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Original Research Article

Effects of dishwashing detergents residues on redox status and cell proliferation in mice liver and kidney

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ABSTRACT

Background: Commonly known for their cleaning and disinfecting properties, dishwashing detergents containing anionic surfactants can be potentially toxic due to misuse. This study aims to investigate the possible harmful effects of detergents residues persisting on utensils after dishwashing.
Methods: Residues were collected after cleaning the utensils in 100 mL of water from 100 households in Beirut, Lebanon. After anionic surfactant determination, water with detergent residues (WDR) was added to drinking water of white mice versus tap water as control: G1 (TW for 2 months), G2 (WDR for 2 months), G3 (TW for 3 months) and G4 (WDR for 3 months), N=6 for each group. Animals were then sacrificed. Biopsies from liver and kidneys were taken for histological examination or preserved at -80˚C for biochemical analysis of lipid peroxidation, superoxide dismutase activity, and expression of PI3K/AKT/mTOR pathway proteins by western blotting.
Results: Our results showed no significant difference in body weight or histological alteration in groups given WDR versus TW groups. An increase of LP (30%) and a decrease of SOD activity (25%) were noted in the liver tissue of G2 and G4 versus G1 and G3 respectively ($p<0.05$). In addition, p-AKT and p-mTOR proteins expression regulating cell proliferation were significantly increased in the liver of G4 versus G3 ($p<0.05$).
Conclusions: We concluded that traces of detergents on utensils do not cause an acute pathology, but they could cause oxidative stress to the liver and an over-expression of cancer pathway over a relative long period of time.

Keywords: Dishwashing residues, Detergents, Surfactants, Mice, Oxidative stress, PI3K/AKT/mTOR

INTRODUCTION

Hygiene is a set of principles and practices aiming to preserve and improve health; it is essentially based on three actions: cleaning, disinfection and conservation. In this perspective, the regular use of detergents is necessary for people's well-being and society's general health. Thirty years ago, the development of synthetic detergent transformed the cleaning processes.[1] Household detergents, including dishwashing detergents, are a mixture of variable ingredients, anionic surfactants being the main active agent.[2] Surfactants tend to accumulate on surfaces or interfaces since they hold a large number of chemical compounds with hydrophilic and lipophilic groups. The hydrophilic part extends to the aqueous phase, while the lipophilic part is directed towards the air or oleaginous phase.[3] Separation and identification of surfactants are challenging due to their diversity, the complex composition of their materials, and the complexity of the sample matrices. Many methods can be used for the qualitative and quantitative analysis of surfactants, including chromatography, capillary

electrophoresis, and optical sensors. Nevertheless, the spectrophotometric determination of surfactants remains the most commonly used method.[4] Despite beneficial cleaning properties, misuse of detergents can sometimes become toxic to humans. There are numerous studies on the toxicity of pesticides, insecticides and laundry cleaning products.[5-7] These detergents can cause poisoning by inhalation or ingestion, eye or skin burns, and allergic sensitization.[8,9] However, few studies have specifically investigated the cellular and systemic toxicity of detergents. Misik et al investigated the oral or intravenous administration of detergent in rodents and Bertinelli et al explored the accidental absorption of detergents in humans, mainly children.[10,11]

Due to massive use of detergents, many environmental and public health regulatory authorities have fixed strict limits for anionic surfactants (0.5 mg/l for drinking water).[12] Water contamination by detergents is a critical environmental problem relative to their low biodegradability, due to their recalcitrant properties.[13] Little evidence shows that dishwasher detergents are a major cause of poisonings. [14]

Studies in the United States found that dishwashers were responsible for only 0.2-0.25% of exposure incidents. Thus, severe consequences from exposure to these products were extremely rare.[14] In 1998, Leu et al showed that anionic surfactants dose-dependently enhance the electrochemical oxidation *in vitro*.[15] Following this discovery, several studies on zebrafish and cultured cells attributed that anionic surfactants were able to cause oxidative stress even at low concentrations.[16,17] The latter finding is crucial, as oxidative stress could in turn promote tumorigenesis via apoptotic pathways, subsequently playing a role in carcinogenesis.[18,19]

Due to a water shortage in many low-income Beirut neighborhoods, housewives are forced to use water sparingly.[20] Therefore, they add large quantities of detergent during dishwashing without properly rinsing, which would contribute to residues remaining on the utensils. Health effects of detergent residues persisting on utensils, as we witnessed in these neighborhoods, is an unexplored facet.

