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Safety assessment of antimicrobials in food packaging paper based on LC-MS method

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Abstract

Many difficulties relating to food safety have been solved thanks to the employment of strong mass spectrometric detectors in conjunction with liquid chromatography. In this study, samples were fractionated using gel permeation chromatography and liquid/liquid extraction, and liquid chromatography/mass spectrometry (LC/MS) and gas chromatography/mass spectrometry were used to detect possible genotoxicant(s) in recycled paperboard. As a genotoxicity indicator, the rec-assay was utilized. Abietic acid (AA) and dehydroabietic acid (DHA) and were discovered in the recycled paperboard to be genotoxic. AA and DHA were found in 2 of 5 virgin products and all seven recycled food-contact products. AA and DHA total levels in virgin goods were 990 and 240 mg/g, respectively, whereas recycled products had 200990 mg/g. The total quantity of AA and DHA content in DNA-damaging activity and paper products were shown to have a strong connection. Furthermore, genotoxic effects in paper products matched standard chemicals well, showing that AA and DHA were primarily responsible for the genotoxic effects of these paper products.

Keywords: food packaging; paper, recycling; liquid chromatography; mass spectrometry.

Practical Application: The application of LC-MS method for Safety assessment of antimicrobials in food packaging.

1 Introduction

Food safety is concerned with the health and well-being of food, which is based on the provision of conditions and methods through which the quality of food is maintained in order to prevent foodborne diseases. Recently, following a series of widely publicized occurrences all around the world, food safety has earned larger notoriety, including salmonella in peanuts and now pistachios in the USA (Casulli et al., 2019), melamine in dairy products from China (Xiu & Klein, 2010), pesticides in soft drinks in India (Erdman et al., 2006; García-Reyes et al., 2008; Johnson et al., 2006), tainted Coca-Cola in Belgium (Johnson & Peppas, 2003), contamination of foods with pesticides in Japan (Maitani, 2004), and France (Nougadère et al., 2012), dioxins in pork and milk products from Belgium (Casey et al., 2010), and beef with bovine spongiform encephalopathy and benzene in carbonated beverages in the United Kingdom (Henson & Mazzocchi, 2002; Kimberlin, 1993). Such events, along with the ongoing debate over genetically modified crops (Kaeppler, 2000), have led to widespread public mistrust of food supplies in many nations. Producers, governments, and consumers alike are increasingly concerned about the quality and safety of food products in today's global economy. Food safety and the

public's impression of wholesomeness have grown more essential (Bjelajac et al., 2021; Cheng et al., 2017; Cui & Shoemaker, 2018; Jagadeesan et al., 2019; Nyarugwe et al., 2020).

One of the most important sectors in the food production industry is the packaging sector. In general, packaging materials play an important role in food safety and quality. Cost and environmental problems after consumption are important issues in the packaging industry. The use of antimicrobial packaging can be considered both in terms of packaging quality and in terms of cost and environment. Optimizing the properties of these materials has been on the agenda of many researchers in this field in recent years. The main types of paper containers are in various forms, the materials used vary. Such as composite paper as the raw material of the paper container, its main types are three kinds.

- Four-cornered paper packets called milk cartons, brick-type paper packets and roof-type paper packets, etc. It can be used for milk and juice and another liquid beverage packaging.

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- Paper cups and paper boxes are made of paper and plastic composite materials and are widely used in frozen food, fast food packaging.
- Combination cans. The body of the can is mostly made of composite cardboard, resin coating on the inner wall, and plastic or metal on the bottom cover.

In addition, there is hardened cardboard made of large barrels used for packaging dry powdered food, cereals, etc. Board and paper are commonly used as packaging materials and food containers, particularly for food boxes, paper towels, plates, and disposable items like cups (Deshwal et al., 2019; Geueke et al., 2018). Virgin paper is manufactured from wood chips, whereas recycled paper is built from recovered fiber (Deshwal et al., 2019). Recycled goods may include a variety of pollutants due to intensive treatment with dyes, adhesives, and other chemicals. Diisopropyl-naphthalenes were discovered in cardboard packaging, which is often made of recycled paper, according to a study (Geueke et al., 2018). 4,40-bis(diethylamino) benzophenone (DEAB) and Michler's ketone (MK), both of which may be utilized in printing inks for cardboard that has been UV-cured, were found in 4% and 26% of a hundred and twenty-one paperboard and paper food packaging samples, respectively, according to research, with recycled fibers being the most likely source (Ozaki et al., 2005). According to another study, fiber-based recycled materials include a wide range of chemicals, including mutagenic and hazardous constituents in some samples (Korhonen et al., 2020).

