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Original article

Evaluation of cytotoxicity, oxidative stress and organ-specific effects of activated carbon from Al-Baha date palm kernels

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ABSTRACT

Background: Activated carbon (AC) is a carbonaceous material derived from carbonization and activation of carbon-containing compounds at high temperature and has a large surface area, providing it with excellent adsorption properties. Human exposure to ACs via ingestion is increasing and, unfortunately, there is little to no evidence related to its level of toxicity

Materials and methods: Activated carbon of powdered date kernels from Al-Baha city in Saudi Arabia were used to treat rats and cell lines (HepG2 and HCT-116). Toxicity, microbiological tests and biochemical analyses were carried out to investigate biological activity of both commercially available AC (CAC), pharmaceutical AC (PAC) and AC from date palm kernels (AAC)

Results: None of the ACs showed activity on *Staphylococcus aureus*, *Bacillus subtilis*, *Protius mirabilis* and *Escherichia coli*. AAC showed the most cytotoxic effect on both HCT-116 and HepG2 cell lines after 24 h, with IC50 of 48.7 ± 17.2 μg/ml and 51 ± 6.24 μg/ml respectively. Rats treated with AAC for 48 h showed no impairment of hepatic and renal functions, unlike those exposed to CAC and PAC. Similarly, AAC-exposed rats did not show oxidative stress in both the liver and kidneys while CAC and PAC exposure resulted in depletion of CAT, GPx, SOD and GSH in both organs. L-arginase and α-fucosidase expression were also induced by both PAC and CAC while α-fucosidase levels were unaffected in AAC-exposed rats

Conclusion: AAC appears to be biologically safe compared with PAC and CAC due to its antioxidant activities and non-effect on both hepatic and renal functions.

1. Introduction

Activated carbon (AC) is a carbonaceous material that is derived from carbonization and activation of carbon containing compounds at temperatures as high as 1300 K in the absence of oxygen (Santhosh and Dawn, 2021). AC has a large surface area and impressive pore structure, features that provide excellent adsorption properties. More specifically, it is believed to have excellent adsorption capabilities for organic and inorganic ions and toxic metal compounds, which is why it is often employed in particle filtration applications. This includes, but is not limited to, waste water treatment plants, gas filters, and drinking water processing plants (Kosheleva et al., 2019). AC has been prepared from numerous sources; including from food waste, palm shells and rice husks, to mention just a few (Boonpoke et al., 2011; Rahman et al., 2012; Kosheleva et al., 2019). Generally speaking, materials used for synthesis of AC have always been driven by their availability and cost, especially in cases where waste materials can be utilized.

Date palm kernel seeds (DPK) are hard and oblong-shaped, with ventral grooves and are found within date palm fruit (*Phoenix dactylifera*). Date palm is mainly grown in semi-arid and arid regions of the Arabian Peninsula, the USA and Africa. Interestingly, revenue from date palm sales constitutes the majority of the income for those living in the Sahara and is a staple in many Middle Eastern countries such as Saudi Arabia, Oman and Kuwait (Mirghani, 2012), and date fruit production was estimated to be 8.5 million tons in 2016 (Altaheri et al., 2019). In terms of the mass of the entire date fruit, DPK comprises around 10%, amounting to approximately 850 thousand tons of date seed produced in 2016. Most of these seeds, however, end up as waste. Clearly then, with

Abbreviations: AB-DPK, Al-Baha date palm kernel; CAC, Commercially available activated carbon; PAC, Pharmaceutical-activated carbon; AAC, AB-DPK-activated carbon.

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proper utilization, DPK can be of immense economic use. For instance, DPK contains a high proportion of carbon compounds and has been successfully used to synthesize AC for water treatment (El Nemr et al., 2008; Reddy et al., 2012).

As with AC, carbon nanotubes (CNT) have also been employed in water filtration systems based on the nano-membrane filters CNT form, which allow for selective water transport (Fornasiero et al., 2008). As such, this CNT system is used as an alternative to polymeric membranes in desalination plants, with CNTs offering the advantages of increased surface area and better water permeability (Wang et al., 2020). However, CNTs have been found to have a cytotoxic effect. Specifically, CNTs have been shown to induce oxidative stress in human alveolar epithelial cell lines (Kayat et al., 2011). A study in a similar vein demonstrated that CNTs induce reactive oxygen species (ROS) production, necrotic and apoptotic cell death, chromosomal aberrations, and alteration of cellular structure in murine macrophages (Di Giorgio et al., 2011). Unfortunately, there is little to no evidence for levels of toxicity of AC both *in vitro* and *in vivo*. To better understand the biosafety of AC, this study thus investigates the biological activity of commercially available AC (CAC), pharmaceutical AC (PAC) and AC from DPK (AAC) as antibacterials, along with their ability to induce oxidative stress, alter liver and kidney functions, and their potential to induce cancer.

2. Materials and methods

2.1. Al-Baha date palm kernel (AB-DPK) collection

Commercially available activated carbons (12.01 g/mol) were used for comparison with Al-Baha data palm kernels (AB-DPKs) and obtained as follows:

1) NEN Tech. Ltd. Brixworth: from the chemical store in the Department of Chemistry, the Faculty of Sciences, Al Baha University in Saudi Arabia.
2) Arkocaps® Vegetable Charcoal: from a local pharmacy.