Objectives

The main objectives of our research include the following steps: collecting residues of detergents after dishwashing from households in Beirut, detecting the presence of anionic surfactants, adding residues to drinking water of mice for 2 or 3 months, consequently observing histopathological sections of liver and kidneys, and evaluating oxidative stress and the apoptosis signalling pathway to identify early alterations at the molecular level.

If the administered dose falls within the range of concentrations that induces oxidative stress, as described previously, it may be the root cause of an installing pathology.[18] This can be considered an original topic due to the scarcity of research in this area.

METHODS

This study was conducted between October 2020 and Mars 2022. Experiments were carried out at the laboratory of physiology, faculty of medical sciences, Lebanese University.

Collection of water from hand washed utensils

100 random households were selected in deprived neighbourhoods of Beirut. These homes accomplished washing dishes by hand using classic detergents (no H_2O_2 or other cleaning products added). After the dishes have been cleaned and washed (not wiped), 2 samples from each household were taken by pouring 100 ml of distilled water (heated to 40°C) into a plate, glass, or Tupperware. After 5 minutes, this water was collected, placed in a bottle, and stored in the refrigerator until analysis.

Surfactant quantification

Quantification of surfactants was carried out by colorimetric methods.[21] The colorimetric (methylene blue) method was used to quantify the total concentrations of anionic surfactant as methylene blue active substances (MBAS). Samples were agitated with a mixture of phosphate buffer (pH=10), neutral methylene blue and chloroform. Then, the separated chloroform layer was agitated with distilled water and acidic methylene blue solution. The extraction from acidic aqueous medium into chloroform was repeated twice by adding chloroform.

The chloroform phase obtained from the acidic solution was filtered and collected in the vial. The intensity of the acquired blue color, which was proportional to the concentration of the extracted anionic surfactant in the organic phase, was measured by spectrophotometer at 652 nm. The acquired intensity of the blue color was proportional to the anionic surfactant concentration in the extracted organic phase. A calibration graph was drawn using standard solutions of sodium dodecyl sulfate, and concentrations of the samples were calculated.

Experimental protocol in mice

Twenty-four male *Swiss albino* mice (*Mus musculus*) weighting 20±1 g was provided by the animal house of Saint Joseph University Beirut-Lebanon. These animals were observed for one week in a room with well-controlled light, ambient temperature and humidity, with access to food and water ad libitum.

Animals showing abnormal behavior were excluded from the study. They were divided randomly into 4 different groups of 6 mice each: G1 and G3 acted as controls,

receiving tap water (TW) for 2 or 3 months respectively, while G2 and G4 received water with detergents residues (WDR) in their drinking water for 2 or 3 months respectively (Figure 1).

