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Original Article

Rhus coriaria (sumac) extract reduces migration capacity of uterus cervix cancer cells

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ABSTRACT

Uterus cervix cancer is one of the most common malignant gynecological tumors in women globally. Its standard treatment includes radiotherapy and chemotherapy are considered highly toxic, expensive and exhaustive for patients. Medicinal plants became increasingly a better and a safer alternative therapeutic approach. *Rhus coriaria* L., Anacardiaceae, is a medicinal plant whose anti-cancer effect has been explored in few cancer types including breast and colorectal cancer. However, its effect on uterus cervix cancer is still unknown. In this study, we showed that non-cytotoxic concentrations of *R. coriaria* reduces uterus cervix cell migration capacity. We have also found that *R. coriaria* has a growth inhibitory effect on cervical cancer cells in a time- and a concentration-dependent manner. We have carried out a phytochemical compound analysis of *R. coriaria* extract using liquid chromatography–mass spectrometry method in order to identify bioactive compounds in *R. coriaria* extract that could potentially induce its anti-cancer effects. Our results are promising to involve *R. coriaria* as a therapeutic drug candidate for uterus cervix cancer.

Introduction

Cervical cancer is the fourth most frequent type of cancer in women worldwide. It results in 300,000 deaths annually. Most cases occur in women of developing countries (Small et al., 2017); Cohen et al., 2019). Both radiotherapy and chemotherapy constitute a major modality used in the treatment of early stage uterus cervix cancer (Zhao et al., 2016). However, radiotherapy can induce vaginal symptoms such as fibrosis or elastosis and sexual problems (Hofsjö et al., 2018). Importantly, several patients in advanced stage with large tumor diameter and lymph node metastasis treated with chemoradiotherapy still suffered from local or distant relapse (Zhao et al., 2016). Therefore, improving the treatment outcome of these patients is a key concern while finding a safer treatment for cervical cancer with lesser or no side effects is primordial.

Rhus coriaria L., Anacardiaceae (traditionally known as sumac in the Middle East) has been used as a treatment for several different ailments in Middle Eastern and South Asian countries since ancient times (Farag et al., 2018). Sumac was used as medicine or as a culinary spice. In addition, it was traditionally used in the treatment of cancer in addition to other ailments (Mirian et al., 2015). Sumac is gifted with several biological properties including antioxidant, anti-inflammatory, hypoglycemic and hypolipidemic activities (Abu-Reida et al., 2014). This could refer to *Rhus coriaria* composition and promising functional compounds such as flavonoids phenolic acids and tannins (Farag et al., 2018).

In this study, we identify *R. coriaria* (sumac fruit) as a potent inhibitor of uterus cervix cancer cells migration and proliferation.

Materials and Methods

Chemicals

All chemicals were of analytical reagent grade and used as received. Double-deionized water was got with a Milli-Q system (Millipore, Bedford, MA). Acetic acid of analytical grade was purchased from Fluka (Buchs, Switzerland). HPLC-grade acetonitrile and methanol were acquired from Labscan (Dublin, Ireland).

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Rhus coriaria *plant extraction*

Commercial sumac samples *Rhus coriaria* L., Anacardiaceae, used in this study was purchased from local practitioner market in Nablus city. Plant identification was carried out at the Pharmacognosy Laboratory at An-Najah National University, and the voucher specimen code Pharm-PCT-2037 has been given to *Rhus coriaria*. After that, it was stored at 5 °C until the extraction process. To extract the secondary plant metabolites from sumac fruit, the samples were treated according to the extraction process previously described in the literature (Abu-Reidah et al., 2015) with some modifications. Briefly, sample (0.5 g) was dissolved with 16 ml of EtOH/H_2O (70:20, v/v) which were sonicated for 60 min in an ultrasonic bath. Then, the mixture was centrifuged at 3800 x *g* for 15 min and the supernatant was collected in a round bottom flask. The solvent was evaporated under vacuum using rotary evaporation at 38 °C. Lastly, the dry deposit was dissolved with 0.5 ml of EtOH/H_2O (70:30, v/v), passed through a 0.22 μm syringe filter, and stored at −20 °C until analysis. Finally, *R. coriaria* extract (RCE) was dissolved in complete media before being added to cells incubation media.

