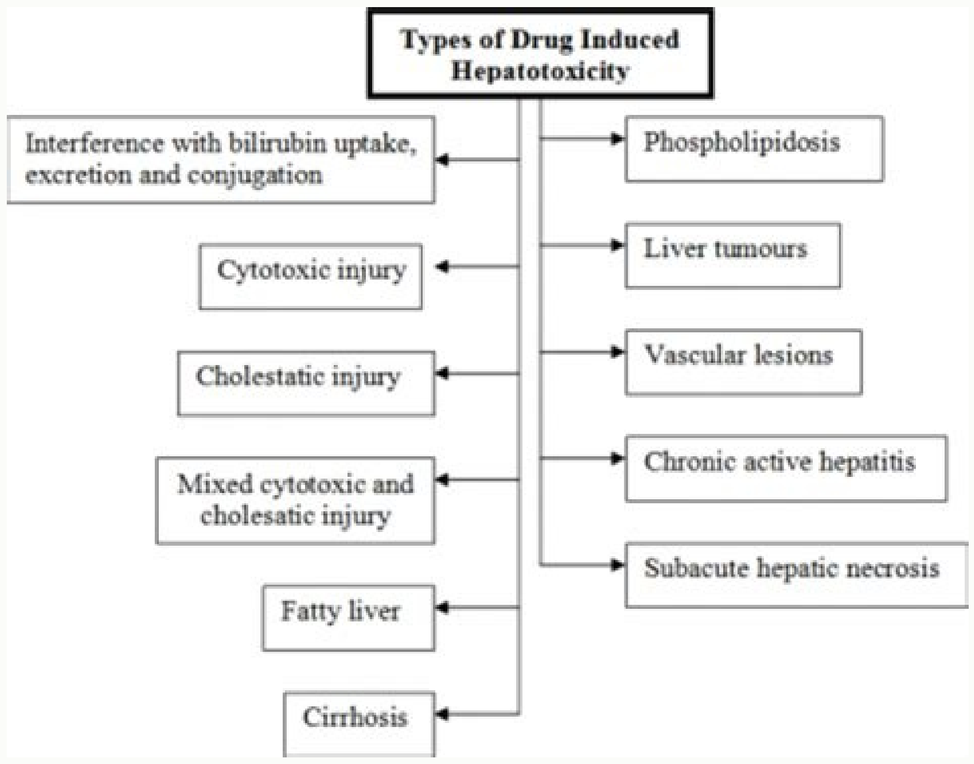
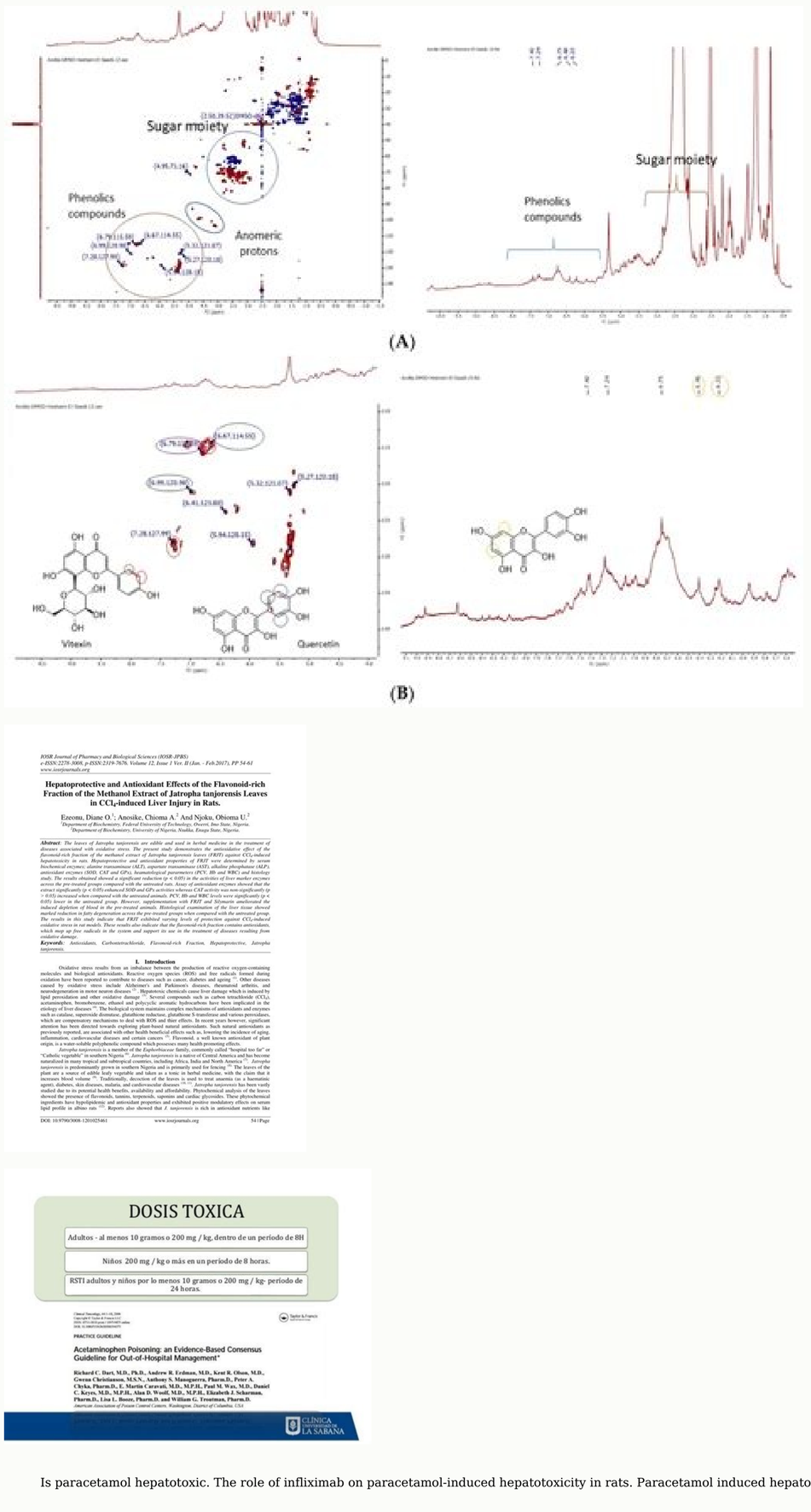
Paracetamol induced hepatotoxicity in rats pdf







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Hepatoprotective and Antioxidant Effects of the Flavonoid-rich Fraction of the Methanol Extract of Jatropha tanjorensis Leaves in CCl_4-induced Liver Injury in Rats.

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Abstract: *The leaves of Jatropha tanjorensis are edible and used in herbal medicine in the treatment of diseases associated with oxidative stress. The present study demonstrates the antioxidative effect of the flavonoid-rich fraction of the methanol extract of Jatropha tanjorensis leaves (FRJT) against CCl_4-induced hepatotoxicity in rats. Hepatoprotective and antioxidant properties of FRJT were determined by serum biochemical enzymes; alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), antioxidant enzymes (SOD, CAT and GPx), heamatological parameters (PCV, Hb and WBC) and histology study. The results obtained showed a significant reduction ($p < 0.05$) in the activities of liver marker enzymes across the pre-treated groups compared with the untreated rats. Assay of antioxidant enzymes showed that the extract significantly ($p < 0.05$) enhanced SOD and GPx activities whereas CAT activity was non-significantly ($p > 0.05$) increased when compared with the untreated animals. PCV, Hb and WBC levels were significantly ($p < 0.05$) lower in the untreated group. However, supplementation with FRJT and Silymarin ameliorated the induced depletion of blood in the pre-treated animals. Histological examination of the liver tissue showed marked reduction in fatty degeneration across the pre-treated groups when compared with the untreated group. The results in this study indicate that FRJT exhibited varying levels of protection against CCl_4-induced oxidative stress in rat models. These results also indicate that the flavonoid-rich fraction contains antioxidants, which mop up free radicals in the system and support its use in the treatment of diseases resulting from oxidative damage.*