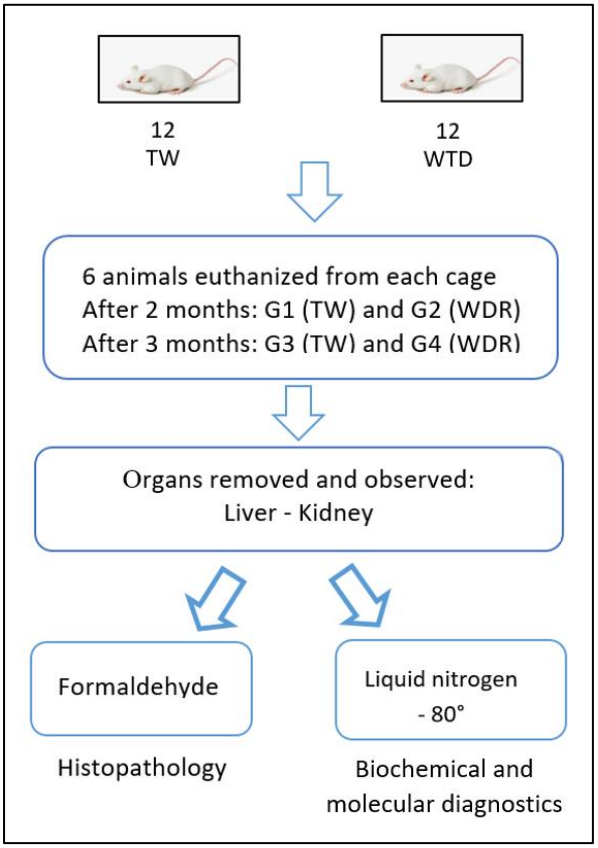

Figure 1: Experimental protocol, G1, G2, G3, G4: group of mice N=6 each, TW: tap water (control), WDR: water with detergents residues.

Weight curve and organ removal

All animals were weighed with a sensitive balance once a week throughout the experimental period in order to establish the growth curve. At the end of the experimental period, animals were sacrificed by cervical dislocation and the main organs were removed, one part introduced into a 5% formalin solution intended to make histological sections and the other part introduced rapidly in liquid nitrogen and then frozen at -80˚C until biochemical assays.

Biochemical assays

Malondialdehyde assay method: malondialdehyde (MDA), a marker of lipid peroxidation, was determined from homogenates of cold-ground organs in phosphate buffer by the TBARS assay kit (Cayman chemical company, Ann Harbor, USA).

The TBARS assay is based on the reaction of MDA with thiobarbituric acid (TBA) at high temperature and acidity. The MDA-TBA complex formed was measured by spectrophotometry, a colorimetric method. The samples of liver, kidney, or the standard were added to the solution of TBA, acetic acid and sodium hydroxide. The mixture was incubated for 1 hour at 100°C. The samples or standards were then cooled on ice for 10 minutes in order to stop the reaction, then were centrifuged for 10 minutes at 1600 g at 4°C. The samples or standards were left for 30 minutes at room temperature before the absorbance of the supernatant was measured at 532 nm.[22]

Superoxide dismutase (SOD) activity assay: we used SOD kit no 706002 (Cayman Chemical Company). SOD activity was measured from organ homogenates prepared on ice in 50 mM potassium phosphate buffer (pH 7.8, with 1.34 mM diethylene triamine pentaacetic acid). This test is based on the competition between SOD and NBT for the production of superoxide from xanthine and xanthine oxidase. Incubation for 45 minutes with 5 mM sodium cyanide was performed to inhibit enzyme activity. SOD activity was determined for each sample.

he assay is a colorimetric method by absorbance at 560 nm.[23] Western blot technique: protein samples (15 µg) were separated by 10% SDS/polyacrylamide gel (Bio-Rad, Hercules, CA, USA) electrophoresis for 1 hour 30 minutes at 130V and were transferred to a polyvinylidene difluoride membrane for 1 hour at 20 V. To saturate the non-specific binding sites, the membranes are stirred for 1 hour in TBS Tween 20 buffer (0.1%), 5% BSA. They are then incubated overnight at 4°C, while shaking, with the primary antibody solution (primary antibody and TBS Tween 20 0.1%, 5% BSA).

The membrane was then incubated with the following primary antibodies overnight at 4°C: rabbit anti-AKT (1:1,000, cell signaling technology); rabbit anti-p-AKT (1:1,000, cell signaling technology); rabbit anti-mTOR (1:1,000, cell signaling technology); rabbit anti-p-mTOR (1:1,000, cell signaling technology); mouse anti-β-actin (1:1,000, Sigma-Aldrich). The membranes were incubated with corresponding horse radish peroxidase-conjugated secondary antibody for 1 hour at room temperature (anti-rabbit 1:2,000 and anti-mouse 1:2,000; ZSGB-BIO, Beijing, China). The protein signal was visualized using the ECL western blotting detection kit (NC15079;

Thermo Fisher Scientific, Waltham, MA, USA). Images were acquired with imaging system (c300; Azure Biosystems, Dublin, CA, USA) and quantified with Image J software (NIH, Bethesda, MD, USA).[24]

Statistical analysis

The results are expressed as the mean ± standard deviation. Statistical studies were performed by one-way analysis of variance (ANOVA), followed by Tukey's test. These results are considered statistically significant if the p value is less than 0.05.