The fresh dates were locally purchased from the Al-Baha region in Saudi Arabia. The kernels (seeds) were extracted from the dates and then washed in clean followed by distilled water. The kernels were kept at room temperature for seven days to air dry. This was followed by oven-drying at 200 °C for 24 h. The oven-dried AB-DPKs were milled (crushed to make powder) and sieved. The resulting AB-DPK powder was calcined in air at 200 °C for 24 h. It was then calcined again at 700 °C, at a heating rate of 5 °C/min, for 2 h under a nitrogen gas atmosphere in a tubular furnace.

2.2. Cell lines and culture medium

The human colorectal cancer cell line (HCT-116) and liver cancer cell line (HepG2) used in the present study were obtained from Dr. Neamatallah's lab, Faculty of Pharmacy, KAU, Saudi Arabia. The cells were cultured in Dulbecco's Modified Eagles Medium (DMEM) supplemented with 10% (v/v) fetal bovine serum (FBS), 1% (v/v) L-glutamine and 100 units/mL penicillin/streptomycin at 37 °C in a humidified 5% CO_2 incubator.

2.3. Extract preparation

100 g of AAC, PAC, or CAC were soaked in absolute alcohol at room temperature for 24 h with continuous stirring. The mixture was filtered twice through Whatman filter paper (No.1). The filtrate was then dried using a rotary evaporator and the obtained material extract (2.57 g) was dissolved in acetone to obtain 1% (10 mg/mL) solution (stock solution). This stock solution was filter-sterilized (0.45 μm, Amicon) and stored at −30 °C.

2.4. MTT assay

To assess the cytotoxic effects of extracts from AAC, CAC and PAC against the HCT-116 cell line, MTT viability assay was employed. Cells were cultured in a 96-well plate at a density of (1×10^5 cells/well). After 24 h of incubation, the cells were treated in triplicates with the compounds at six serial dilutions (250–3.9 μg/mL) for 72 h. Control wells of untreated cells were prepared at the same time. The medium was removed and replaced with MTT solution (2 mg/mL). Following this, the plates were covered with aluminum foil and incubated for 4 h at 37 °C. The plates were then incubated for 5 mins at 37 °C in a 5% CO_2 incubator, and the colorimetric signals were measured at 570 nm with a SpectraMax M3 plate reader.

2.5. Antimicrobial susceptibility testing (AST)

The antimicrobial activity of AAC, PAC, and CAC compounds (100 μg) was assessed against *Staphylococcus aureus, Bacillus subtilis*, *Protius mirabilis* and *Escherichia coli*. The bacterial suspension (inoculum) obtained from the overnight culture was diluted with sterile saline solution to 10^8 CFU/mL (McFarland standard: OD = 0.5 at 600 nm). The agar well diffusion method was adopted, as previously described, to evaluate the antimicrobial activity of the extracts using Muller Hinton agar media (Kilany, 2017). The experiment was conducted in triplicate.

2.6. In vivo studies

To test acute cytotoxicity, oxidant/antioxidant and carcinogenic effects – all of which might be found in AAC, PAC, or CAC compounds – five healthy, adult Sprague Dawley rats weighing between 200 and 250 g were injected with a single dose regimen of 500 μg (equivalent to 500 μL) of the extracts (Ghramh et al., 2020). The rats used in this study were generously provided by Animal House at King Khalid University and treated following guidelines by the Research Ethics Committee at King Khalid University in Saudi Arabia. Untreated rats (n = 10) and 10 rats treated with 500 μL acetone were used as controls. All rats were euthanized after 48 h exposure, and their sera, livers and kidneys were collected after perfusion with phosphate buffered saline. The collected livers and kidneys were homogenized (10% w/v) in ice-cold 0.1 M Tris-HCl buffer (pH 7.4) using an electrical homogenizer. The homogenate was then centrifuged for 15 min at 22,000 g and 4 °C (Ogunlana et al., 2018). The supernatant was collected and used for all subsequent parameter measurements. All data are expressed as per gram of tissue unless otherwise indicated.

Liver function tests were conducted by evaluating the level of total protein and total bilirubin, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT), and the kidney function was assessed by quantitating serum creatinine and urea using the method previously described (Ibrahim et al., 2021).

Lipid peroxidation capacity, total antioxidant capacity, superoxide dismutase, and levels of catalase and glutathione in liver and kidney homogenate supernatants were analyzed to evaluate oxidative stress in the organs, as described by Ibrahim et al. (2021). Similarly, arginase activity in sera was estimated using the methods described by Ibrahim et al. (2021). Filtered sera in a 10 KdDa cutoff filter (Amicon® Ultra-4) was used to remove any urea found in the serum. α-L-Fucosidase activity was then estimated using a colorimetric assay kit (IAZYME) according to the manufacturer's instructions.

2.7. Statistical analysis

Results are expressed as mean values ± SD of the number of experiments. Analysis of variance using Tukey's multiple comparison was carried out to determine the significance levels within and between groups using GraphPad Prism-Version 7.0 for Microsoft Windows. A p value $\leq$ 0.05 was considered statistically significant.

3. Results

3.1. Antimicrobial potential

The antibacterial potential of AAC, CAC and PAC was assessed by AST on *S. aureus, B subtilis* and *E. coli*. Findings show that none of the activated carbon types evidenced antibacterial activities on any of the bacterial strains (see Fig. 1 and Table 1). This was confirmed by the positive control of N 30 antibacterial-inhibited bacterial growth, as shown by the clear area surrounded by less bacteria growth. This phenomenon, however, was not observed for any of the ACs.