Keywords: *Antioxidants, Carbontetrachloride, Flavonoid-rich Fraction, Hepatoprotective, Jatropha tanjorensis.*

I. Introduction

Oxidative stress results from an imbalance between the production of reactive oxygen-containing molecules and biological antioxidants. Reactive oxygen species (ROS) and free radicals formed during oxidation have been reported to contribute to diseases such as cancer, diabetes and ageing [1]. Other diseases caused by oxidative stress include Alzheimer's and Parkinson's diseases, rheumatoid arthritis, and neurodegeneration in motor neuron diseases [2]. Hepatotoxic chemicals cause liver damage which is induced by lipid peroxidation and other oxidative damage [3]. Several compounds such as carbon tetrachloride (CCl_4), acetaminophen, bromobenzene, ethanol and polycyclic aromatic hydrocarbons have been implicated in the etiology of liver diseases [4]. The biological system maintains complex mechanisms of antioxidants and enzymes such as catalase, superoxide dismutase, glutathione reductase, glutathione S-transferase and various peroxidases, which are compensatory mechanisms to deal with ROS and thier effects. In recent years however, significant attention has been directed towards exploring plant-based natural antioxidants. Such natural antioxidants as previously reported, are associated with other health beneficial effects such as, lowering the incidence of aging, inflammation, cardiovascular diseases and certain cancers [5]. Flavonoid, a well known antioxidant of plant origin, is a water-soluble polyphenolic compound which possesses many health promoting effects.