RESULTS

Surfactant analysis

Among the 100 samples collected, 40 were found to contain detergent residues. They were pooled with a mean value of 0.54 mg/l of anionic surfactants. Given that mice weighing around 20 g drink about 3 ml per day, the average concentration of anionic surfactant in drinking water has been estimated 0.081 mg/kg/24 hour.

Body weight and histopathology

No significant body weight difference was noted between animals receiving TW and those receiving WDR. Likewise, no significant alterations were identified in the liver of kidney tissue of animals in G2 or G4 (data not illustrated).

Effect of detergent traces on the oxidant profile

Traces of detergents present in the drinking water caused a significant increase ($p<0.05$) in the levels of MDA in liver tissue (542.2±50.5) as compared to control (416.5±48.2) for 3 months, which reflects lipid peroxidation (Figure 2A). In addition, a significant decrease of SOD activity was observed in liver tissue (158±22.5) as compared to control (210.5±25.7) for 3 months (Figure 3A). However, the kidney tissue does not appear to be affected significantly by the traces of detergents (Figure 2B and 3B).

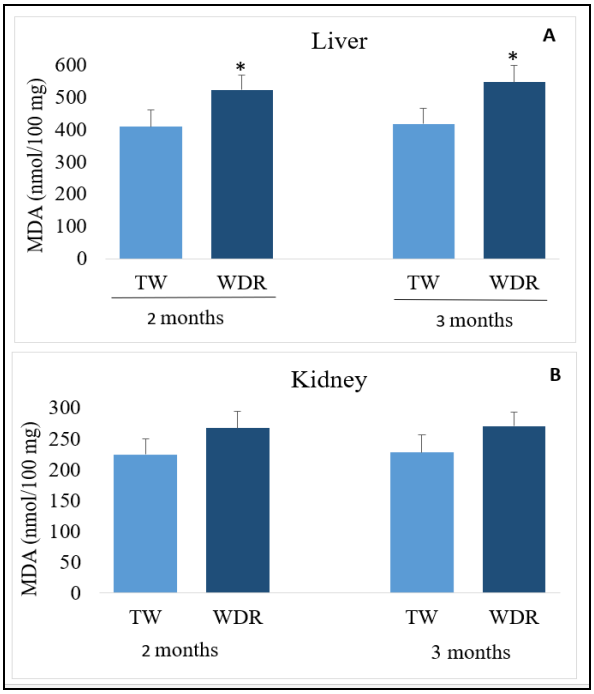

Figure 2: Amounts of malondialdehyde (A) in liver tissue; and (B) kidney tissue of control mice verses mice given water containing traces of detergent.

Note: *P<0.05 versus control, N=6, TW: tap water (control), WDR: water with detergents residues.

