Chemosphere 260 (2020) 127557

Contents lists available at ScienceDirect

Chemosphere

journal homepage: www.elsevier.com/locate/chemosphere

Transformation of resveratrol under disinfection conditions

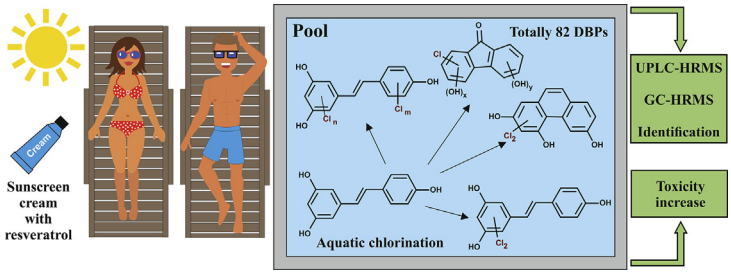
Elena A. Detenchuk [a], Polonca Trebše [b], Aleksandra Marjanović [c], Dmitry S. Kosyakov [d], Nikolay V. Ul'yanovskii [d], Mojca Bavcon Kralj [b, **], Albert T. Lebedev [a, *]

[a] Moscow State University, Department of Chemistry, Moscow, Russia
[b] University of Ljubljana, Faculty of Health Sciences, Ljubljana, Slovenia
[c] University of Sarajevo, Faculty of Pharmacy, Sarajevo, Bosnia and Herzegovina
[d] Northern Arctic Federal University, Arkhangelsk, Russia

HIGHLIGHTS

- *Trans*-resveratrol becomes more and more popular all over the world as a powerful antioxidant.
- The first study of transformation of resveratrol and its formulations in aquatic chlorination.
- Over 80 transformation products were tentatively identified using GC-HRMS and UPLC-HRMS.
- Toxicity estimation of resveratrol products was carried out using luminescent bacteria *V. fischeri*.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 27 April 2020
Received in revised form
10 June 2020
Accepted 26 June 2020
Available online 8 July 2020

Handling Editor: Keith Maruya

Keywords:
Trans-resveratrol
Aquatic chlorination
Disinfection by-products
GC-HRMS
LC-HRMS
Toxicity

ABSTRACT

Trans-resveratrol becomes more and more popular all over the world as a powerful antioxidant. Since its positive properties, including antioxidant, anti-inflammatory, anti-tumor are indisputable, nowadays *trans*-resveratrol is used as a component of various products from nutriceutics to body care formulations, where it is supposed to behave as natural antioxidant and anti-aging compound. It is also added to food packaging materials to increase their stability or/and prevent oxidation. Nevertheless, being released to the environment resveratrol easily forms various transformation products with potentially negative environmental and health effects. The present paper deals with transformation of pure resveratrol and its formulation used as UV-protectors in conditions of aquatic chlorination. Over 80 transformation products were tentatively identified using gas chromatography-high resolution mass spectrometry (GC-HRMS) and ultra pressure liquid chromatography-high resolution mass spectrometry (UPLC-HRMS). Chlorinated phenols and biphenyls are the most relevant among them. Estimation of toxicity of resveratrol products was carried out using luminescent bacteria *V. fischeri* tests.

1. Introduction

Photons of UV light cause breakage of covalent bonds and thus induce different oxidation processes leading to aging and weathering of different construction materials, coatings, plastics, rubber, etc. UV-radiation is particularly harmful for biological systems, causing damage to skin cells, resulting in accelerated aging of the

* Corresponding author.
** Corresponding author.
E-mail addresses: mojca.kralj@zf.uni-lj.si (M.B. Kralj), a.lebedev@org.chem.msu.ru (A.T. Lebedev).

https://doi.org/10.1016/j.chemosphere.2020.127557
0045-6535/

skin and the emergence of various diseases, from inflammatory processes to cancer (Velasco et al., 2008; Kullavanijaya and Lim, 2005).

Protection against ultraviolet (UV) radiation is the major function of sunscreen lotions as well as UV-protective coatings for different kind of material. Various substances are used as UV protectors either reflecting or absorbing UV light. In addition to inorganic pigments, efficiently reflecting UV light, organic compounds absorbing UV light are usually called UV filters. Based on the literature survey on the use and effects of old and new formulations, the list of substances permitted by law is regularly updated. The European Union (EU) currently allows 28 organic substances (EC Regulation 1223/2009 on cosmetics, 2009), while some other compounds are allowed in countries around the world, such as Japan and the USA, where they are treated as biological agents, available without prescription (Over-the-Counter (OTC) Drug Monograph Process, 2020; Standards for Cosmetics, 2000). Actually, in 2019 FDA tightened regulation of over-the-counter sunscreen products. Besides that, FDA called for more research on 14 non-prescription sunscreen ingredients and increased maximum SPF values on sunscreen labels from 50 to 60 (FDA advances new proposed regulation to make sure that sunscreens are safe and effective, 2019). Due to fairly broad spectral range, 400-290 nm (UVA and UVB), individual compounds, possessing rather narrow absorption peaks, cannot prevent the exposure to the whole spectrum of UV light. Thus, formulations of different compounds are used.

Sunscreen products are used primarily in special conditions, such as swimming in the sea, open swimming pools, and on the snow and in the mountains, where a really thorough protection is needed. Several recent studies showed that they may decompose by light. Mostly, two types of reactions occur: a) direct photolytic reactions, and b) chlorination of aromatic rings or side chains due to the presence of active chlorine medium (mainly pools).

If we take into account that UV-filters do not afford 100% protection to the skin and that most of UVA-induced damage is mainly mediated by ROS generated after UV exposure (Nichols and Katiyar, 2010; Norval and Wulf, 2009), the addition of antioxidants to sunscreens is needed (Gilaberte and Gonzalez, 2010). Natural antioxidants, mainly polyphenols and carotenoids, are used in sunscreens due to their efficacy in reducing free radical generation and thereby decreasing skin photodamage (Aziz et al., 2005; Bando et al., 2004; Darvin et al., 2011; Huang et al., 2010; Lee et al., 2013; Nichols and Katiyar, 2010), especially after sun exposure, when the levels of endogenous antioxidants are significantly depleted (Godic et al., 2014).

Trans-resveratrol (RES) is a biologically important stilbene showing antioxidant (Džeba et al., 2012; Gülcin, 2010), anti-inflammatory (Xiao et al., 2013) and anti-tumor (Chao et al., 2014; Wang et al., 2012; Yin et al., 2013) properties. It is a phytoalexin produced by various plants to protect them in stress conditions due to micobacterial infections, extremal temperatures, and dryness (Piñeiro et al., 2006).

Nowadays *trans*-resveratrol is used as a component of various products from nutriceutics (Rossi et al., 2012) to body care formulations (Soby et al., 2003), where it is supposed to behave as a natural antioxidant and antiaging compound. Additionally, resveratrol may be added to plastic films for the food packaging in order to increase their stability or/and prevent oxidation (Agustín-Salazar et al., 2014; Barbosa-Pereira et al., 2014). The related problem involves low stability of resveratrol and possible products of its transformation with unknown chemical and biological properties. Thus the number of products forming from resveratrol in chlorinated water may be rather high. Our earlier studies on the aquatic chlorination of the known UV-protectors diethylaminohydroxybenzoyl hexyl benzoate (DHHB) (Grbović et al., 2013) and especially avobenzone (Trebše et al., 2016; Wang et al., 2017; Detenchuk et al., 2019; Lebedev et al., 2020) demonstrated formation of various disinfection products mainly with the unknown biological activity. Belonging to the classes of halogenated phenols, aldehydes, acetophenones, these compounds may be rather harmful for humans.

This study was focused on stability of resveratrol as a pure substance as well as a sunscreens' ingredient after aquatic chlorination as a common disinfection processes for swimming pool waters. Given that the use of sunscreen products is essential, with resveratrol being an antioxidant and a substance of benefit in such formulations, we investigated resveratrol aquatic chlorination products. For the identification of the corresponding DBPs (disinfection by-products) gas chromatography-high resolution mass spectrometry (GC-HRMS) with electron ionization for the determination of semi volatile compounds and ultra pressure liquid chromatography-high resolution mass spectrometry (UPLC-HRMS) with electrospray ionization for the determination of polar and non volatile ones have been used.