3.2. Toxicity

3.2.1. Cytotoxicity and IC_{50}

To select the optimum concentration of the ACs that were used in subsequent biological and biochemical assays, the cytotoxicity of the ACs was assessed on HCT-116 and HepG2 cell lines. This was also pertinent since the anticancer effect of the ACs was to be tested on the same cell line. As shown in Fig. 2, all ACs induced a dose-dependent increase in cytotoxic effect through reduction of the cell viability in both cell lines. For HCT-116 cells, AAC was the most cytotoxic based on its IC_{50} value (48.7 ± 17.2 μg/ml) after 24 h of exposure, while CAC had the highest IC_{50} of 88.5 ± 8.9 μg/ml. Similarly, for the HepG2 cell line, AAC was the most cytotoxic, with IC_{50} of 51 ± 6.24 μg/ml, while CAC had the least cytotoxic effect, with IC_{50} of 74.6 ± 5.03 μg/ml after 24 h exposure.

3.2.2. Effect of AAC, PAC, and CAC on liver and kidney functions

The kidneys and liver are often the first set of organs affected by toxic compounds. To assess the effect of ACs on both organs, rats were exposed to 500 μg of the ACs for 48 h. Analysis of liver function biomarkers showed that AAC did not influence the levels of any of the biomarkers assayed (Fig. 3A). However, both CAC and PAC induced a significant increase in the total level of bilirubin and the liver function enzymes AST and ALT. Similarly, AAC did not influence the biomarkers of kidney function while both CAC and PAC significantly reduced the levels of serum creatinine, serum urea and serum total protein (Fig. 3B). These findings suggest AAC is safe compared to PAC and CAC.

3.3. Oxidative stress

The potential for oxidative stress within the livers and kidneys of the exposed rats was assessed through the evaluation of seven markers; namely, TBAC, H_2O_2, TAC, CAT, SOD, GSH, and GPx. The results are shown in Figs. 4 and 5. Findings shown in Fig. 4 indicate that AAC did not influence the levels of TAC and GPx, but there were significant increases in the levels of TBARS, H_2O_2 and GSH. Conversely, a significant decrease in the levels of SOD and CAT was observed. However, both PAC and CAC treatments resulted in significant decreases in the levels of GPx, TAC and GSH, unlike the increase observed for AAC exposure. In addition, PAC and CAC exposure resulted in significant decreases in the levels of SOD and CAT, as observed for AAC, but these levels were also significantly lower than AAC-induced levels of the markers. A significantly higher increase in the level of TBARS and H_2O_2 was observed for both PAC and CAC exposure compared with AAC-exposed and control (untreated) rats.

In the kidneys (Fig. 5), the trends for all assessed oxidative stress markers between AAC-exposed rats and rats exposed to

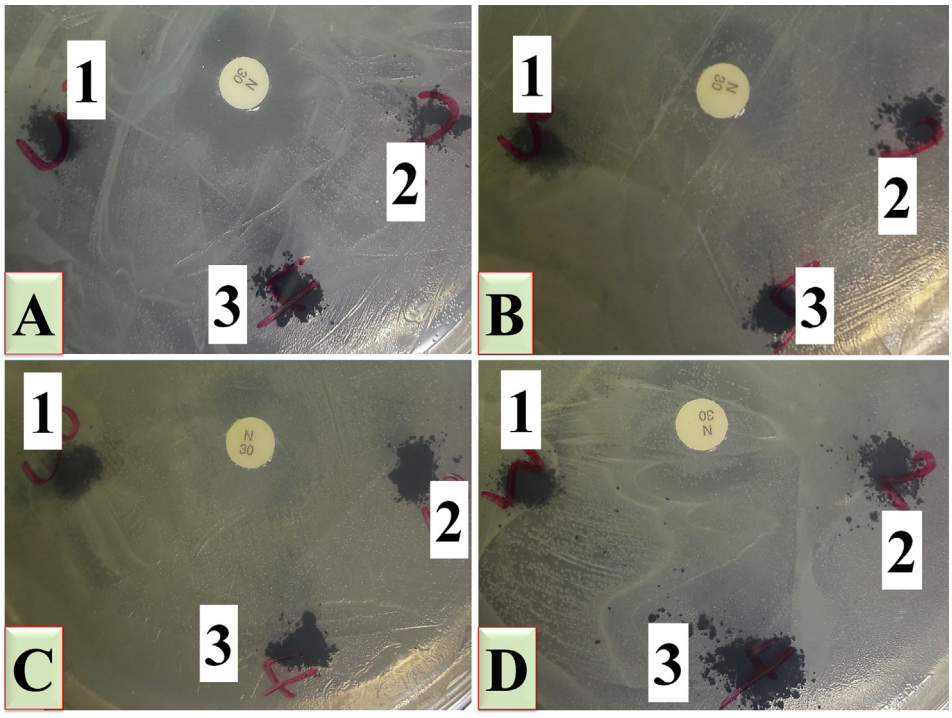

Fig. 1. Antimicrobial activity of AAC (1), PAC (2), and CAC (3) against *Staphylococcus aureus* (A), *Bacillus subtilis* (B), *Protius mirabilis* (C) and *Escherichia coli* (D), where N 30 is 30 μg of neomycin.