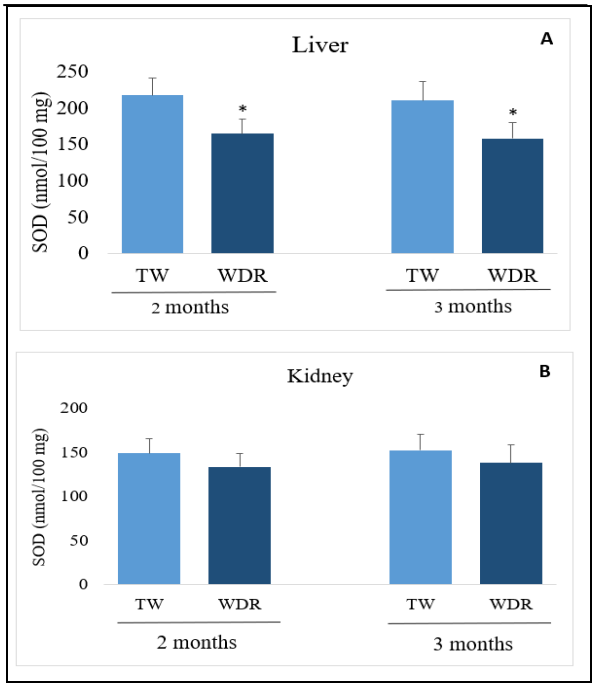

Figure 3: Amounts of superoxide dismutase activity (A) in liver tissue; and (B) kidney tissue of control mice vs. mice given water containing traces of detergent.

Note:*P<0.05 verses control, N=6, TW: tap water (control), WDR: water with detergents residues.

Western blot analysis

In order to study the PI3K/AKT/mTOR pathway activation state, we evaluated the level of expression of phosphorylated AKT (p-AKT) and phosphorylated mTOR (p-mTOR) proteins in the liver and kidney tissues. Representative western blot of p-AKT and p-mTOR in control mice verses mice given traces of detergent in water for 2 or 3 months in liver and kidney tissues, respectively are shown in (Figure 4 and 6).

The comparative levels of proteins expression were quantified with β-actin normalization and evaluated by detecting a band (molecular weight of p-AKT: 62 kDa; molecular weight of p-mTOR: 289 kDa) and measuring their density in the 4 groups. Results are presented as the mean±standard deviation of pooled data from the 4 groups as depicted in (Figure 5 and 7).

The mean value of p-AKT (Figure 5A) and p-mTOR (panel B) proteins expression for liver tissue of mice given traces of detergent in water for 3 months is shown in (Figure 5). It is significantly increased as compared to control ($p<0.05$).

In kidney tissue (Figure 7A), p-AKT and p-mTOR (panel B) mean value of proteins expression of mice given traces of detergent in water for 2 or 3 months (G2 and G4), were not significantly increased as compared to control.

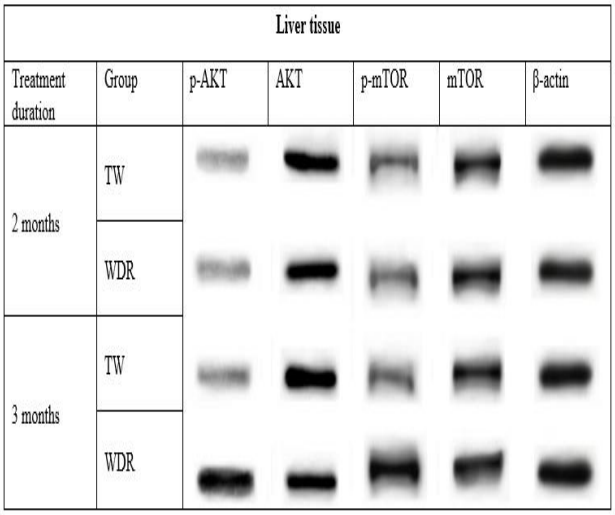

Figure 4: Representative western blot for expression of phosphorylated AKT and phosphorylated mTOR (p-mTOR) in control mice verses mice given traces of detergent in water for 2 or 3 months in liver tissue. The comparative levels of expression were quantified with β-actin normalization, control (TW), detergent (WDR).