2. Experimental

2.1. Chlorination experiments

Resveratrol standard or sunscreen, containing resveratrol and oxybenzone (10 mg of sunscreen, containing 1% resveratol and 5% oxybenzone), was dissolved in 25 mL of chlorine water, prepared by dissolving one chlorine tablet containing 17,0 mg of sodium dichloroisocyanurate anhydrous in 1L of distilled water and producing 10 mg L^{-1} of active chlorine. According to the producer's instructions, 10 min are needed for solution to become saturated with chlorine. That time, when we dissolved studied compound in chlorine water, we mark as $t = 0$. The experiment was conducted in ultrasonic water bath at 35 °C, samples were taken at time 0 and after 120 min, filtrated (Chromafil CA-45/25, Celluloseacetat, 0.45 μm, HPLC certified) and analysed by HPLC-DAD.

For the elucidation of chlorination products resveratrol standard was added into two flasks with 250 ml phosphate buffer solution (pH 7.2) to final concentration 3.04 mg L^{-1}. Ultrasonic bath was used for 10 min. Then sodium hypochlorite was added into one flask to achieve concentration of active chlorine 3 mg L^{-1}. Ultrasonic bath was used again for 60 min. Reaction was stopped by sodium thiosulfate. SPE was performed with Supelclean ENVI-18 cartridges. Conditions of extraction were as follows: 5 mL methanol, 5 mL deionized water, sample loading (pH 2, sulfuric acid) with flow rate 5 ml/min, washing with 10 ml of deionized water, drying for 30 min in nitrogen stream, eluting with 10 mL methanol, and final evaporation to 500 μl. 200 μl were taken for GC-MS analysis. To another portion of 100 μl of extract 100 μl of deionized water was added. After centrifugation HPLC-MS analysis was conducted.

2.2. Sample analysis

2.2.1. HPLC-DAD

The kinetic studies were performed with Agilent 1100 HPLC-DAD chromatograph. The separation was achieved using Supelco Ascentis® Express 5 μm C18 column (5 μm, 150 mm × 4.6 mm). The mobile phase for resveratrol analysis constituted of a mixture of acetonitrile and 0.1% H_3PO_4 40:60(v/v). The flow rate was 1 mL/min. The column thermostat was maintained at 40 °C. The detector was set at 303 nm. Analysis time was 25 min, while the retention

time of resveratrol was 1.8 min.

2.2.2. GC-HRMS

GC-HRMS analysis was conducted with orbitrap instrument Exactive GC, coupled to gas chromatograph Trace 1310 with autosampler TriPlus RSH (Thermo, USA). Capillary column TG-5SILMS, 30 m, 0.25 mm, 0.25 mcm (Thermo, USA) was used. Injection volume 1 μl with Split 5, injector temperature 280°C. Carrier gas – helium (6.0, NIIKM, Russia), He speed 1.2 ml/min. Column program: initial temperature 50°C (3 min), ramp to 320°Cat 5°C/min, 320°C (8 min). Transfer line temperature 280°C. Ion source temperature 200°C, electron ionization (EI) 70 eV. Full Scan mode in the range 35–550 Da, resolving power 30 000, allowing reliably obtaining elemental compositions of the ions (Lebedev et al., 2013), AGC Target 5e5.

2.2.3. UPLC-HRMS

UPLC-HRMS QTOF system TripleTOF 5600+ (AB Sciex, Canada), with DuoSpray ion source and chromatograph LC-30 (Shimadzu, Japan) was used. Nucleodur PFP 150 × 2 mm, 1.8 mcm (Macherey-Nagel, Germany) column was used in gradient mode. Mobile phase consisted of deionized water with 0.1% formic acid (A) and acetonitrile with 0.1% formic acid (B). Column program: 0–1 min – 10% B; 1–15 min increase of B to 100%; 15–25 min – 100% B. Liquid phase speed 0.25 ml/min. Injected volume 5 μl, thermostat temperature 40°C. Electrospray ionization (ESI) in positive ion mode was applied. Ion source parameters were as follows: sheath gas 30 psi, spraying and drying gas 40 psi, ion source temperature 300°C, capillary voltage 5500 V, declusterization potential 80 V. Detection was carried out in information dependent acquisition (IDA). Full scan spectra (TOFMS) were recorded in the mass range 100–1000 Da. Collision induced decomposition (CID) was applied to the eluating components with the abundance exceeding 100 cps. CID was carried out simultaneously for not more than 15 ion precursors. DIC parameters: collision energy 40 eV, with spread 20 eV, mass range 20–1000 Da. Sodium formate was used for the mass spectrometer calibration before every analysis.

2.3. Toxicity measurements

The toxicity of resveratrol and its chlorination by-products mixtures were determined using liquid dried luminescent bacteria *V. fischeri* with system LUMIStox, Dr. Lange according to ISO 11348-2 (International Organisation for Standardisation, 1998). The toxicity endpoint was determined as reduced luminescence emission after incubation in the presence of a selected compound. pH of all tested aqueous samples was adjusted to 7 with hydrochloric acid or sodium hydroxide in order to avoid possible adverse effects due to incorrect pH value. An aliquot of *V. fisheri* was added to each vial in two parallels and luminescence was measured immediately. Afterwards the selected sample of chlorinated resveratrol aqueous solution was added to the vial with bacteria and thermostated at 15 ± 1 °C. The luminescence of bacteria within the sample was measured after 30 min of exposure. The inhibition of luminescence (with 95% confidence limit) was calculated using a computer software-supported model. The blank tests were performed with 2%, w/v sodium chloride and chlorine water without resveratrol or sunscreen.

3. Results and discussion

3.1. Resveratrol persistence under conditions of aquatic chlorination

Fig. 1 illustrates the persistence of pure resveratrol and resveratrol in a sunscreen during aquatic chlorination process.

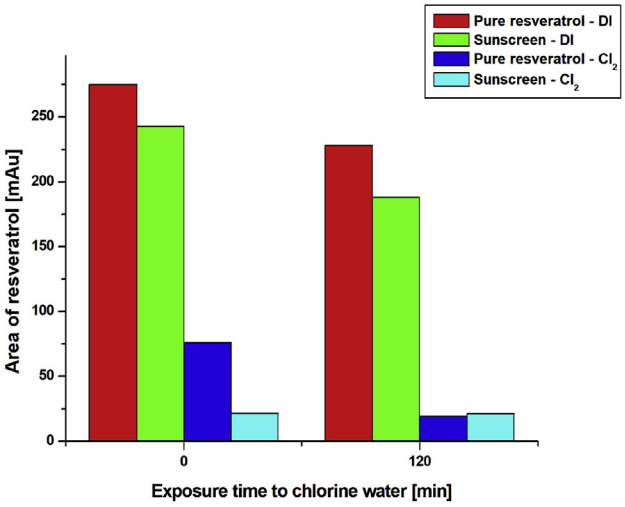


Fig. 1. Persistence of pure resveratrol and resveratrol in a sunscreen in conditions of aquatic chlorination.