According to research, virgin paper had none or very low levels of bisphenol A (BPA), but recycled paper towels had significant levels of BPA (Jurek & Leitner, 2017). A study revealed that paper created from recycled fiber had much greater overall quantities of chemicals than paper generated from pulp made of virgin fibers, implying that only a small number of compounds are derived from virgin fiber (Mertoglu-Elmas, 2017). Recycled paper has been the subject of certain toxicological investigations (Birkholz et al., 2003; Blecher & Korting, 1995; Bull, 1987; Nadal et al., 2018; Ozaki et al., 2004; Suominen et al., 2001; Vinggaard et al., 2000). There have been studies that virgin paper has lower in-vitro toxicity than recycled paper, but no toxicants have been discovered (Binderup et al., 2002; Groh & Muncke, 2017; Vinggaard et al., 2000). We recently studied the genotoxicity of 28 recycled food-contact and virgin goods, concluding that recycled products were more likely to cause DNA damage than virgin products.

Pentachlorophenol, BPA, MK, DEAB, 4-dimethylaminobenzophenone, and Benzophenone were found in high concentrations in recycled paper goods, according to chemical analysis (Ma et al., 2021; Ozaki, 2005; Ozaki et al., 2006a; Parisi et al., 2015; Peters et al., 2019; Stocchi & Iacopini, 2019; Von Wright, 2007; Zhong & Li, 2012). However, the genotoxic effects of these compounds could not be explained by their levels in recycled paper products (Muñiz-González & Martínez-Guitarte, 2020). Throughout this research, the rec-assay has been utilized as somewhat of a genotoxicity index, and recycled paperboard was fractionated using multiple gel

permeation chromatography (GPC) and liquid/liquid extraction, then analyzed using liquid chromatography/mass spectrometry (LC/MS) and gas chromatography/mass spectrometry (GC/MS).

2 Materials and methods

2.1 Material

Wako Pure Chemical Industries, Ltd. (Osaka, Japan) provided dehydroabietic acid (DHA), while Tokyo Kasei Kogyo Co., Ltd. provided abietic acid (AA). Kanto Chemical Co., Inc. and Wako Pure Chemical Industries, Ltd. provided organic solvents, ammonium acetate, and dimethyl sulfoxide (DMSO). All of the organic solvents utilized were residual pesticide analytical reagent or HPLC grade. Fractionation was carried out using recycled paperboard (recycled fiber > 95%). Seven recycled paper products and five virgin paper products in food-contact usage were utilized to investigate the connections between the concentrations of AA and DHA and the genotoxicity of paper products.

2.2 Methods

The rec-assay was carried out using Kada et al. (1980). *Bacillus subtilis* wild strain H17 Rec⁺ and a recombination-free strain, M45 Rec⁻, were utilized in the study. In a nutshell, plates were made by adding 2×10⁵ spores/mL of strain H17 and M45 to B-2 (5g of NaCl, 10 g of polypeptone, 10 g of beef extract, 1000 mL of pH 7.0 water) agar (1.5 percent), preparing at 42 °C 10 mL of resultant spore agar, and in order to harden it thoroughly putting it inside a 90 mm plastic Petri dish. A paper disc (diameter of 8 mm) was put on the surface, and 40 mL of the sample solution or chemical was impregnated into it. The diameters of the killing zone were determined after 24 hours of incubation at 37 °C. The sample solution or chemical was determined to produce DNA damaging activity in *Bacillus subtilis* when the death zone was smaller in H17 Rec⁺ than in M45 Rec⁻. To evaluate the connections between AA and DHA content and genotoxicity, at each stage of the fractionation process, recycled-paperboard solutions were dissolved in DMSO after the nitrogen stream made them dry. DMSO was used to disperse AA and DHA (Souton et al., 2018; Vandermarken et al., 2019).