Jatropha tanjorensis is a member of the *Euphorbiaceae* family, commonly called "hospital too far" or "Catholic vegetable" in southern Nigeria [6]. *Jatropha tanjorensis* is a native of Central America and has become naturalized in many tropical and subtropical countries, including Africa, India and North America [7,8]. *Jatropha tanjorensis* is predominantly grown in southern Nigeria and is primarily used for fencing [9]. The leaves of the plant are a source of edible leafy vegetable and taken as a tonic in herbal medicine, with the claim that it increases blood volume [6]. Traditionally, decoction of the leaves is used to treat anaemia (as a haematinic agent), diabetes, skin diseases, malaria, and cardiovascular diseases [10,11]. *Jatropha tanjorensis* has been vastly studied due to its potential health benefits, availability and affordability. Phytochemical analysis of the leaves showed the presence of flavonoids, tannins, terpenoids, saponins and cardiac glycosides. These phytochemical ingredients have hypolipidemic and antioxidant properties and exhibited positive modulatory effects on serum lipid profile in albino rats [12]. Reports also showed that *J. tanjorensis* is rich in antioxidant nutrients like

Is paracetamol hepatotoxic. The role of infliximab on paracetamol-induced hepatotoxicity in rats. Paracetamol induced hepatotoxicity in rats pdf. Does paracetamol cause hepatotoxicity. The protective effect of pomegranate juice in paracetamol-induced acute hepatotoxicity in rats. How does paracetamol overdose cause hepatotoxicity. Why paracetamol causes hepatotoxicity.

...but your activity and behavior on this site made us think that you are a bot. Note: A number of things could be going on here. If you are attempting to access this site using an anonymous Private/Proxy network, please disable that and try accessing site again. Due to previously detected malicious behavior which originated from the network you're using, please request unblock to site. Rats are thin-tailed, medium-size rodents that originated in Asia and Australia but are now found all over the world. "True rats" are members of the genus Rattus, but other rodent genera are also referred to as rats and share many of the same characteristics. Rats differentiate from mice by being larger, with longer, thinner bodies and long legs.According to the Integrated Taxonomic Information System (ITIS) there are more than 60 species of rat, which means they come in all sizes. They are typically 5 inches (12 centimeters), or longer, according to Encyclopedia Britannica. The largest species is the Bosavi woolly rat, which was discovered in 2009 in the rainforest of Papua New Guinea (and doesn't have a scientific name yet). It is about the size of a cat — 32.2 inches (82 cm) from nose to tail and weighs around 3.3 lbs. (1.5 kilograms), according to CNN. One of the smallest rats is Osgood's Vietnamese rat. It is typically 5 to 7 inches (12 to 17 cm) long.According to the Australian Broadcasting Corp., male rats are called bucks; females are does. Infants are called pups or kittens. A group of rats is called a mischief. HabitatRats are found all over the world. For example, the rice-field rat is found in Southeast Asia, the Australian swamp rat is found in Eastern Australia, and the Norway rat, also called brown rats, is found on every continent of the world except Antarctica, according to the Animal Diversity Web at the University of Michigan. The brown and the house rat are the most common rats in the world because they have taken boats to every country over the past few centuries. House rats typically like warmer climates, while brown rats live in temperate climates. They typically live anywhere humans live. Many rat species also live in trees. Overall, rats live to forage and mate. Most rats are nocturnal, though the brown rat is often awake day or night. Rats usually stick together in groups called packs. New packs are formed when a male and female go off on their own and nest in an area that doesn't already contain a pack. Brown rats are usually led by the largest male in the pack. Other rats may have several dominant males or females in a pack.Norway Rat (Rattus norvegicus), (Image credit: CDC) DietRats are omnivores, but many prefer meat when they can get it. House and brown rats usually use humans for their primary food