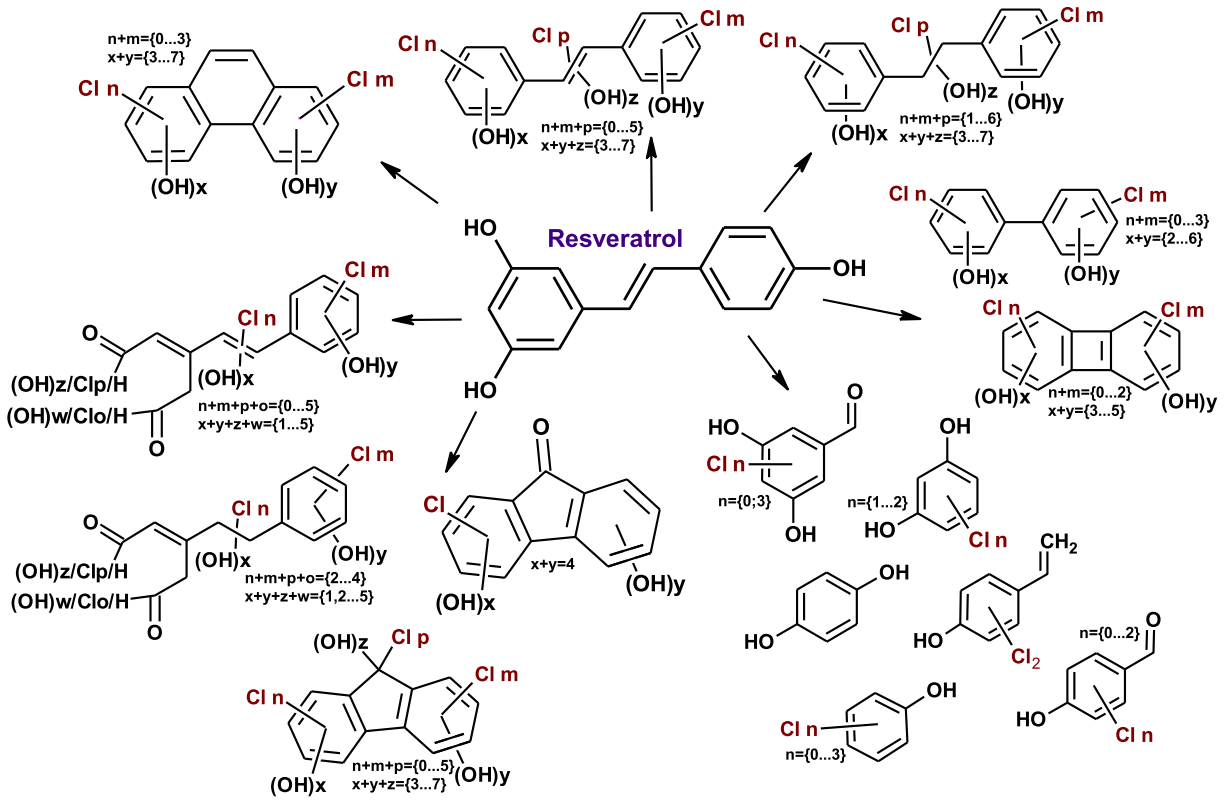
Chlorination of resveratrol is very fast and there is practically no difference in case of resveratrol formulation or pure resveratrol chlorination rate. In fact, a decrease of resveratrol concentration was observed immediately after dissolving resveratrol standard or resveratrol sunscreen in chlorine water. After 120 min less than 10% of the resveratrol remained in both experiments.

3.2. Products identification

The assortment of the aquatic chlorination products strongly depends on the structure of the initial substrate. Taking into account the diversity of the reactive particles in these conditions (Lebedev et al., 2004), sometimes even the nature of the primary products may not be obvious (Grbović et al., 2013; Santos et al., 2013; Crista et al., 2015). In the case of resveratrol, we tentatively identified 82 products of its transformation. Unfortunately, toxicity of only few of them is known. The main pathways of transformation may be illustrated by general scheme (Scheme 1). For the presented structures various combinations of chlorine atoms and hydroxyl groups in the molecules as well as the presence of numerous isomers should be taken into account.

The principal task of the study involved identification of the chlorination products. As there were no standards of the forming in the reaction compounds quantification was carried out as semi quantitative estimation based on the area of chromatographic peaks. Fig. 2 presents gas chromatogram based on the total ion current of the reaction mixture after resveratrol aquatic chlorination. All the major semi volatile products are listed in Table S1 in the Supplement material. It is worth mentioning that these compounds constitute over 95% of the whole bunch of semi volatile products. The major products identified with UPLC-MS are summarized in Table S2 in the Supplement. Based on the resveratrol standard its conversion in the experimental conditions was ~20%.

There were several primary reactions of resveratrol in conditions of aquatic chlorination. In all these cases the number of carbon atoms remains equal 14. The first reaction involves electrophilic addition to the double bond with possible formation of compounds 2(A-G), presented in Fig. 3a. Even without taking into account optical isomers a pair of positional isomers should form by conjunctive addition of HOCl to the double bond as Markovnicov rule (Markownikoff, 1870) does not work due to close values of the energy of chloronium intermediates.



Scheme 1. Principal pathways of resveratrol aquatic chlorination.

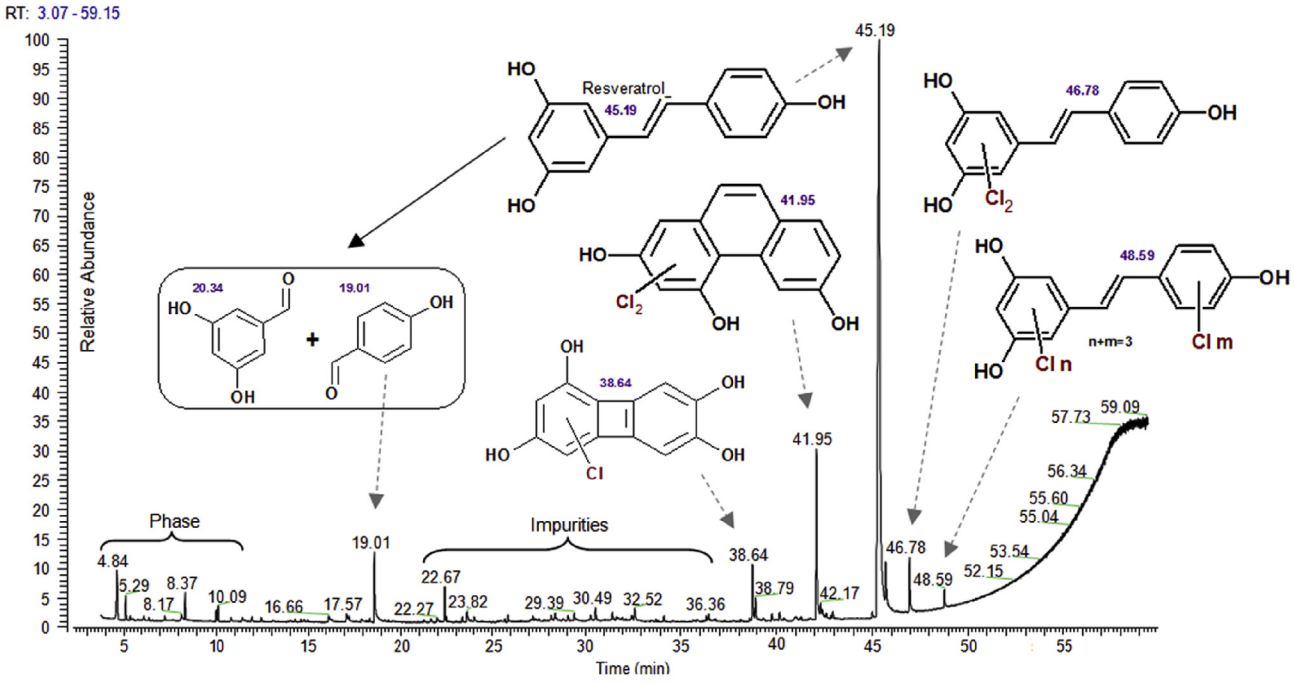


Fig. 2. TIC chromatogram of the resveratrol aquatic chlorination reaction mixture (Orbitrap, Thermo).

However, only dichlororesveratrol 2(A) was reliably identified in the reaction mixture. The absence of other compounds 2 in the reaction mixture may be rationalized by the fact that although double bond represents an extremely reactive moiety in aquatic chlorination (Sinikova et al., 2014; Lebedev, 2007), the forming compounds 2 immediately react further by the mechanism of electrophilic substitution in the aromatic ring or with the cleavage of the central aliphatic C–C bond.