10 g of recycled paperboard was refluxed with 200 mL ethanol for 2 hours when put in a flask and after being cut into 11 cm pieces. After filtering, it was diluted with ethyl acetate to 2 mL, and ethanol solution was vaporized. A funnel for segregating was used to transfer one milliliter of the solution containing 19 milliliters of ethyl acetate, and 20 milliliters of 0.01M HCl solution was extracted. Following the removal of the aqueous layer, a saturated NaHCO₃ solution of 20 mL was used to extract the organic layer. Using 20 mL of the solution of alkali buffer, when the aqueous layer was disposed of once more, the organic layer was retrieved. After removing the aqueous layer, sodium sulfate was used to dehydrate the recovered material, then evaporated and diluted with methanol to 1 mL. To clean up the samples, a column for solid-phase extraction was used. 500 mg graphitized non-porous carbon contained in a 6 mL tube column was used. After rinsing the column with 10 mL methanol, the

sample of 1 mL was put to the column, which with methanol of 9 mL was then eluted. After that, the eluate was diluted and vaporized with tetrahydrofuran to 1 mL. Then, the solution was filtered before being exposed to GPC and spectrophotometry. Utilizing a spectrophotometer (Hitachi U-2000), we scanned the paperboard extract from 190 to 800 nm. Every wavelength had its background absorbance removed.

A Waters fraction collector, a Waters 486 tunable absorbance detector, a Waters 717 autosampler, and a Waters 600E system controller were utilized in the gel permeation chromatography (GPC) system. The following were the chromatographic separation conditions:

KF-801 (3004.6 mm i.d., 6 mm particle size, 20A° pore size) and Shodex GPC KF-G (104.6mm i.d., 8 mm particle size) guard and analytical columns; ambient oven temperature; tetrahydrofuran, mobile phase; injection volume, 50 mL; flow rate, 1 mL/min, UV detection, 254 nm. Every 30 s, the paperboard sample was fractionated. GPC calibration standards included n-propylbenzene, benzene, and polystyrene standards. A Hewlett-Packard 6890 gas chromatograph (GC) with a 5973 mass-selective detector was used to carry out the chromatographic analysis. Here were the GC parameters:

Injection volume, 1 mL; carrier gas, at 1 mL/min; injection temperature, 280 °C; oven temperature maintained at 50 °C for 2 minutes, then increased to 280 °C at 10 °C/min for 5 minutes; HP-1MS column (100 percent dimethylpolysiloxane, 0.25 mm i.d. 30 m, film thickness 0.25 mm). The following were the MS conditions:

Ionization via electron impact; ion source temperature and voltage: 220 °C, and 70 eV.

Over the m/z 50 to 500 range, the mass spectrometer (MS) was monitored. NIST Library (National Institute of Standards and Technology) was used to perform qualitative identification of the identified chemicals.

To eliminate the effect of the printing inks, the printed surfaces of the paperboard and paper were scraped away. 100 mL ethanol was used to reflux five grams. After filtering and diluted with methanol to 5 mL, the ethanol solution was evaporated. A methanol solution of 1 mL was dissolved in 100 mL DMSO for the rec-assay after being dried under a nitrogen stream. With LC/MS, a methanol solution of 1 mL was diluted to a 10 mL mobile phase. The analysis was done using LC/MS after the solution had been filtered.

Using a liquid chromatograph (Hewlett-Packard 1100), chromatographic analysis was carried out like McMartin et al. (2002), with minor modifications, utilizing a mass spectrometer (API 2000) with a negative-ion functioning electrospray ionization interface (ESI). The following were the LC conditions:

Injection volume, 10 mL; flow rate, 0.2 mL/min; mobile phase, 50 mM ammonium acetate in water/acetonitrile (2:8); oven temperature maintained at 30 °C; ZORBAX Eclipse XDBC18 column (1502.1 mm i.d., 5 mm particle size). The following were the MS conditions:

Entrance potential, 4.5 V for AA, 10 V for DHA; focusing potential, 200 V for AA, 330V for DHA; de-clustering potential, 66 V; ion source temperature, 550 °C; Ion spray voltage, 3800 V.