Table 1
Summary of the antimicrobial activity of AAC (1), PAC (2), and CAC (3) against four different bacteria.

Antimicrobial activity	Sensitivity			
	30 μg neomycin (N 30)	AAC (1)	PAC (2)	CAC (3)
Staphylococcus aureus (A)	+	–	–	–
Bacillus subtilis (B)	+	–	–	–
Protius mirabilis (C)	+	–	–	–
Escherichia coli (D)	+	–	–	–

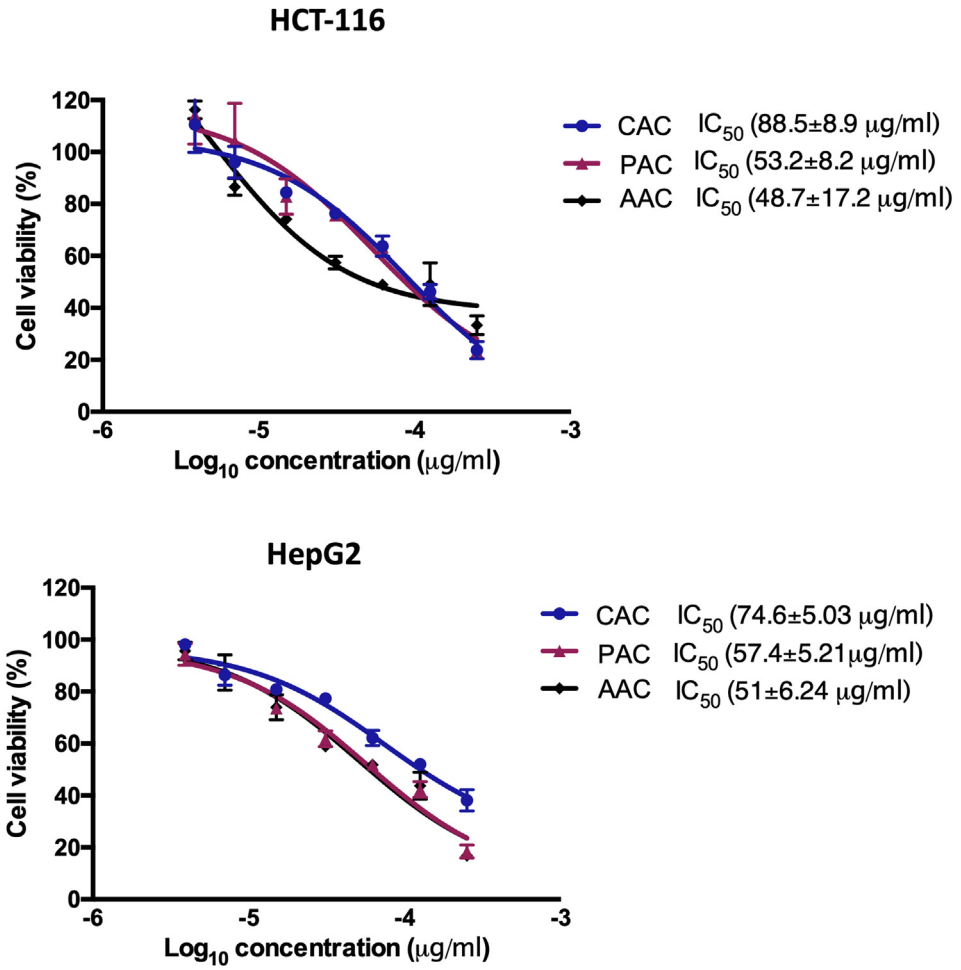

Fig. 2. The effects of AC compounds (CAC, PAC and AAC) on the viability of HCT-116 and HepG2 cell lines after 24 h exposure.

CAC and PAC were similar, as also observed in the liver. However, unlike within the liver, H_2O_2 production and CAT levels in the kidneys were not induced by AAC exposure. Furthermore, none of the ACs caused significant changes in TAC levels, and AAC exposure did not influence the levels of SOD and GSH.

3.4. Serum tumor markers

Anti-tumor activities of all the ACs were assessed by evaluating arginase and α-L-Fucosidase protein levels, which are widely assayed tumor markers. As shown in Fig. 6, all ACs significantly induced arginase production when compared to the control. However, both PAC and CAC-induced levels of arginase were significantly higher than those of AAC. Contrastingly, AAC exposure did not influence the production of α-L-Fucosidase, while PAC and CAC significantly increased α-L-Fucosidase levels in the rats when compared to both AAC-exposed rats and control (untreated) rats.

4. Discussion

The use of ACs in water and air purification, waste treatment, and chemical decontamination has dramatically increased over the last two decades, and this has substantially increased human exposure. Despite ACs being widely applied though, there are few studies that have investigated them in terms of their potential to suppress drug toxicity and as anticancer agents (Sun et al., 2010; Zhong et al., 2010). Furthermore, ACs have been investigated as carriers for drugs (Miriyala et al., 2017). ACs can be functionalized by chemical methods; for instance, treatment of ACs with nitric acid can add nitro-, carboxylic and phenolic groups to the crystal structure of the AC (Ternero-Hidalgo et al., 2016). Using Fourier transform infra-red (FTIR) spectroscopy, these functional groups have been empirically shown to be good interaction points for drugs, such as paracetamol and ibuprofen, in pores formed within the ACs, where the drugs are also released physiologically