The latter process brings to the corresponding products with one benzene ring in the molecule (Fig. 4): hydroxybenzaldehyde,

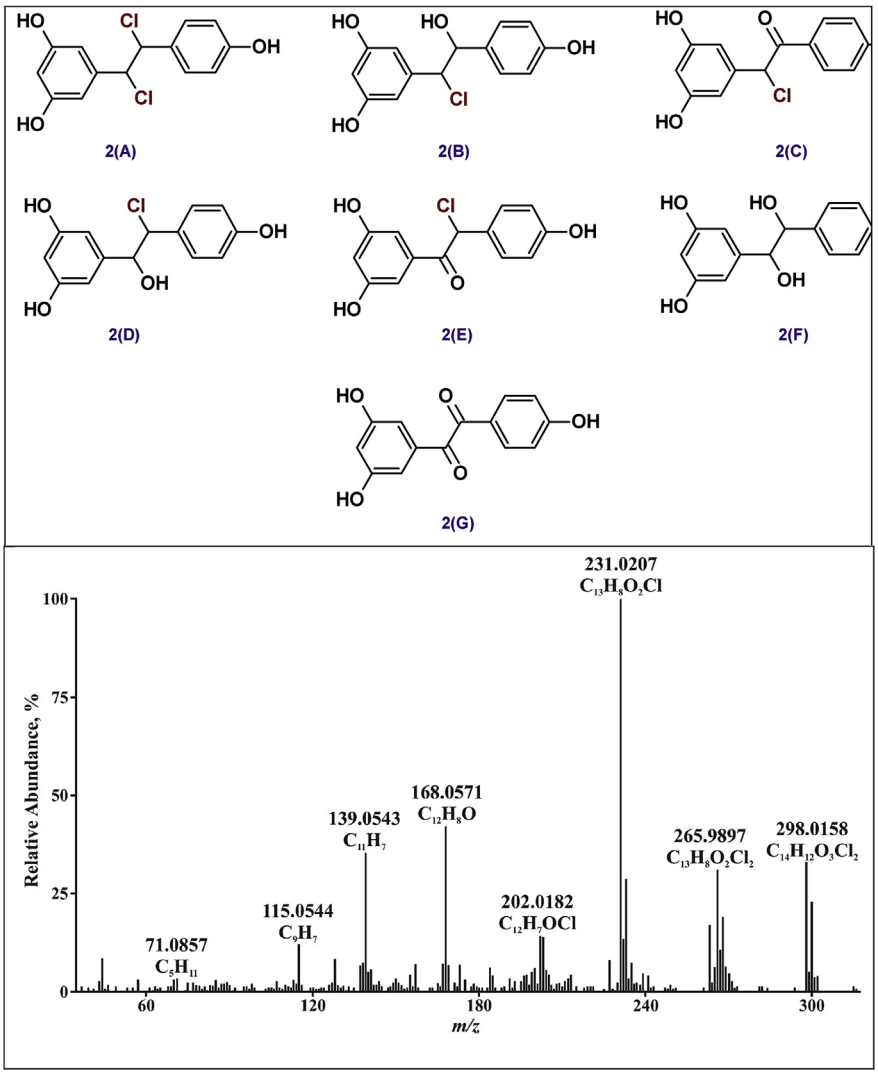


Fig. 3. a: Structures of compounds 2 (A-G), forming by electrophilic addition to the double bond; b EI mass spectrum of dichlororesveratrol 2(A).

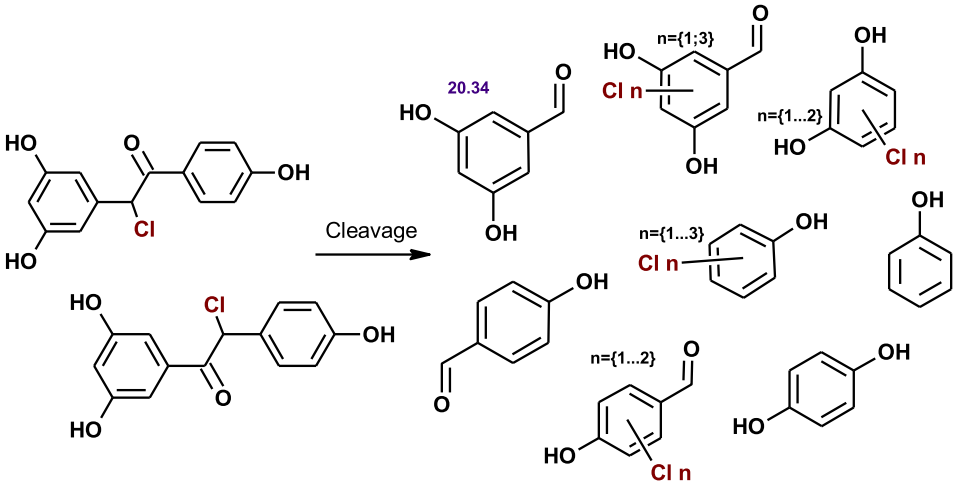


Fig. 4. Formation of chlorination products with one benzene ring.

mono- and di-chloro- hydroxybenzaldehyde, dihydroxybenzaldehyde and its derivatives with 1–3 chlorine atoms in the cycle, hydroquinone, chloro and dichlorohydroquinone, phenol, and chlorophenols with 1–3 chlorine atoms. It is worth mentioning

that only compounds of that group were studied earlier by toxicologists (Vlastos et al., 2016). Chlorophenols are the most well-known among them, being included in the list of priority pollutants of US EPA already in 1970th.

The second pathway of transformation of resveratrol or its products of electrophilic addition 2 involves electrophilic substitution in the aromatic ring. Both benzene rings of resveratrol are highly reactive due to the presence of strongly activating and *ortho-para*-directing hydroxyl groups. Two ortho-positions to the hydroxyl represent the most reactive sites in the phenolic ring. In the diol ring all positions are very reactive although the most reactive one situates between two hydroxyls. Previously it was demonstrated for the aquatic chlorination of resorcinol (Rook, 1976) and orcinol (Tretyakova et al., 1994).

Mono-di- and trichloro substituted resveratrols were the main semi volatile products of its aquatic chlorination. GC-MS allowed detecting two isomeric monochloro derivatives (RT = 44.85, 45.55), one dichloro derivative (RT = 46.78), and one trichloro (RT = 48.59). UPLC-MS allowed detecting tetrachloro derivative (RT = 9.05; $C_{14}H_8O_3Cl_4$ *m/z* 363.9290). The structures of these compounds are presented in Fig. 5, while exact positions of chlorine atoms were not obvious.

An important reaction taking place in experimental conditions involves substitution of chlorine atoms for hydroxyl moiety. Eleven compounds of that group were detected and presented in Fig. 6.

Combination of electrophilic addition to the double bond and electrophilic aromatic substitution brought to 13 compounds listed in Table 3S. Structures with higher number of Cl and OH moieties were detected using LC-MS. Unfortunately, fragmentation of these compounds (neither in EI, no in ESI-MS/MS conditions) did not allow defining exact positions of these groups in the molecules. Thus, general formulas or schematic structures are presented.

One more pathway of resveratrol transformation engages cyclization by *ortho*-positions of the aromatic rings. Although that reaction may be considered as oxidation with the loss of two corresponding hydrogen atoms, elimination of HCl molecule from the primary chlorinated products may be more probable. Fig. 7 illustrates that pathway. One should take into account that that process may involve numerous species forming at the earlier stages. Moreover, the forming phenanthrene-like molecules may react further. Mass spectrum of the dominant chlorination product is presented in Fig. 7 (bottom). It contains two chlorine atoms tentatively placed into the resorcinol ring. Peak area of that compound was about 12% vs the area of all peaks in GC and LC TIC chromatograms. Eleven similar structures with maximum of 7 OH-groups and 3 chlorine atoms were detected (Table 4S in the Supplement). Some structures with 4 and 6 hydroxyls do not contain chlorine atoms at all.

Resveratrol aquatic chlorination by-products of another group have 13 carbon atoms. One can propose several routes of their formation. Thus, similarly to orcinol chlorination (Tretyakova et al., 1994) diol containing ring may be opened. The corresponding mechanism involves substitution of hydrogens for chlorines in keto form and is presented in Fig. 8. A wide range of dicarbonyl products may form due to haloform reaction (Table 5S).

Another mechanism may involve decarbonylation of phenanthrene-like products with formation of the corresponding fluorenes. The latter structures may further lose another CO molecule forming biphenylenes (Fig. 9). Several biphenylene structures with 12 carbon atoms were detected with GC-MS (Table S6 in the Supplement), while compound with RT 38.64 was one of the most abundant chlorination by-products representing 2.6% of the total ion current. Its EI spectrum is presented in Fig. 9. Trihydroxybiphenylene was registered in ESI experiments in positive mode (RT6.09; *m/z* 200.0538).