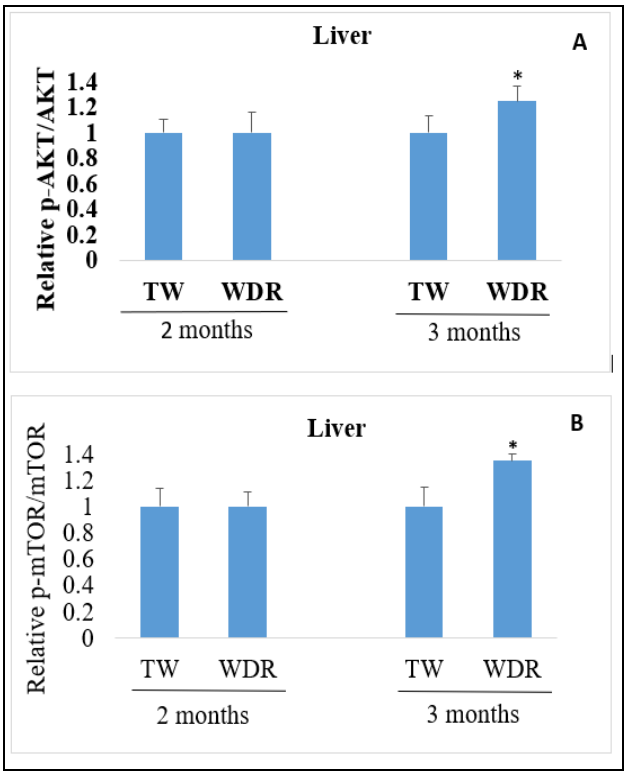

Figure 5: Quantification histograms (A) for liver tissue, mean±standard deviation for the expression of phosphorylated AKT; and (B) phosphorylated mTOR (p-mTOR) panel B in control mice verses mice given traces of detergent in water for 2 or 3 months.
Note: *indicates a significant difference, p<0.05 verses TW: tap water, WDR: water with detergents residues.

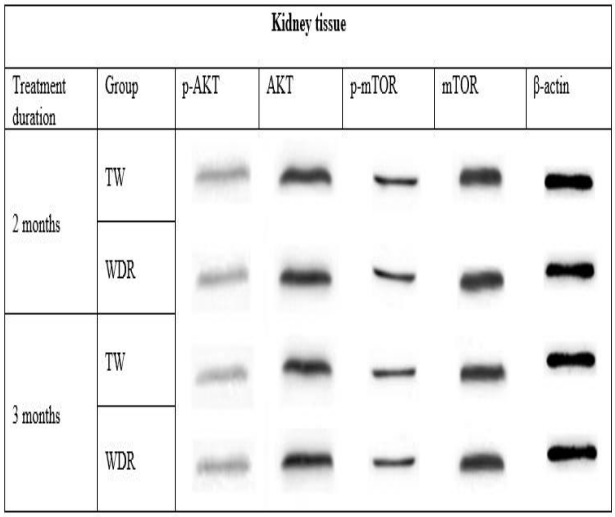

Figure 6: Representative western blot for expression of phosphorylated AKT (p-AKT) and phosphorylated mTOR (p-mTOR) in control mice verses mice given traces of detergent in water for 2 or 3 months in kidney tissue. The comparative levels of expression were quantified with β-actin normalization, control (TW), detergent (WDR).