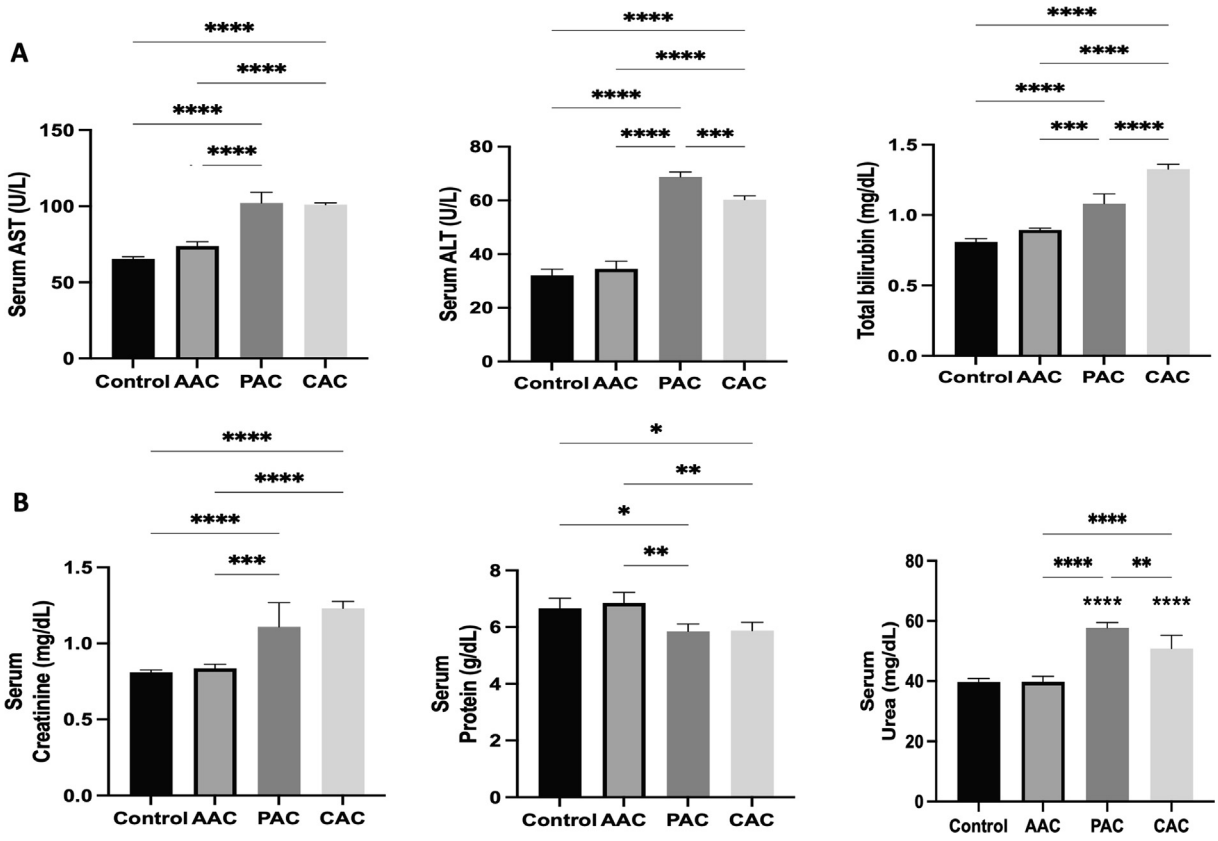

Fig. 3. Assessment of liver and kidney function post-exposure to ACs. Rats were exposed to 500 μg of AAC, PAC or CAC for 48 h and (A) AST, ALT. Total bilirubin (B) serum creatinine, protein and urea was assessed. Data are presented as mean ± SD of n = 10 rats.