Phenolic compounds analysis by rapid resolution liquid chromatography-diode array detection/electrospray ionization tandem mass spectrometry (RRLC-DAD-ESI/MS)

Samples of sumac were analyzed by using an Agilent-1100 series high pressure liquid chromatograph equipped with a Zorbax C18 reverse phase column (10 mm × 4.6 mm, particle size 5 μm; Agilent Technologies, Palo Alto, CA, USA. A mobile phase (A) of water + formic acid 1%, v/v) and methanol (B) was used with following gradient: 5–15% B (0–5 min), 15–25% B (5–7.5 min), 25–50% B (7.5–25 min), 50–85% B (25–33 min), and a 3 min post-run was used after each analysis. The temperature was maintained at 25 °C and flow rate was 0.2 ml/min. The detection was done with a diode array detector (DAD) for multi wavelength detection detector in a wavelength range of 190–580 nm and interfaced with an AB Sciex API-5000 MS equipped with Turbo V ESI source (Foster City, CA). The mass spectrometer system was achieved by using the full scan in the negative ionization mode. Source and capillary voltages were −10 V and 4.0 kV, respectively, and the capillary temperature was 270 °C. The sheath gas used was N_2 at a flow rate of 8 l/min. In addition, nitrogen was used at a normalized collision energy of 50%.

Cell culture technique: HeLa cells culture

HeLa cells are immortalized human epithelial cell line from a cervical carcinoma transformed by human papilloma virus 18 (HPV18) (Mizikar, 2014). HeLa cells were maintained in RPMI-1640 media. All media were complemented with 10% fetal bovine serum (FBS), 1% penicillin/streptomycin and 1% L-glutamine. Cells were incubated at 37 °C in a humidified atmosphere of 5% CO_2.

Cell proliferation assay

HeLa cells were cultured in RPMI-1640 media supplemented with 10% FBS, 1% penicillin/streptomycin antibiotics and 1% L-glutamine. Cells were grown in a humidified atmosphere with 5% CO_2 at 37 °C. Cells were seeded at 2.6×10^4cells/well in a 96-well plate and were incubated with 2000, 1000, 750, 500, 250, 125, 62.5, 31.25 g/ml of *R. coriaria* extract for 24 h or 48 h. Cell viability was assessed by CellTiter 96® Aqueous One Solution Cell Proliferation (MTS) Assay according to the manufacturer's instructions (Promega Corporation, Madison, WI). Briefly, at the end of the treatment, 20 μl of MTS solution per 100 μl of media was added to each well and incubated at 37 °C for 2 h. Absorbance was measured at 490 nm.

Trypan blue exclusion assay of cell viability

Cell viability was determined using trypan blue dye exclusion assay by the end of wound healing assay. Four wells of viable cells for each concentration were pooled together and counted using a hemocytometer after trypsinization in three independent experiments. Cell viability was quantified and represented as a percentage of viable cells relative to the total number of cells in each condition. In addition, the total cell count of viable and dead cells was evaluated.

Wound healing technique: migration assay

HeLa cells were grown in 24-well plate until confluence. A wound was scratched through the confluent monolayer of cells with a sterile plastic pipette tip (10 μl) in the vertical diameter of each well. Each condition was represented in four wells per experiment (Quadruplicates). Afterwards, the plates were washed with PBS and incubated at 37 °C in fresh RPMI-1640 media supplemented with 10% fetal bovine serum in the presence of complete media without or with the indicated concentrations of RCE. This technique is done similarly as described in (Jemaà et al., 2017) with some modifications (See supplementary videos/Materials and Methods in Jemaà et al., 2017).