source. They will scavenge through trash or eat any food that is left unprotected. Rats have also been known to eat grain or kill insects, water creatures such as snails, fish and mussels, small birds, mammals and reptiles for food. Other rats, such as the Sulawesi white-tailed rat and Hoffman's rat, prefer vegetarian fair such as seed and fruits, according to Encyclopedia Britannica. OffspringBefore their offspring are born, rats build nests from any material that can be foraged from the area, including branches, grass, trash and paper. These nests are usually built in crevices, in rotting trees or in buildings. Rats, generally, are baby-making machines. Female rats can mate around 500 times in a six-hour period and brown rats can

produce up to 2,000 offspring in a year, according to Discover Magazine. Brown rats can have up to 22 young at once, though eight or nine is more the average. Tropical rats tend to only have one to six babies at once. After a gestation period of 21 to 26 days, babies that weigh only around 6 to 8 grams (.21 to .28 ounces) are born, according to the American Fancy Rat and Mouse Association. By the age of three months, the brown rat is ready to reproduce. Rats typically live around two or three years. Most house rats — 91 to 97 percent — die within their first year of life, according to the University of Michigan. Classification/taxonomyHere is the taxonomy of rats according to ITIS:Kingdom: Animalia Subkingdom: Bilateria Infrakingdom: Deuterostomia Phylum: Chordata Subphylum: VertebrataInfraphylum: Gnathostomata Superclass: Tetrapoda Class: Mammalia Subclass: Theria Infraclass: Eutheria Order: Rodentia Suborder: Myomorpha Superfamily: Muroidea Family: Muridae Subfamily: Murinae Genus: RattusSpecies include:Rattus argentiventer — Rice-field ratRattus hoffmanni — Hoffmann's Sulawesi ratRattus lutreolus — Australian swamp ratRattus norvegicus — Norway rat, or brown ratRattus osgoodi — Osgood's Vietnamese ratRattus rattus — House rat, or black ratRattus xanthurus — Northeastern Xanthurus rat, or Sulawesi white-tailed rat Conservation statusThe International Union for Conservation of Nature (IUCN) lists 16 rat species on its Red List of Threatened Species. They are considered threatened with extinction due to loss of habitat and decreasing populations. Near ThreatenedRattus elaphinus (Sula Archipelago rat)Rattus feliceus (Spiny Seram Island rat)Rattus jobiensis (Yapen rat)VulnerableRattus hoogerwerfi (Hoogerwerf's Sumatran rat)Rattus palmarum (Zelebor's Nicobar rat)Rattus richardsoni (Glacier rat)Rattus satarae (Sahyadris forest rat)Rattus stoicus (Andaman rat)Rattus xanthurus (Northeastern Xanthurus rat)EndangeredRattus burrus (Miller's Nicobar rat)Rattus hainaldi (Hainald's Flores Island rat)Rattus lugens (Mentawai Archipelago rat)Rattus montanus (Sri Lankan mountain rat)Rattus ranjiniae (Ranjini's field rat)Rattus simalurensis (Simalur Archipelago rat)Rattus vandeuseni (Van Deusen's rat) Other factsBrown and house rats have made a number of mammal, bird and reptile species extinct, especially on oceanic islands, according to Encyclopedia Britannica. They have also spread of diseases among humans, including bubonic plague.Rats aren't all bad, though. Brown rats are used in laboratories for research. In fact, according to the Foundation for Biomedical Research, 95 percent of all lab animals are mice and rats.A rat's front teeth grow 4.5 to 5.5 in (11 to 14 cm) each year, according to Discover Magazine.Additional resources Open Access Peer-reviewed Acetaminophen or paracetamol (APAP) overdose is a common cause of liver injury. Silymarin (SLM) is a hepatoprotective agent widely used for treating liver injury of different origin. In order to evaluate the possible beneficial effects of SLM, Balb/c mice were pretreated with SLM (100 mg/kg b.wt. per os) once daily for three days. Two hours after the last SLM dose, the mice were administered APAP (300 mg/kg b.wt. i.p.) and killed 6 (T6), 12 (T12) and 24 (T24) hours later. SLM-treated mice exhibited a significant reduction in APAP-induced liver injury, assessed according to AST and ALT release and histological examination. SLM treatment significantly reduced superoxide production, as indicated by lower GSSG content, lower HO-1 induction, alleviated nitrosative stress, decreased p-JNK activation and direct measurement