Selective ion scanning of 301.2 m/z for AA and 299.1 m/z for DHA was used for quantitative analysis. The calibration curves for AA and DHA, which range from 0.1 to 100 ng, were used to carry out the measurements.

3 Results

DNA-damaging behavior was evaluated using a rec-assay in every phase of the fractionation procedure. The organic layer had DNA-damaging activities upon the retrieval of 0.01M HCl solution with a paperboard solution. After extracting a saturated NaHCO_3 solution with the organic layer, DNA-damaging activity was discovered. Using a solution of alkali buffer, the organic layer was then retrieved, and DNA-damaging activity was discovered once more, showing that the genotoxicant is a neutral substance. The organic layer's DNA-damaging activity remained constant throughout the extraction procedure, and it managed to stay unaltered when the solution was applied for clean-up to an Envi-carb cartridge.

A spectrophotometric examination was performed on the liquid/liquid extraction fraction. The absorbance ranged from 200 to 800 nm, with maximum absorption of 210 to 250 nm. GPC is a technique for determining the molecular weight that is also known as size exclusion chromatography. The DNA-damaging activity of the fraction produced by liquid/liquid extraction was tested every 30 s. The chromatogram revealed one peak, and fractions around it showed DNA-damaging behavior (Figure 1).

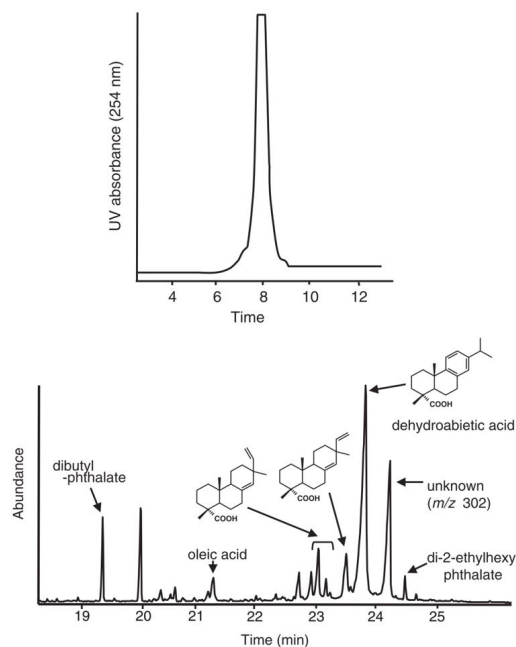


Figure 1. GPC total ion chromatogram fractionated of mass spectrometry and gas chromatography (above) and GPC liquid/liquid extraction of recycled paperboard fractionated by (below). The National Institute of Standards and Technology (NIST) library was used to identify the peaks.

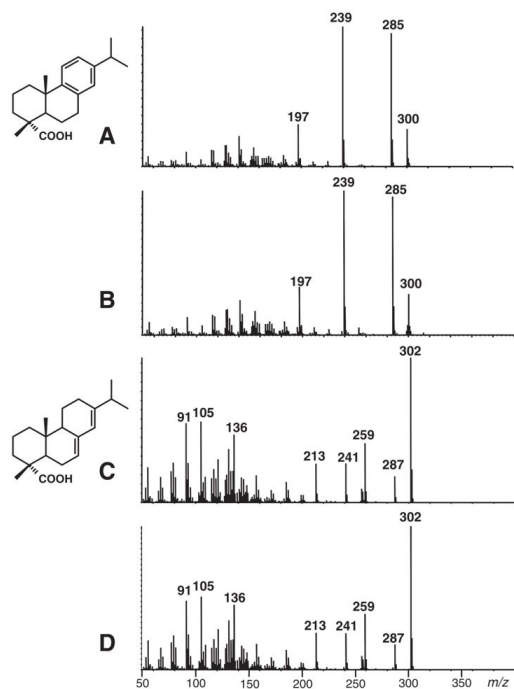


Figure 2. A standard solution's DHA mass spectra (A) and paperboard made from recyclable materials (B), AA in a typical solution (C), and recycled paperboard (D).