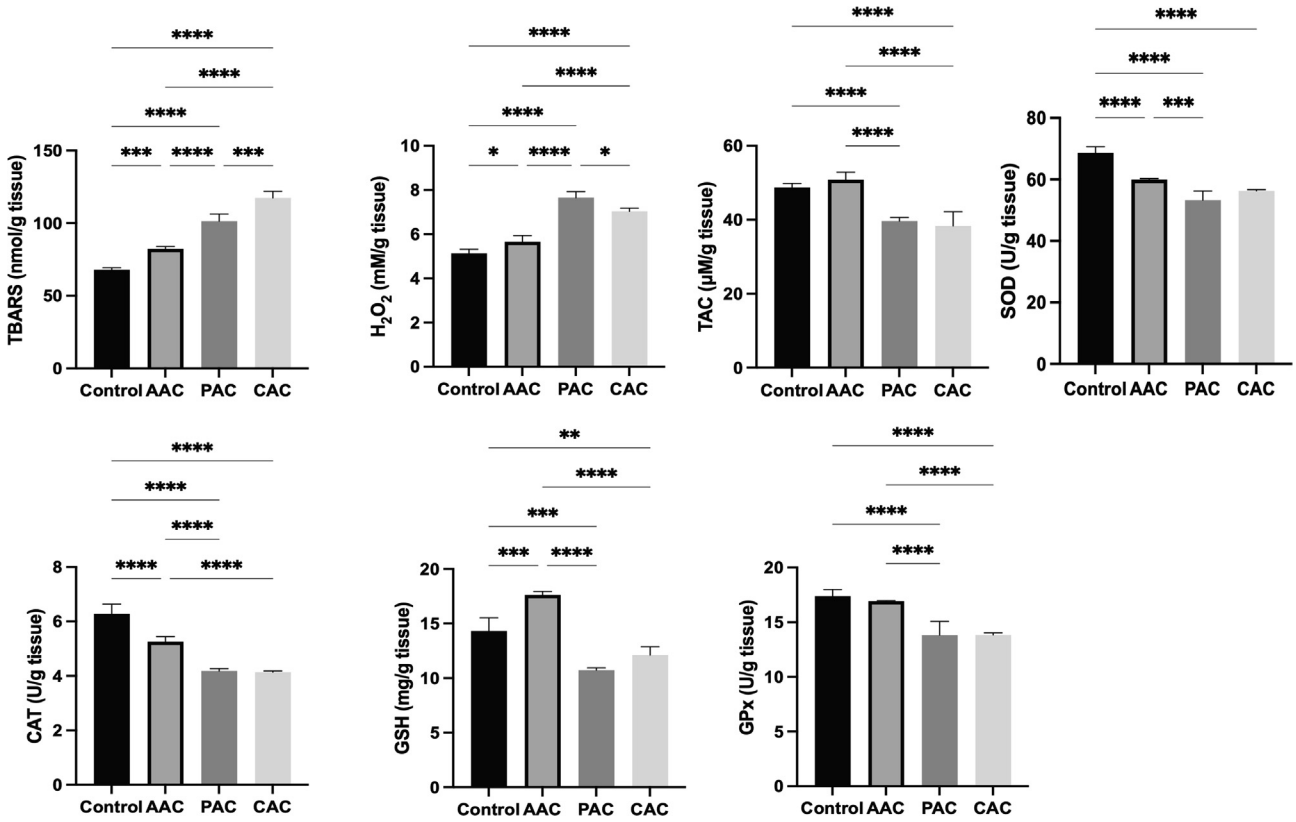

Fig. 4. Levels of oxidative stress markers in rat livers post-exposure to AAC, PAC and CAC. Rats were exposed to the 500 μg of ACs for 48 h, and the levels of TBAC, H_2O_2, TAC, CAT, SOD, GSH, and GPx were assessed. Data are presented as mean ± SD of n = 10 rats.

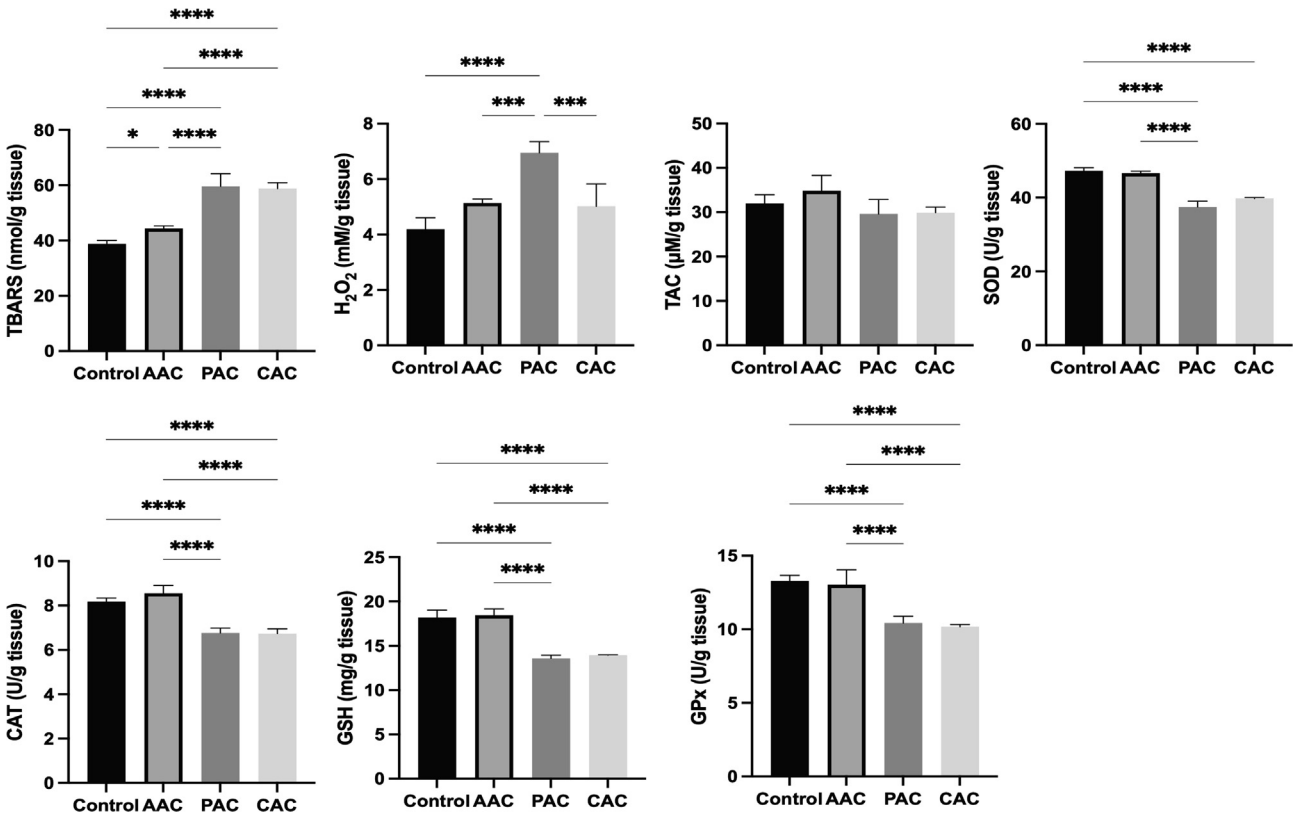

Fig. 5. Levels of oxidative stress markers in rat kidneys post-exposure to AAC, PAC and CAC. Rats were exposed to the 500 µg of ACs for 48 h, and the levels of TBAC, H_2O_2, TAC, CAT, SOD, GSH, and GPx were assessed. Data are presented as mean ± SD of n = 10 rats.