The mechanism of formation of 12 detected by-products with biphenyl skeleton (Table S7) is not obvious. Nevertheless, these compounds worth special mentioning being representatives/derivatives of the well-known priority pollutants polychlorinated biphenyls. These are highly toxic compounds regulated all over the world. Being prohibited as industrial products 30–40 years ago (depending on the country), they are still detected in environment (Polyakova et al., 2012) due to their extraordinary stability. Although hydroxyl groups in the molecules of chlorinated biphenyls forming during resveratrol aquatic chlorination make the molecules more hydrophilic and therefore less cumulative in the fat tissues of humans and animals, their toxicities definitely should be taken into consideration.

Therefore 82 compounds were identified in the reaction mixtures of resveratrol chlorination, while only few of them belong to the classes studied from the toxicological point of view. These are chlorophenols and hydroxylated polychlorinated biphenyls. It is possible only to assume that other polychlorinated compounds identified in the present study should be toxic to some extent as well. It would be interesting to estimate toxicities of these compounds. However, they are too numerous and may be represented by various isomers. Moreover, they are commercially unavailable. Thus, in terms of the investigation the overall toxicity of the rection

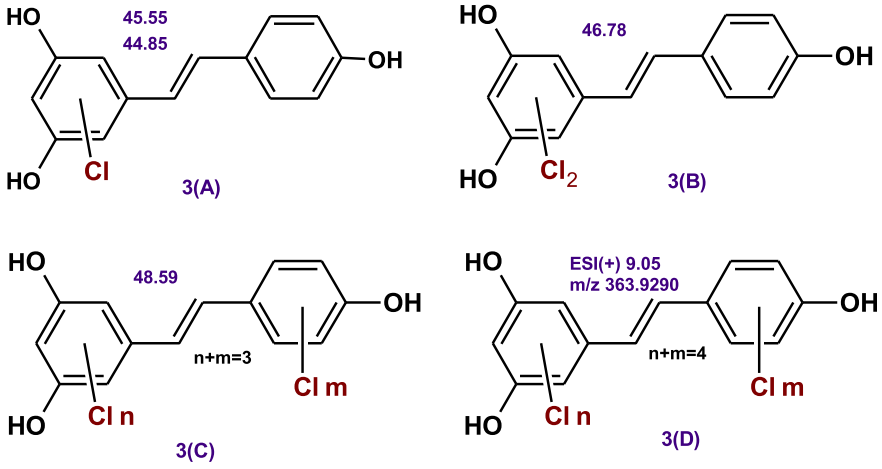


Fig. 5. Structures of mono-, di- and trichloro substituted resveratrols.

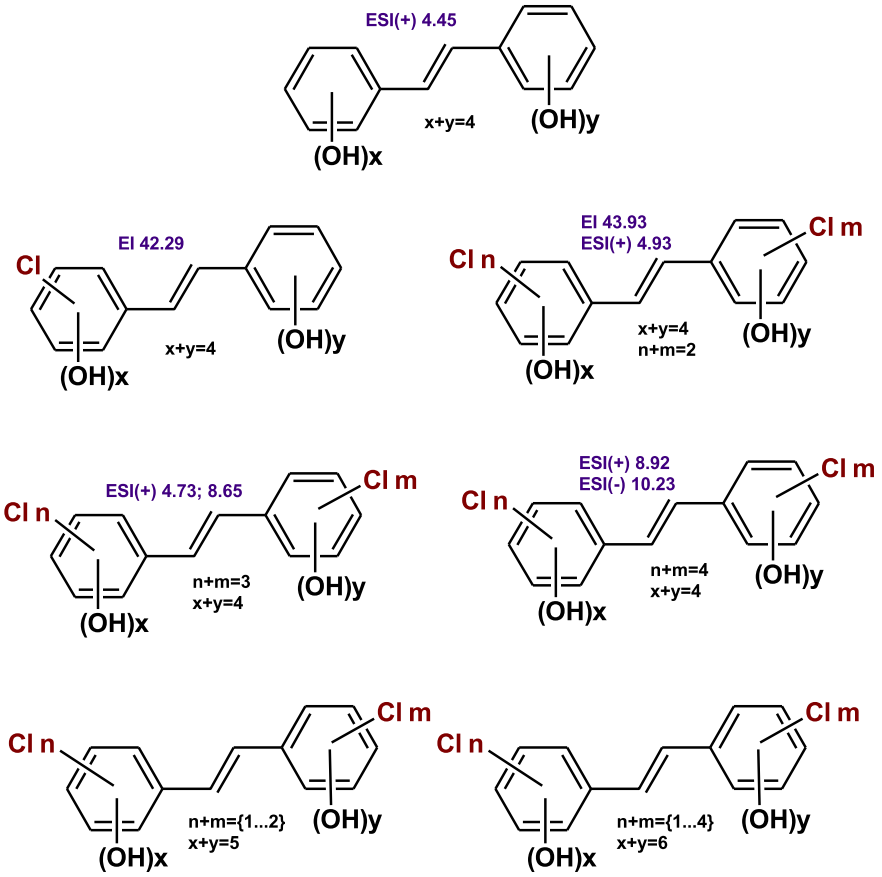


Fig. 6. Compounds, formed by substitution of chlorine atoms in the aromatic rings for hydroxyl groups.

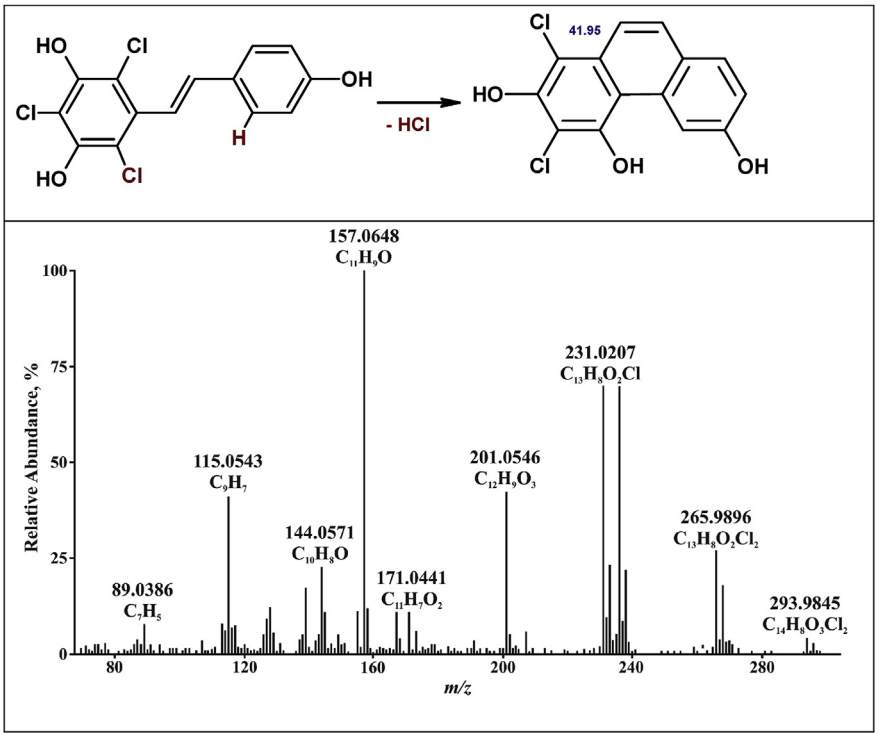


Fig. 7. Cyclization of resveratrol by ortho-positions of the aromatic rings (top); EI mass spectrum of the most abundant chlorination product RT = 41.95 (bottom).