of mitochondrial superoxide production in vitro. SLM did not affect the APAP-induced decrease in CYP2E1 activity and expression during the first 12 hrs. Neutrophil infiltration and enhanced expression of inflammatory markers were first detected at T12 in both groups. Inflammation progressed in the APAP group at T24 but became attenuated in SLM-treated animals. Histological examination suggests that necrosis the dominant cell death pathway in APAP intoxication, which is partially preventable by SLM pretreatment. We demonstrate that SLM significantly protects against APAP-induced liver damage through the scavenger activity of SLM and the reduction of superoxide and peroxynitrite content. Neutrophil-induced damage is probably secondary to necrosis development. Citation: Papackova Z, Heczkova M, Dankova H, Sticova E, Lodererova A, Bartonova L, et al. (2018) Silymarin prevents acetaminophen-induced hepatotoxicity in mice. PLoS ONE 13(1): e0191353. Hiroyasu Nakano, Toho Daigaku, JAPANReceived: August 3, 2017; Accepted: January 3, 2018; Published: January 17, 2018Copyright: © 2018 Papackova et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.Data Availability: All relevant data are within the paper and its files.Funding: This study was supported by grant 17-08888S from the Czech Science Foundation (, Czech Republic to MP and by MH CZ – DRO "Institute for Clinical and Experimental Medicine – IKEM, IN 00023001" to MC. (. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.Competing interests: The authors have declared that no completing interests exist. Acetaminophen (N-acetyl-p-aminophen, APAP) is a safe and effective analgesic/antipyretic drug when used at therapeutic levels [1]. However, APAP overdose results in centrilobular hepatic necrosis, which can be fatal [2]. APAP toxicity is initiated by the formation of the reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI). NAPQI is catalysed by cytochrome P450 CYP2E1, which is responsible for liver injury through the depletion of glutathione [3]. Once GSH is exhausted, any remaining NAPQI formed will react with alternative targets, in particular cellular proteins such as mitochondrial proteins, and induce mitochondrial oxidative stress and dysfunction [4]. Increased superoxide production is central to consecutive pathological processes. The spontaneous reaction of superoxide and nitric oxide gives rise to the generation of peroxynitrite. Knight et al. [5, 6] confirmed that peroxynitrite plays a critical role in the mechanisms of APAP-induced hepatotoxicity. Increased oxidant stress results in the activation of c-Jun N-terminal kinases (JNK) 1/2, which translocate to the mitochondria, eventually triggering the opening of the mitochondrial membrane permeability transition (MPT) pore [7] and releasing mitochondrial intermembrane proteins such as apoptosis-inducing factor (AIF). The translocation of these proteins to the nucleus causes nuclear DNA fragmentation [8]. The extensive mitochondrial dysfunction resulting in ATP depletion together with nuclear DNA damage leads to necrotic cell death [9]. Currently, APAP-induced liver injury is a popular mechanistic model for testing phytotherapeutic and other hepatoprotective interventions. The use of natural products in the prevention and treatment of liver disease has gained considerable popularity [10]. Silymarin (SLM) is a polyphenolic component isolated from the fruits and seeds of the milk thistle plant Silybum marianum (Asteraceae family) [11]. Silymarin extract contains approximately 65% to 80% flavonolignans (silybin A, silybin B, isosilybin A, isosilybin B, silychristin and silydianin), a small proportion of flavonoids and approximately 20% to 35% fatty acids and polyphenolic compounds, which possess a range of metabolic regulatory effects [12]. The hepatoprotective properties of silymarin in APAP intoxication have been previously described [13–16]. Nevertheless, most of these studies only concentrate on the final effect of silymarin in terms of reducing death rate and not on the detailed mechanisms of its protective effects. Furthermore, a substantial number of studies have been performed on rats, which are an unsuitable model for APAP toxicity. In humans, APAP-induced liver injury involves mitochondrial damage, oxidative stress, c-Jun terminal kinase activation and nuclear DNA