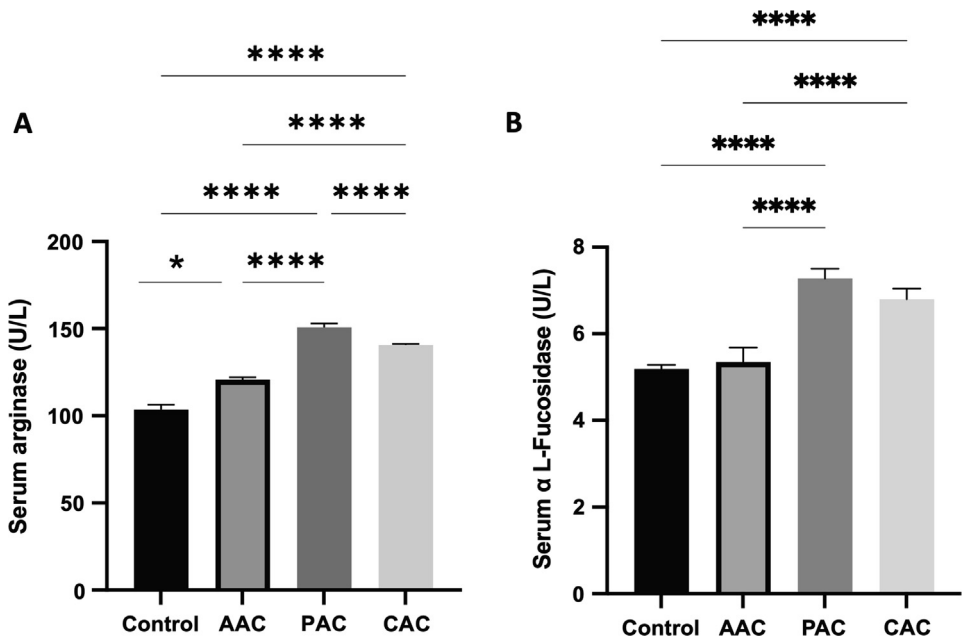

Fig. 6. Anti-tumor effect of AAC, PAC and CAC. Levels of serum (A) Arginase and (B) α-L-Fucosidase in the control (unexposed) and AAC-, PAC- and CAC-exposed rats (n = 10) are shown. Data are presented as mean ± SD, $^{*}p \leq 0.05$ and $^{****}p \leq 0.0001$.

(Miriyala et al., 2017). Interestingly, these pores are high capacity stores for drugs, and this, coupled with the low toxicity of ACs, is one of the reasons why ACs may potentially be useful as drug carriers. It is worth noting though, that ACs are being increasingly applied with very little information on their biosafety.

In this study, the antibacterial activities of all ACs were investigated, and findings show that none of these ACs exhibited antibacterial activity. Although ACs have been explored in the past for antibacterial application, evidence from studies in the literature reveal that these ACs are conjugated to antibacterial compounds.

For instance, Srinivasan et al. (2013) loaded plasma-activated ACs with silver nanoparticles to enhance the antibacterial effects of silver nanoparticles in disinfection of water. Similarly, Altintig et al. (2016) loaded ACs prepared from corn cobs with silver nanoparticles. In both cases, the silver nanoparticle-loaded ACs showed enhanced activity against *E. coli* while the latter study also showed activity against *S. aureus*. Although none of the ACs evidenced antibacterial activities in themselves, they all induced a dose-dependent reduction in cell viability of HCT-116 and HepG2 cell lines. Our findings indicate that AAC is the most cytotoxic to the cancer cells of all ACs. Similar to the antibacterial applications of AC with conjugated antibacterial compounds, findings in the literature related to the anti-cancer application of ACs are in line with other anticancer agents. For instance, exposure of human lung cancer cell line H-1299 to bamboo AC, in addition to laser irradiation, was found to induce significant cancer cell death (Chu et al., 2013). Interestingly, addition of bamboo AC with lasers induced cancer cell death at much greater rates compared to using the laser alone, which strongly suggests that bamboo AC contributes to the destruction of cancer cells.