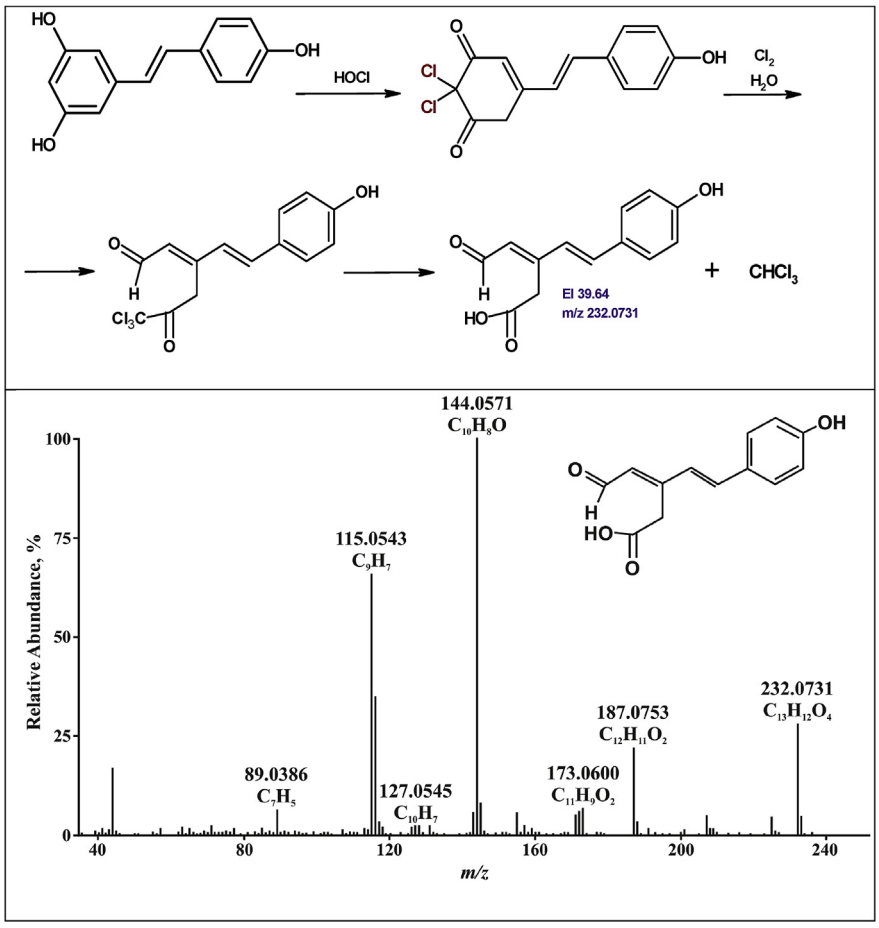


Fig. 8. Haloform reaction in resveratrol aquatic chlorination (top); EI spectrum of aldehydoacid $C_{13}H_{12}O_4$ (bottom).

mixture was measured.

3.3. Toxicity assessment with V. fischeri of resveratrol

When just few compounds arise in the reaction under the study it is quite possible to estimate their individual toxicities (Grbović et al., 2013). However, when a high number of products is formed the measuring of overall toxicity helps to estimate at least an overall toxic effect of the products (Lebedev et al., 2020). To get the overall toxicity of the sample during chlorination process usually a selected toxicity test is applied for the whole mixture. The most widespread is the standardised test with *V. Fischeri* (Vlastos et al., 2016).

The results of toxicity measurements on resveratrol aquatic chlorination are presented at Fig. 10. The samples of resveratrol and a sunscreen with resveratrol in distilled water showed no inhibition effect on *V. fischeri* at the beginning and after 120 min of exposure, demonstrating the result similar to the blank samples. At the beginning of the experiment (0 min) the inhibition of bacteria was 50,45% ± 2,47% (for pure resveratrol) and 53,69% ± 1,55% (for resveratrol in creame formulation). After 120 min it was 54,95%, ±1,48% (for pure resveratrol) and 54,82% ± 2,12% (for resveratrol in sunscreen).

The toxicity of the reaction mixture of resveratrol aquatic chlorination was higher already at the beginning of experiment and remained almost the same through the whole experiment. Active chlorine reacted immediately with resveratrol no matter if it was present as a pure substance or a component of the sunscreen. At the beginning of the experiment (0 min) the inhibition of bacteria was 79,73% ± 0,42% (for pure resveratrol) and 82,05% ± 3,32% (for resveratrol in sunscreen). After 120 min it was 79,05%, ±1,48% (for pure resveratrol) and 81,41% ± 0,70% (for resveratrol in sunscreen).

In the perspective of regulations of disinfection by-products for drinking water several questions are raised and have to be addressed also in terms of swimming pool waters. One of them is whether we are regulating the right DBPs to protect human health, and if not, what should be done. New approaches may involve the use of in vitro data, using surrogate metrics of finished waters, using toxicity assays for whole drinking water extracts and invoking different treatment strategies to reduce the toxicity (Richardson and Plewa, 2020).

4. Conclusions

The study of *trans*-resveratrol and its UV-protecting formulations demonstrated the fast transformation of that compound under aquatic chlorination conditions. The toxicity of the resveratrol aquatic chlorination products is substantially higher than that of pure resveratrol or its sunscreen formulatons. GC-HRMS and LC-HRMS allowed tentatively identifying 82 aquatic chlorination products of resveratrol, including chlorophenols and polychlorinated biphenyls. The principal mechanisms of the corresponding chlorination reactions and transformation schemes are proposed. Electrophilic addition to the aliphatic double bond and

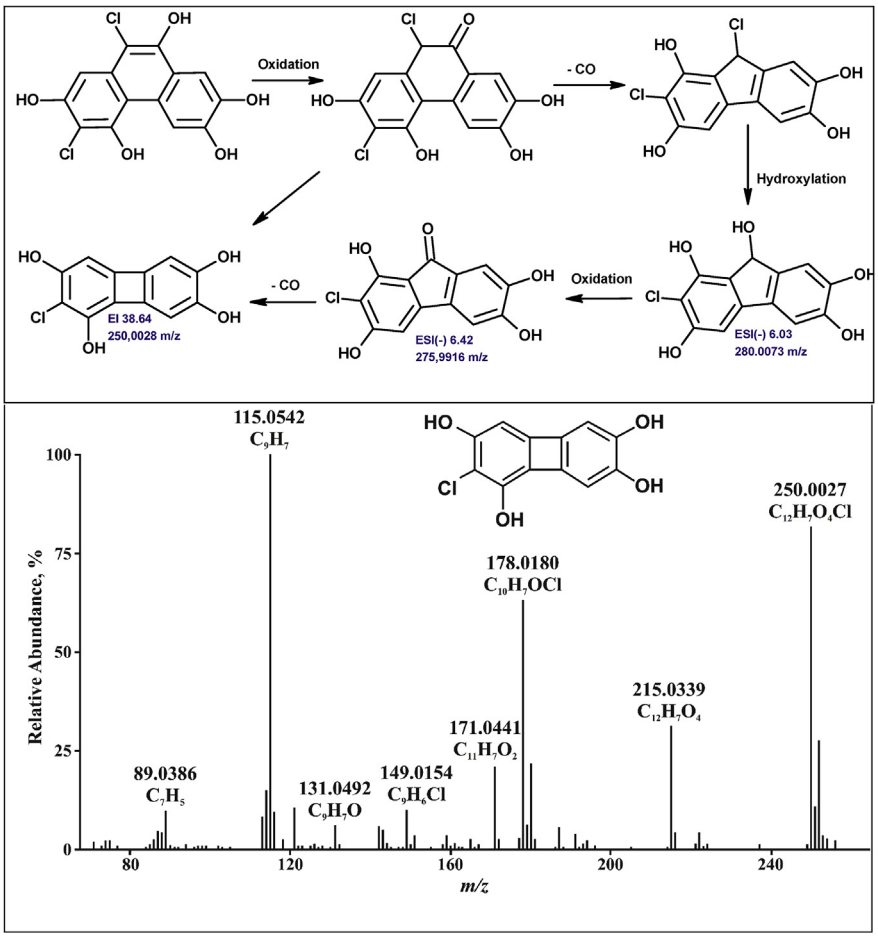


Fig. 9. Formation of fluorenyl and biphenylene products of resveratrol aquatic chlorination(top); EI spectrum of the biphenylene product with RT 38.64 (bottom).