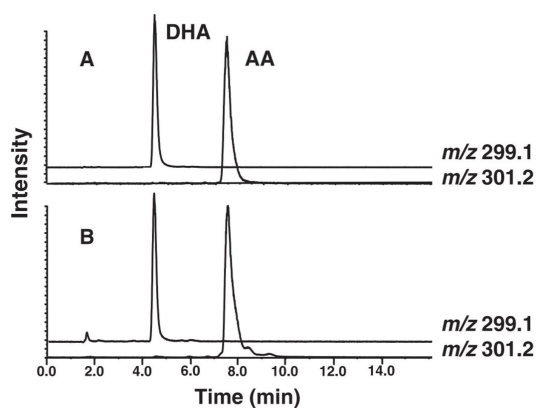


Figure 3. AA and DHA Mass chromatograms in reference solution (A) and food box made of recycled materials (sample no. 5) (B).

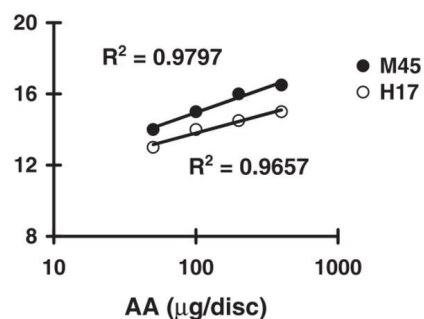
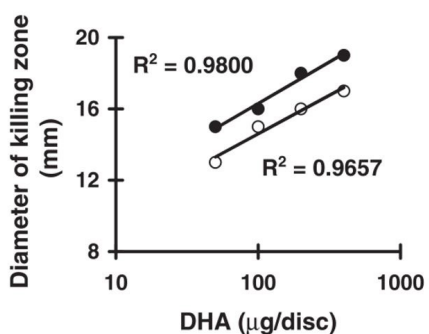


Figure 4. AA and DHA rec-assay.

The genotoxicant(s) had a molecular weight of 150350 daltons, according to the calibration standards. In GPC, gas chromatography and mass spectrometry were carried out on the fractions that exhibited DNA-damaging activity. Figure 1 depicts a total ion chromatogram. There were two significant, two mediums, and many tiny peaks found. The NIST Library was used to do qualitative characterization of these peaks, and three peaks were recognized as di(2-Ethylhexyl)phthalate, oleic acid, and dibutyl phthalate. DHA was found as the largest peak, while the structural formula for smaller peaks was the same. The largest peak's mass spectra and preservation time, which NIST Library identified as DHA, were checked with a reference DHA solution (Figure 2). Abietic acid (AA), a substance associated with DHA, was discovered as the comparatively big peak, which exhibited 302 m/z and stayed unidentified utilizing the NIST Library. Because AA and DHA are too polar to be determined using GC, they were determined using LC/ESI/MS. Table 1 shows the concentrations of AA and DHA in recycled and virgin paper and paperboard products. AA and DHA were found in 2 out of every five virgin goods and all recycled items. AA and DHA total levels in virgin goods were 990 and 240 mg/g, respectively, whereas recycled products had a total of 200990 mg/g. Figure 3 shows the mass chromatograms of the food box made from recyclable materials (sample no. 5) and the reference solution. Figure 4 shows the outputs of the rec-assay for AA and DHA. In both the M45 Rec⁻ and H17 Rec⁺ strains, AA and DHA generated in a linear pattern death zone.

Table 1. AA and DHA concentrations in recycled and virgin paperboard and paper used in packages of food.