fragmentation. The mode of cell death is oncotic necrosis, a similar mechanism to the one that occurs during APAP intoxication in mice. However, rats develop low or no oxidative stress and thus no injury; hepatoma cells may develop injury but through a different mechanism to the mechanisms in mice and humans [17]. In this mouse model study, we examined the effect of silymarin on critical events during the initiation and progression of APAP hepatotoxicity, particularly CYP2E1 metabolism, superoxide production, oxidative and nitrosative stress, inflammation and apoptotic and necrotic cell death. Male BALB/c mice were kept in a temperature-controlled room under a 12:12 hour light-dark cycle. The animals had free access to drinking water and were fed a standard chow diet. All experiments were performed in agreement with the Animal Protection Law of the Czech Republic 311/1997, which is in compliance with the Principles of Laboratory Animal Care (NIH Guide to the Care and Use of Laboratory Animals, 8th edition, 2013) and were approved by the ethical committee of the Institute for Clinical and Experimental Medicine. Fifty-six mice were randomly divided into 7 groups (n = 8): (1) vehicle control, (2) APAP 6 hours, (3) APAP 6 hours + SLM, (4) APAP 12 hours, (5) APAP 12 hours + SLM, (6) APAP 24 hours, (7) APAP 24 hours + SLM. The effect of SLM on CYP2E1 activity or expression and GSH/GSSG content was tested in separate group designated as SLM. Micronized silymarin was purchased from Favea s.r.o., Koprivnice, CR. The suspension of the silymarin and 25% xanthan gum in the appropriate dose was administered per os by intragastric gauche. Mice were pretreated with four doses (1 dose per day) of silymarin (100 mg/kg). The last dose was applied two hours prior to APAP administration. On the fourth day after fasting for 8 hours, mice were treated with APAP (300 mg/kg). APAP (Sigma Aldrich, St. Louis, MO USA) was dissolved in 0,6 ml of warm (37°C) sterile phosphate buffered saline (PBS) and injected intraperitoneally. Animals were killed 6 (T6), 12 (T12) and 24 (T24) hours after APAP administration, after which serum and liver tissue were collected. Plasma levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured using a commercially available kit (Sigma Aldrich, St. Louis, MO, USA) according to the manufacturer's instructions. Liver pieces were fixed in formalin and embedded in paraffin. Samples were then sectioned and stained with haematoxylin-eosin to further evaluate liver damage. Nitrotyrosine staining was performed according to Knight [5]. For detection of antigen three step visualization system was used: primary anti-nitrotyrosine antibody (MyBioSource, Inc., San Diego, CA, MBS 2001557, dilution 1:2000), biotinylated goat anti rabbit IgG (H+L), Vectastain Elite ABC Reagent (Vector Laboratories, Inc., Burlingame, CA, USA) and DakoLiquid DAB+ Substrate Chromogen System (Dako, Glostrup, Denmark). The total cytochrome P450 concentration in liver homogenate and microsomes was determined spectrophotometrically using a method described by Guengerich et al. [18]. Cytochrome P450 concentration was calculated using a carbon monoxide difference spectrum between 450 and 490 nm for dithionite-reduced samples. CYP2E1 enzyme activity was determined using a method based on chlorzoxazone 6-hydroxylation [19]. In brief, 1 ml of the reaction mixture (100 mM phosphate buffer, pH 7.4, NADPH generating system, 2.5 mM chlorzoxazone) was incubated with liver homogenate or liver microsomes (160 pmol P450) for 20 min. The reaction was terminated by adding 50 μl of 42.5% phosphoric acid and 2 ml of a mixture of propan-2-ol/chloroform 15/85 (w/w). The mixture was centrifuged at 1000 g for 10 min, sediment was dried under nitrogen and the residue was dissolved in 200 μl of a mobile phase (0.5% acetic acid in 75% acetonitrile). 