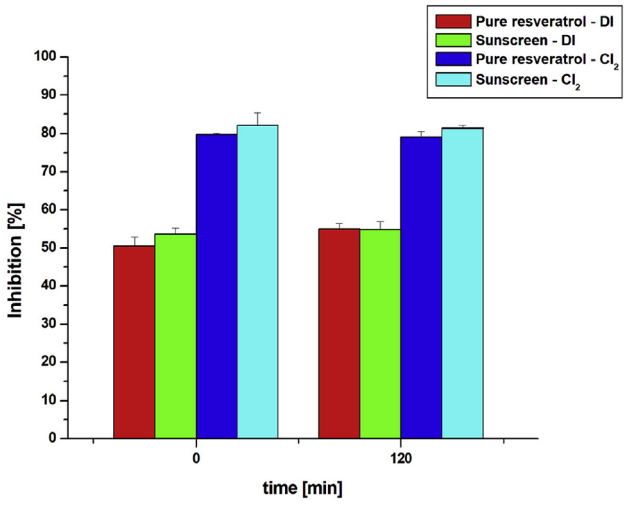


Fig. 10. Bioluminescence inhibition for V. fischeri of the aquatic chlorination mixture of resveratrol standard and resveratrol sunscreen at 0 and 120 min (chlorination experiment).

electrophilic substitution in the aromatic ring are the most important primary reactions of aquatic chlorination, followed by cyclization, resorcinol cycle opening, and aliphatic C–C bond cleavage. Additional studies should be undertaken to understand what particular chlorination products increase the toxicity of the reaction mixture.

CRediT author statement

Albert Lebedev: Methodology, Software, Validation, Resources, Writing - Review & Editing, Supervision, Funding acquisition. **Mojca Bavcon Kralj:** Conceptualization, Methodology, Visualization, Supervision. **Aleksandra Marjanović:** Investigation. **Elena A.Detenchuk:** Investigation. **Dmitry Kosyakov:** Formal analysis. **Nikolay Uljanovskii:** Formal analysis. **Polonca Trebše:** Methodology, Resources, Writing - Review & Editing, Project administration, Funding acquisition.

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.

Acknowledgement

The reported study was funded by RFBR, project number 19-33-90042. This work was performed using instrumentation of the Core Facility Center “Arktika” of the Northern (Arctic) Federal University under financial support of the Ministry of Science and Higher Education of the Russian Federation (state assignment project No. 0793-2020-0007).

The authors acknowledge the financial support from the Slovenian Research Agency, the research core funding No. P3-0388 (Mechanisms of health maintenance), No. J2-8162 (Closing material flows by wastewater treatment with green technologies) and bilateral scientific collaboration between Slovenia and Russia (The research of micropollutants' path in wastewater and the reduction of environmental risk by green technologies).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.chemosphere.2020.127557.

References

Agustín-Salazar, S., Gamez-Meza, N., Medina-Juárez, L.A., Soto-Valdez, H., Cerruti, P., 2014. From nutraceutics to materials: effect of resveratrol on the stability of polylactide. ACS Sustain. Chem. Eng. 2, 1534–1542. https://doi.org/10.1021/sc5002337.

Aziz, M.H., Afaq, F., Ahmad, N., 2005. Prevention of ultraviolet-B radiation damage by resveratrol in mouse skin is mediated via modulation in survivin. Photochem. Photobiol. 81, 25–31. https://doi.org/10.1562/2004-08-13-RA-274.

Bando, N., Hayashi, H., Wakamatsu, S., Inakuma, T., Miyoshi, M., Nagao, A., Yamauchi, R., Terao, J., 2004. Participation of singlet oxygen in ultraviolet-A-induced lipid peroxidation in mouse skin and its inhibition by dietary beta-carotene: an ex vivo study. Free Radic. Biol. Med. 37, 1854–1863. https://doi.org/10.1016/j.freeradbiomed.2004.09.004.

Barbosa-Pereira, L., Aurreokoetxea, G.P., Angulo, I., Paseiro-Losada, P., Cruz, M.J., 2014. Development of new active packaging films coated with natural phenolic compounds to improve the oxidative stability of beef. Meat Sci. 97, 249–254. https://doi.org/10.1016/j.meatsci.2014.02.006.

Chao, W., Xuexin, Z., Jun, S., Ming, C., Hua, J., Li, G., Tan, C., Xu, W., 2014. Effects of resveratrol on cell growth and prolactin synthesis in GH3 cells. Exp. Ther. Med. 7, 923–928. https://doi.org/10.3892/etm.2014.1544.

Crista, D.M.A., Miranda, M.S., Esteves da Silva, J.C.G., 2015. Degradation in chlorinated water of the UV filter 4- tert-butyl-4'-methoxydibenzoylmethane present in commercial sunscreens. Environ. Technol. 36 (10), 1319–1326. https://doi.org/10.1080/09593330.2014.988184.

Darvin, M.E., Fluhr, J.W., Meinke, M.C., Zastrow, L., Sterry, W., Lademann, J., 2011. Topical beta-carotene protects against infra-red-light-induced free radicals. Exp. Dermatol. 20, 125–129. https://doi.org/10.1111/j.1600-0625.2010.01191.x.

Detenchuk, E.A., Chen, J., Polyakova, O.V., Trebše, P., Pokryshkin, S.A., Lebedev, A.T., 2019. Study of aquatic chlorination of UV-filter avobenzone in the presence of inorganic salts by gas chromatography combined with high resolution mass spec-trometry. J. Anal. Chem. 74 (13), 1271–1276. https://doi.org/10.1134/S1061934819130069. Original Russian version in Mass-spektrometria (Rus) 2018, 15, 226-232.

Džeba, I., Pedzinski, T., Mihaljevic, B., 2012. Reaction kinetics of resveratrol with tert-butoxyl radicals. Radiat. Phys. Chem. 81, 1294–1296. https://doi.org/10.1016/j.radphyschem.2011.11.025.

EC Regulation 1223/2009 on cosmetics, 2009. Annex XI. Official Journal of the European Union. L 342, 201–202. https://ec.europa.eu/growth/tools-databases/cosing/pdf/COSING_Annex%20VI_v2.pdf.

Evaluation and Licensing Division Pharmaceutical Safety and Environmental Health Bureau Ministry of Health, Labour and Welfare, 2000. Standards for Cosmetics. Ministry of Health and Welfare. Notification No.331 of 2000. https://www.mhlw.go.jp/file/06-Seisakujouhou-11120000-Iyakushokuhinkyoku/0000032704.pdf.

Gilaberte, Y., Gonzalez, S., 2010. Update on Photoprotection. Novedades en fotoprotección. Actas Dermo-Sifiliográficas 101, 659–672. https://doi.org/10.1016/S1578-2190(10)70696-X.

Godic, A., Poljšak, B., Adamič, M., Dahmane, R., 2014. The role of antioxidants in skin cancer prevention and treatment. Oxid. Med. Cell. Longev. 6. https://doi.org/10.1155/2014/860479. Article ID 860479.

Grbović, G., Trebše, P., Dolenc, D., Lebedev, A.T., Sarakha, M., 2013. LC/MS study of the UV filter hexyl 2-[4-(diethylamino)-2-hydroxybenzoyl]-benzoate (DHHB) aquatic chlorination with sodium hypochlorite. J. Mass Spectrom. 48, 1232–1240. https://doi.org/10.1002/jms.3286.

Gülcin, I., 2010. Antioxidant properties of resveratrol: a structure-activity insight. Innovat. Food Sci. Emerg. Technol. 11, 210–218. https://doi.org/10.1016/j.ifset.2009.07.002.

Huang, J.-H., Huang, C.-C., Fang, J.-Y., Yang, C., Chan, C.-M., Wu, N.-L., Kang, S.-W., Hung, C.-F., 2010. Protective effects of myricetin against ultraviolet-B-induced damage in human keratinocytes. Toxicol. Vitro 24, 21–28. https://doi.org/10.1016/j.tiv.2009.09.015.

Kullavanijaya, P., Lim, H.W., 2005. Photoprotection. J. Am. Acad. Dermatol. 52 (6), 937–958. https://doi.org/10.1016/j.jaad.2004.07.063.