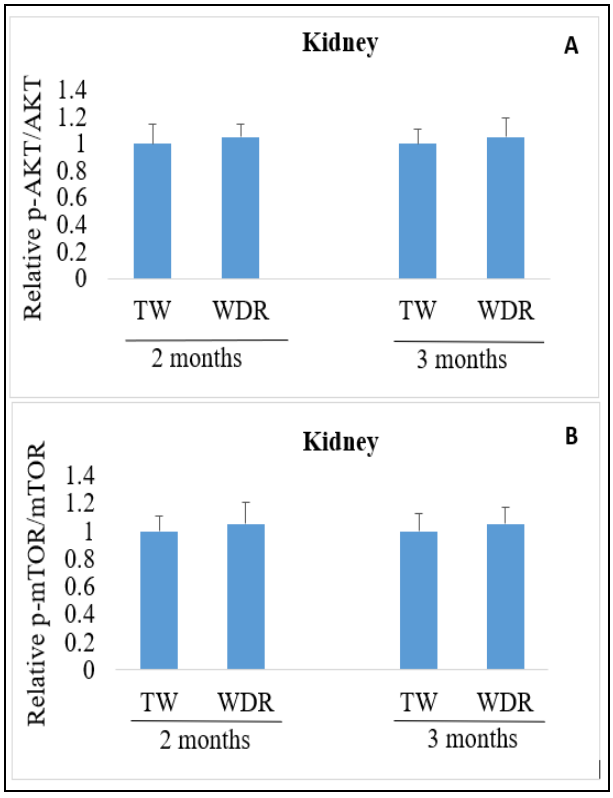

Figure 7: Quantification histograms (A) for kidney tissue, mean±standard deviation for the expression of phosphorylated AKT; and (B) phosphorylated mTOR panel B in control mice verses mice given traces of detergent in water for 2 or 3 months.
Note: TW: tap water, WDR: water with detergents residues.

DISCUSSION

There are numerous studies concerning the toxicity of pesticides, insecticides, and laundry cleaning products.[25,26] However, there are limited research regarding the cytotoxicity of dishwashing detergents worldwide and no investigations conducted at the national level. Most studies related to dishwashing products focus on allergy or accidental absorption of detergents.[27,28] The first study concerning the toxicity of dishwashing detergents in animals was performed in Germany. [27]. In this context, no serious health problems were detected following chronic skin absorptions of detergents.[29,30] Nevertheless, the study was conducted by researchers from Proctor and Gamble Company, which manufactures the detergent; this is a major bias factor, raising a conflict of interest.[30] Thus, we intended to fill the gaps in this critical problem by conducting this innovative study. To our knowledge, no prior research has been carried out to test the chronic toxicity of dishwashing detergents residues in mice.

Acceptable standards for surfactants in drinking water vary between 0.01 mg/l and 2 mg/l, depending on the country, with an average value of 0.5 mg/l.[31] The cytotoxic effects of detergents have been reported in rats via oral or intravenous administration of acute doses, thus establishing a lethal dose between 15 and 20 mg/kg, 6 mg/kg being the acute non-fatal toxic dose.[32] Our study showed that traces of detergents (0.54 mg/l) were present in 40% of water samples collected from 100 Beirut kitchens. After 2 or 3 months of introducing these samples (0.081 mg/kg) in drinking water to mice, there was apparently no significant abnormalities in histopathology diagnostic in the main organs versus control. No irregularities were noted in the appearance or behavior of the animals receiving WDR. There was no significant difference in the physical development of the control mice, as per the weight curve.

Since Leu et al discovery, several studies have claimed that anionic surfactants are able to generate oxidative stress at concentration between 0.019 and 116.9 mg/l.[16] As oxidative stress may promote tumorigenesis we therefore explored the effect of detergents at the molecular level.[33] We evaluated the role of oxidative stress (lipid peroxidation and antioxidant status) in liver and kidney tissues, as well as apoptotic signaling pathways, by assessing the activation of the PI3K/AKT pathway and the expression profile of phosphorylated AKT (p-AKT) and phosphorylated (p-mTOR) involved in the etiology of cancer. In fact, previous studies support the key role of the signaling pathway in oxidative stress and the biology of human cancers. Activation of this pathway contributes to cell cycle proliferation, growth, protein synthesis, and glucose metabolism, all important aspects of tumorigenesis.[34] Results regarding the oxidant profile displayed a modification in treated groups versus control. Thus, the traces of detergent in drinking water of the two treated groups increased lipid peroxidation and decreased the activity of superoxide dismutase significantly in liver cells, but to a lesser extent in kidney cells. An increase in oxidative stress indicates a cell aggression by free radicals. Our results are consistent with those performed on laundry detergents in crustaceans while our work is unique in mammals using dishwashing detergents.[35] Free radicals have been reported to play a major role in tumor initiation and survival induced by a variety of agents both in animal models and humans, by mediating cellular signal transduction pathways. These signaling pathways are involved in the transmission of inter- or intracellular information and are critical for supporting tumor cell survival and establishing cell fate. Under sustained environmental stress, free radicals are produced over a long time, and therefore significant damage may occur to cell structure and functions, potentially inducing somatic mutations and neoplastic transformation. Cancer initiation and progression has been linked to oxidative stress by increasing DNA mutations or inducing DNA damage, genome instability, and cell proliferation.[36]