Product	Coffee filter		Dish		Tissue	
Sample No.	1	2	3	4	5	
Products of virgin-paper	(µg/g)					
AA	not detected	not detected	910	200	not detected	
DHA	not detected	not detected	77	38	not detected	
DHA + AA	-	-	990	240	-	
Product	Cardboard box		Food box		Newspaper	
Sample No.	1	2	3	4	5	6
Products of recycled-paper	(µg/g)					
AA	580	380	150	620	840	590
DHA	170	59	53	370	67	210
DHA + AA	750	440	200	990	910	800

Furthermore, the M45 Rec⁻'s killing zone was bigger than the H17 Rec⁺'s. A discrepancy of more than 2 mm in one dosage among the death zones of M45 Rec⁻ and H17 Rec⁺ strains are thought to suggest DNA-damaging activity. Killing zones in our investigation were all visible and precisely assessed, with an error rate of less than 1%.

4 Conclusion

AA and DHA were discovered to be the genotoxicants after several fractionations of recycled paperboard. According to the liquid/liquid extraction, the genotoxicant(s) may be neutral chemical(s), according to the liquid/liquid extraction. Because AA and DHA are tricyclic, they have a low water solubility (DHA 6.6, AA 4.3 mg/L, pH 7). Furthermore, DHA and AA have pKa values of 5.7 and 6.4, respectively; as a result, they are nearly neutral. All recycled products included AA and DHA, and there was a strong connection between DNA-damaging activity, AA, and DHA concentration. Resin acids such as AA and DHA are significant toxins found in paper and pulp mill effluents (Luchnikova et al., 2019).

According to several studies, resin acids are responsible for somewhere within twenty and seventy percent of the untreated effluents' toxicity (Ahtiainen et al., 2020; Hutchins, 1979; Kostamo & Kukkonen, 2003; Rigol et al., 2003; Vepsäläinen et al., 2011; Verta et al., 2020). The pimaric and abietic kinds of resin acids present in rosin are most common. AA and DHA are two main abietic acids present in many types of rosin, and they are the principal causes of poisoning in fish. Fungi and bacteria that produce DHA may easily degrade or oxidize AA (Abe et al., 2010; Melo & Almeida-Muradian, 2011).

AA and DHA concentrations in kraft paper and pulp mill effluents were reported to be as much as 11.4 and 10.3 mg/L, respectively, and DHA concentrations in water utilized in paper recycling operations were shown to be 4.0-6.5 mg/L (Quinn et al., 2003). Rainbow trout are the most widely utilized fish for assessing the acute toxicity of effluents. For AA and DHA, in rainbow trout, the fatal concentrations generating a 50% death rate in 96 hours (LC₅₀/96 h) were 0.7-1.5 and 0.8-1.7 mL, respectively (Gregory & James, 2014; Wu et al., 2020), while in *Daphnia Magna*, the LC₅₀/48 h values were 2.5-6.4 and 19.2 mg/L, respectively (Roy et al., 2020). Furthermore, allergic effects have been documented for AA and DHA.

In human fibroblast and epithelial cells, however, DHA has been proven to trigger cell death and toxicity in human erythrocytes and polymorph nuclear leukocytes in a few cytotoxicological investigations (Mohanta et al., 2019; Niu et al., 2021). The AA has reportedly lysed human alveolar epithelial cells. In a mammalian microsome/salmonella test, AA and DHA were shown to be non-genotoxic (Ozaki et al., 2006b).

AA and DHA were shown to have DNA-damaging action in the rec-assay in this investigation. Several more in vivo or in vitro assays, such as the comet assay, may be required to establish their genotoxicity (Bijur et al., 1999). AA and DHA were found in several virgin-paper goods as well as recycled-paper products in the current investigation. Broadleaf trees and Conifer are common wood supply sources used to make virgin pulp. Because AA and

DHA are important constituents of conifer oleoresin, which is present in fir trees, spruce, and pine, the virgin pulp wood type could be connected to the concentration of these chemicals. Due to different kinds of recycled paper products made from post-consumer paper, pulps are combined, and AA and DHA were discovered in all recycled goods. Two hours were spent refluxing paper samples in ethanol in the current investigation. In an attempt to discover which genotoxic chemicals were present in the samples, the extraction technique was quite thorough.

Further research investigating migration into real foods or food simulants seems essential to determine the safety of utilizing recycled and virgin-paper products in contact with food. In conclusion, we used LC/MS, GC/MS, GPC, and multiple liquid/liquid extraction to characterize the genotoxicants in recycled and virgin-paper products.

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