50 μl of the solution was injected into the Shimadzu HPLC system (LC Prominence, Shimadzu, Kyoto, Japan) at a constant flow rate of 1 ml/min and with UV detection at 287 nm. Liver mitochondria were prepared by differential centrifugation as described by Bustamante et al. [19] with some modifications. Liver tissue was homogenised at 0°C using a teflon-glass homogeniser as a 10% homogenate in a medium containing 220 mM mannitol, 70 mM sucrose and 1 mM HEPES, pH 7.2 (MSH medium). Crude impurities were removed by centrifugation at 800 g for 10 min and the remaining supernatant was centrifuged for 10 min at 8 000 g. The pelleted mitochondria were resuspended in the MSH medium, washed twice under 10-min centrifugation at 8 000 g and finally resuspended at a concentration of 20–30 mg protein/ml. Mitochondrial proteins were determined using the BCA method (Thermo Fisher Scientific, Waltham, MA, USA). Submitochondrial particles (SMP) were prepared according to Ide et al. [20]. Briefly, isolated mitochondria were sonicated and pelleted by centrifugation at 48 000 g for 10 min. The resultant pellet was washed three times in MSH buffer in order to get rid of matrix components and then stored at -80°C. ROS production in SMPs in vitro was measured using a DCFDA (Cell Biolabs, San Diego, CA, USA) probe, as described previously [21]. Briefly, the assay was performed with approximately 0.2 mg of mitochondrial protein per ml in MAS buffer (70 mM sucrose, 220 mM mannitol, 10 mM KH2PO4, 5 mM MgCl2, 2 mM HEPES, 1 M EGTA, pH = 7.2). The measurement was performed either in basal MAS buffer only or in a medium supplemented with either 10 mM NADH -/+ 10 μM antimycin or 10 mM succinate -/+ 10 μM antimycin. The final concentration of DCFDA was 10 μM and the excitation/emission wavelength was 485/528 nm. The fluorescence signal rose linearly from 0 until the 45th minute of the assay. The data presented were obtained 45 min after the start of the assay. All experiments were repeated in the absence of mitochondria, while background fluorescence changes were subtracted. The obtained values were normalised per mg of protein and expressed as a percentage of fluorescence under basal conditions (without substrates). Thiobarbituric acid-reactive substance (TBARS) content was determined using the ELISA TBARS determination kit (Exiqon, Woburn, MA, USA). Levels of reduced (GSH) and oxidised glutathione (GSSG) were assayed with the Glutathione in Whole Blood–HPLC detection kit (Chromsystems, Gräfelfing, Germany). Liver homogenate (20% wt/vol) was prepared using the Ultra-Turrax homogeniser (IKE, Worke, Staufen, Germany) in a homogenisation buffer (10 mM TRIS, 250 mM sucrose, 1 mM EDTA, 1 mM PMSF, 10 ug/ml leupeptin, 10 ug/ml aprotinin). Protein concentration was determined using the BCA method (Thermo Fisher Scientific, Waltham, MA, USA). Proteins were separated under denaturing conditions using SDS-PAGE and electroblotted to PVDF membranes. Phosphorylation of JNK was assessed by immunodetection using a specific antibody (Cell Signaling Technology, Danvers, MA, USA). The total expression of JNK was determined on the same membrane after striping and reblotting using a specific antibody (Cell Signaling Technology, Danvers, MA, USA). Bands were visualised by ELC and quantified using the FUJI LAS-3000 imager (FUJI FILM, Tokyo, Japan). Other proteins were quantified using specific antibodies: RIP-3 (Cell Signaling Technology, Danvers, MA, USA) and CYP2E1 (Abcam, Cambridge, UK). These membranes were exposed to medical X-Ray films and scanned using CanoScan Toolbox software, ver. 5.0. Medical X-ray films were analysed using ElfoMan software, ver. 2.6 (Semecky Inc., Prague, Czech Republic). Liver samples were dissected and immediately frozen in liquid nitrogen. Total RNA was extracted using the Qiagen Mini RNeasy isolation kit (Qiagen, Hilden, Germany). A DNAase step was included to avoid possible DNA contamination. A standard amount of total RNA (1600 ng) was used to synthesise first-strand cDNA with the High Capacity RNA-to-cDNA Kit (Applied Biosystems, Foster City, CA, USA). The RT-PCR amplification mixture (25ul) contained 1 ul template cDNA, Syber Green master mix buffer (QuantiTect, Qiagen, Hilden, Germany) and 400nM (10 pmol/reaction) sense and antisense primer. The reaction was run on the ViiA 7 Real-Time PCR System (Thermo Fisher Scientific, USA). Results were analysed using SDS software, ver. 2.3 (Applied Biosystems, Foster City, CA, USA). The expression of genes of interest was normalised to the housekeeper gene (B2M) and calculated using the ΔΔCt method. Data are presented as mean ± SEM. Statistical analysis was performed using the Kruskal-Wallis test with multiple comparisons (n = 7–8). Differences were considered statistically significant at the level of p

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