The liver and kidneys are the first set of organs in the body exposed to the toxic effect of pharmacoactive substances. This is mostly due to the liver being the main organ that processes these substances and the metabolic products or unmetabolized compounds being filtered from the system by the kidneys. As such, it is not uncommon for biosafety tests on drugs to include liver and kidney function assays (Newsome et al., 2018). Liver function assays involve measurement of total bilirubin levels and the levels of intracellular enzymes, such as AST and ALT, which are sensitive and significant indicators of hepatic assault. AST and ALT levels are used as indicators of cell membrane leakage, which translates to loss of membrane integrity. High levels of bilirubin are an indication of liver injury as a consequence of impaired biliary function of the liver (Senior, 2012). Furthermore, kidney function is routinely assessed by quantitating serum creatinine, total protein and urea content (Manal Said et al., 2012). An increase in creatinine levels is a measure of the renal functional capacity, and an increase in serum urea indicates renal function in terms of its ability to handle nitrogenous compound, since urea is the main route of excretion of nitrogen-based substances such as proteins. Collectively, both parameters are a measure of the glomerular filtration rate (GFR) and high levels of these parameters are indicative of renal function impairment or likely kidney damage.

In this present study, unlike the PAC and CAC rat exposure, we found that exposing the rats to AAC did not affect the levels of any of the liver and kidney function biomarkers, suggesting that AAC does not adversely affect the liver and kidney functions. This is in agreement with the findings of Wu et al. (2013), whereby mice were treated with up to 300 mg/mL of optically activated carbon, finding that the liver and kidney functions were not impaired. Conversely, there is evidence that carbon nanotubes induce liver damage (Ji et al., 2009; Zhang et al., 2010; Patlolla et al., 2011; Wu et al., 2013). Interestingly, ACs effect on liver detoxification through adsorption or clearance of bilirubin has been shown to be superior to that of other natural materials such as jojoba seeds or microalgae (Mathew et al., 2018). Similarly, there are reports within the literature documenting the damaging effect of carbon nanotubes to the kidney in different animal models (Qu et al., 2009; Zamani et al., 2021). This indicates that AAC, in contrast to the other ACs in this study, as well as carbon nanotubes, might be a safer choice with respect to potential risk to the liver and kidneys.

Oxidation of intracellular biomolecules or structures occurs mainly through the activities of reactive oxygen or nitrogen species (ROS or RNS). Formation of superoxide, for instance, is dissipated in the formation of H_2O_2 and hydroxyl radicals. The ROS generated can further attack the DNA, causing DNA damage or peroxidation of lipids that may subsequently result in hepatic injury (Schieber and Chandel, 2014). To combat this assault, hepatic cells are equipped with defence mechanisms in the form of antioxidant enzymes against the oxidative stress that may ensue. Some of these enzymes include SOD, CAT and GPx. SOD catalyses the conversion of superoxide to H_2O_2 and oxygen; CAT is a defence mechanism against H_2O_2-induced intracellular damage; GPx protects against free radical damage that causes peroxidation of lipids (Salem et al., 2018). In our study, CAC and PAC exposure resulted in reductions in the levels of CAT, GSH SOD and GPx while the levels of H_2O_2 were increased in both the liver and kidneys. Taken together, this evidence suggests that CAC and PAC induce oxidative stress through generation of free radicals that result in lipid peroxidation. This is coupled with a reduction in the antioxidants that scavenge the free radicals, resulting in an imbalance in redox. In addition, levels of GSH, an intracellular antioxidant tripeptide that scavenges free radicals, and TBARS, a metabolite of lipid peroxidation, were also increased. On the contrary, AAC exposure did not affect the levels of GPx and TAC in both organs. While AAC exposure only slightly reduced SOD levels in the liver, these were not affected in the kidneys. This finding, in addition to no increase in H_2O_2, indicates there is very little or no superoxide generation that requires SOD activity in the kidneys and liver. This is supported by the increased GSH and reduced CAT levels, a finding that indicates there is no superoxide oxidant activity that would otherwise deplete the GSH or raise the CAT levels. Our findings for CAC and PAC here are supported by the findings of Salem et al. (2018), who showed that paracetamol-induced oxidative stress in rat livers depletes the levels of GPx, GAT, SOD, and GSH through generation of ROS and RNS. Furthermore, leaf extract of *Phoenix dactylifera* was shown to protect against this oxidative stress by stabilising the levels of the antioxidants and reducing free radical generation, similar to our observations for AAC.

L-arginase and α-fucosidase are biomarkers used to assess tumor development in liver cells. High levels of these enzymes are usually compared between cancer patients and healthy, matched individuals (Ayude et al., 2000; Kolanjiappan et al., 2002). α-fucosidase levels have been shown to be an indicator of cellular senescence induced either by oncogenes or replicative DNA damage (Hildebrand et al., 2013). Here, we found significant increases in the levels of both L-arginase and α-fucosidase due to exposure to CAC and PAC. However, only L-arginase levels were increased due to exposure of AAC. As such, further investigation is required to ascertain the tumor-associated effect of AAC. The differences in the biological effects of AAC compared with the other ACs evidence the markedly beneficial effects of AACs regarding its anti-oxidant activities and absence of negative impact on liver and kidney function. This would indicate that AAC is a safer choice in the applications that result in potential exposure to activated carbon.

5. Conclusion

PAC and CAC showed oxidant activities and impairment of liver and kidney function; however, AAC did not adversely affect the liver and the kidneys. In addition, AAC showed antioxidant activities, which may have protective effects on oxidizing compounds. These findings are indicative of the positive impact of the potential use of AAC in applications currently explored for ACs, such as in water and air filtration, waste treatment, and other medical applications such as in drug encapsulation for improved delivery of antibacterial or anticancer drugs.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethics approval and consent to participate

Ethical approval of the study protocol was provided by the Research Ethics Committee at King Khalid University in Saudi Arabia.

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