Concerning the signaling pathway, analysis of the p-AKT and p-mTOR proteins did not show a significant difference between TW control group G1 and WDR G2 group submitted to 2 months detergent traces in drinking water. This indicates that the activity of these two proteins is not altered and the traces of detergents are not sufficient. However, a significant difference has been noted in the liver tissue, but not kidney, in the G4 group submitted to 3 months detergent traces in drinking water, which could lead to changes in the metabolic process of liver cells that may eventually turn them into cancer cells.[37] This is not surprising, knowing that the metabolism of anionic surfactant is mainly carried out by the liver which is continuously exposed to xenobiotic detoxification, the phenomenon is probably happening slowly in the course of time.[38]

PI3K pathway is a signal transduction pathway that participates in the regulation of cell growth, proliferation, differentiation; and, it plays an important role in the occurrence, development, treatment, and prognosis of malignant tumors. AKT is considered to be part of the key step in the PI3K/AKT/mTOR signal transduction pathway. Phosphorylation of AKT can activate AKT, and activated AKT regulates a series of physiological cell processes through regulating the substrate proteins. Abnormal activation of AKT can occur in many malignant cells. Activated AKT can participate in multiple signaling pathways; it can regulate transcription and protein synthesis via downstream activation of mTOR directly, or through cytokines, playing an important role in the growth and proliferation of tumor cells. PI3K/AKT/mTOR signal transduction pathway controls a large number of tumor markers involving many functions such as cell cycle, cell survival, metabolism, cell movement, and genomic instability.[37,39] We administered the traces of detergents in drinking water of mice for two or three months. In fact, the mouse model is

commonly used to study toxicity of chemical products.[40] The average lifespan of a laboratory mouse is about 2 years, while the average human life is about 80 years; therefore, 3 months represents between 6-7 human years.[41]

This period may be sufficient to test the repeated toxicity of a substance, since most studies are being carried out between 4 and 8 weeks.[42] In our experimental conditions, this period was sufficient to induce oxidative stress but did not produce a change in the PI3K/AKT/mTOR intracellular signal pathway, which was able to be done in 12 weeks. Such durations were used by some authors.[43] Although the oral administration of a product is more meticulous, due to dosing specificity, we opted for drinking water, since it is closer to reality and less stressful to animals.[44]

The transposition of these experimental results from animals to humans is a crucial problem in toxicology. Historically, it has often been assumed that experimental results can be extrapolated between species if the administered dose is standardized using the compound concentration per body weight unit or per unit body surface area per day. With the development of physiological pharmacokinetic models, it has become possible to provide a reasonably accurate description of the pharmacokinetics of a compound and its metabolites in mice, rats, and humans, using the same model.

If such a model has been validated, it is no longer necessary to extrapolate experimental results on the basis of administered dose. The effective dose at the target tissue level can be estimated using the pharmacokinetic model, and cross-species transposition can be performed on this basis. It is generally accepted that the most appropriate dosing measure at the target tissue level is the time-dependent concentration profile of the toxic entity in the target tissue.[45]

Limitations

Samples of detergent residues were taken from resource-limited streets in Beirut and administered to mice in their drinking water. The administration of a product by oral route would have been more meticulous using a gavage syringe with specific doses; however, this administration method was opted because it is closer to reality and less stressful to animals. As perspectives, studying the concentration of detergent traces on utensils should also be conducted in resource-rich communities to help understanding the dimension of their impact. Further studies at the molecular level of detergent residues harmfulness should be implemented since literature is still lacking.

CONCLUSION

In conclusion, traces of detergents on utensils do not cause an acute pathology. However, it could induce oxidative stress to the liver and an over expression of cancer pathways long term, which by extrapolation should not be neglected in case of hepatic dysfunction.

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