Lebedev, A.T., 2007. Mass-spectrometry in the study of mechanism of aquatic chlorination of organic substrates. Eur. J. Mass Spectrom. 13, 51–56. https://doi.org/10.1255/ejms.852.

Lebedev, A.T., Shaydullina, G.M., Sinikova, N.A., Harchevnikova, 2004. N.V. GC-MS comparison of the behavior of chlorine and sodium hypochlorite towards organic compounds dissolved in water. Water Res. 38, 3713–3718. https://doi.org/10.1016/j.watres.2004.06.007. N 17.

Lebedev, A.T., Polyakova, O.V., Mazur, D.M., Artaev, V.B., 2013. The benefits of high resolution mass spectrometry in environmental analysis. Analyst 138, 6946–6953. https://doi.org/10.1039/c3an01237a.

Lebedev, A.T., Bavcon Kralj, M., Polyakova, O.V., Detenchuk, E.A., Pokryshkin, S.A., Trebše, P., 2020. Identification of avobenzone by-products formed by various disinfectants in different types of swimming pool waters. Environ. Int. 137, 105495. https://doi.org/10.1016/j.envint.2020.105495.

Lee, C.W., Ko, H.H., Lin, C.C., Chai, C.Y., Chen, W.T., Yen, F.L., 2013. Artocarpin attenuates ultraviolet B-induced skin damage in hairless mice by antioxidant and anti-inflammatory effect. Food Chem. Toxicol. 60, 123–129. https://doi.org/10.1016/j.fct.2013.07.029.

Markownikoff, W., 1870. Ueber die Abhangigkeit der verschiedenen Vertretbarkeit des Radicalwasserstoffs in den isomeren Buttersauren. Ann. Pharm. (Poznan) 153, 228–259. https://doi.org/10.1002/jlac.18701530204.

Nichols, J.A., Katiyar, S.K., 2010. Skin photoprotection by natural polyphenols: anti-inflammatory, antioxidant and DNA repair mechanisms. Arch. Dermatol. Res. 302, 71–83. https://doi.org/10.1007/s00403-009-1001-3.

Norval, M., Wulf, H.C., 2009. Does chronic sunscreen use reduce vitamin D production to insufficient levels? Br. J. Dermatol. 161, 732–736. https://doi.org/10.1111/j.1365-2133.2009.09332.x.

Piñeiro, Z., Palma, M., Barroso, C.G., 2006. Determination of trans-resveratrol in grapes by pressurized liquid extraction and fast high-performance liquid chromatography. J. Chromatogr. A 1110, 61–65. https://doi.org/10.1016/j.chroma.2006.01.067.

Polyakova, O.V., Mazur, D.M., Seregina, I.F., Bolshov, M.A., Lebedev, A.T., 2012. Estimation of contamination of atmosphere of Moscow in winter. J. Anal. Chem. 67, 1039–1049. Original Russian version in Mass-spektrometria (Rus). 2012, 9, 5 – 15.

Richardson, S.D., Plewa, M.J., 2020. To regulate or not to regulate? What to do with more toxic disinfection by-products? J. Environ. Chem. Eng. 8 (4), 103939. https://doi.org/10.1016/j.jece.2020.103939.

Rook, J.J., 1976. Haloforms in drinking water. J. Am. Water Works Assoc. 68, 168–172. https://doi.org/10.1002/j.1551-8833.1976.tb02376.x.

Rossi, D., Guerrini, A., Bruni, R., Brognara, E., Borgatti, M., Gambari, R., Maietti, S., Sacchetti, G., 2012. Trans-resveratrol in nutraceuticals: issues in retail quality and effectiveness. Molecules 17, 12393–12405. https://doi.org/10.3390/molecules171012393.

Santos, A.J.M., Crista, D.M.A., Miranda, M.S., Almeida, I.F., de Silva, J.P.S., Costa, P.C., Amaral, M.H., Lobão, P.A.L., Lobo, J.M.S., Esteves da Silva, J.C.G., 2013. Degradation of UV filter 2-ethylhexyl-4-methoxycinnamate and 4-tert-butyl-4-methoxydibenzoylmethane in chlorinated water. Environ. Chem. 10 (2), 127–134. https://doi.org/10.1071/EN15013.

Sinikova, N.A., Shaydullina, G.M., Lebedev, A.T., 2014. Comparison of chlorine and sodium hypochlorite activity in the chlorination of structural fragments of humic substances in water using GC–MS. J. Anal. Chem. 69 (14), 1300–1306. https://doi.org/10.1134/S106193481414010X. Original Russian version in Mass-spektrometria (Rus) 2014, 11, 22-28.

Soby, L., Theophilus, E.H., Ptchelintseu, D., Attar, P.S., 2003. Resveratrol analogs for treatment of skin disorders. U.S. Pat. Appl. Publ. US. https://doi.org/10.1016/j.abb.2010.12.030, 20030118617 A1 20030626.

Trebše, P., Polyakova, O.V., Baranova, M., Bavcon, Kralj M., Dolenc, D., Sarakha, M., Kutin, A., Lebedev, A.T., 2016. Transformation of avobenzone in conditions of aquatic chlorination and UV-irradiation Water Research, 101, 95–102. https://doi.org/10.1016/j.watres.2016.05.067.

Tretyakova, N.Y., Lebedev, A.T., Petrosyan, V.S., 1994. Degradative pathways for aqueous chlorination of orcinol. Environ. Sci. Technol. 28, 606–613. https://doi.org/10.1021/es00053a012.

U.S. Department of Health and Human Services Food and Drug Administration, 2019. FDA Advances New Proposed Regulation to Make Sure that Sunscreens Are Safe and Effective. U.S. Department of Health and Human Services, Washington, DC. Food and Drug Administration Center for Drug Evaluation and Research (CDER), February 21st, 2019. https://www.fda.gov/news-events/press-announcements/fda-advances-new-proposed-regulation-make-sure-sunscreens-are-safe-and-effective.

U.S. Department of Health and Human Services Food and Drug Administration, 2020. Over-the-Counter (OTC) Drug Monograph Process. U.S. Department of Health and Human Services, Washington, DC. Food and Drug Administration Center for Drug Evaluation and Research (CDER), March 30th, 2020. https://www.fda.gov/drugs/over-counter-otc-drug-monograph-process.

Velasco, M.V.R., Sarruf, F.D., Nunes Salgado-Santos, I.M., Haroutiounian-Filho, C.A., Telma Mary Kaneko, T.M., Baby, A.R., 2008. Broad spectrum bioactive sunscreens International Journal of Pharmaceutics 363, 50–57. https://doi.org/10.1016/j.ijpharm.2008.06.031.

Vlastos, D., Antonopoulou, M., Konstantinou, I., 2016. Evaluation of toxicity and genotoxicity of 2-chlorophenol on bacteria, fish and human cells. Sci. Total Environ. 551–552, 649–655.

Wang, C., Hu, Z., Chu, M., Wang, Z., Zhang, W., Wang, L., Li, C., Wang, J., 2012. Resveratrol inhibited GH3 cell growth and decreased prolactin level via estrogen receptors. Clin. Neurol. Neurosurg. 114, 241–248. https://doi.org/10.1016/j.clineuro.2011.10.035.

Wang, C., Bavcon Kralj, M., Kosmrlj, B., Yao, J., Kosenina, S., Polyakova, O.V.,

Artaev, V.B., Lebedev, A.T., Trebse, P., 2017. Stability and removal of selected avobenzone's chlorination products. Chemosphere 182, 238–244.
Xiao, J., Song, J., Hodara, V., Ford, A., Wang, X.L., Shi, Q., Chen, L., Vandeberg, J.L., 2013. Protective effects of resveratrol on TNF-a-induced endothelial cytotoxicity in baboon femoral arterial endothelial cells. Diabetes Res. 1–9. https://doi.org/10.1155/2013/185172.
Yin, H.T., Tian, Q.Z., Guan, L., Zhou, Y., Huang, X.E., Zhang, H., 2013. In vitro and in vivo evaluation of the antitumor efficiency of resveratrol against lung cancer. Asian Pac. J. Cancer Prev. APJCP 14, 1703–1706. https://doi.org/10.7314/apjcp.2013.14.3.1703.