Quantification of snapshot pictures: migration assay

Three images were taken in each well to include the length of wound spread over well diameter and the wound area was measured using MRI Wound Healing Tool (http://dev.mri.cnrs.fr/projects/imagej-macros/wiki/Wound_Healing_Tool). Finally, twelve reads were taken for each condition in each experiment as four wells were considered for each condition (4 wells × 3 images = 12 reads per condition per experiment). The width of the wound was photographed with an inverted microscope (LaboMed- ARCO Med TCM-400 microscope, https://www.laboamerica.com/products/life-materials-sciences/tcm-400#specifications) at a total magnification of 40× (objective lens 4× * 10×/22 mm eyepiece) at 0 h and 24 h. Wound closure was determined by measuring the area of the wound at 0 h and 24 h using ImageJ software. Quantification of the area invaded by migrating cells was represented as follows: (Area of the wound at t = 0 h − Area of the wound at t = 24 h). Finally, migration areas were expressed as percentages over control values.

Data analysis

Data has been analyzed and graphs were designed using Graph pad Prism version 7.

Results

Rhus coriaria *has a growth inhibitory effect on uterus cervix cancer cells after 48 h treatment*

First, we wanted to determine whether RCE has an effect on cell viability. Therefore, we used MTS assay to test this hypothesis. As shown in (Fig. 1A), the treatment with 2000, 1000, 750, 500, 250, 125, 62.5 and 31.25 μg/ml of RCE had no significant effect on cell viability after 24 h of incubation compared to non-treated cells (Control). However, RCE had a significant effect on HeLa cells viability after 48 h of treatment. Increasing concentrations of RCE have gradually reduced the cell viability by around (30–65%) compared to control (Fig. 1B). To conclude, these results show a growth inhibitory effect of RCE on cervical cancer cells after 48 h treatment.

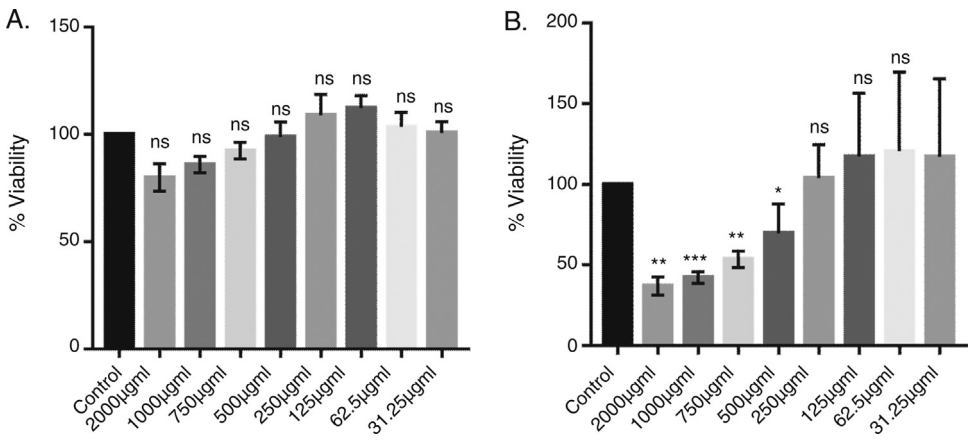

Fig. 1. *Rhus coriaria* has a growth inhibitory effect on uterus cervix cancer cells after 48 h treatment. Quantification of HeLa cells viability using MTS assay after incubating cells with 2000, 1000, 750, 500, 250, 125, 62.5, 31.25 µg/ml of RCE during 24 h (**A**) or 48 h (**B**) compared to non-treated cells (Control). Viability is expressed as a percentage. Data are reported in SEM; n = 3 for A and n = 4 for B (performed in triplicate wells/condition). ns = non-significant.*($p < 0.05$), ** ($p < 0.01$) or *** ($p < 0.001$) indicates statistical difference from control condition at each time point (Paired t-test).

Rhus coriaria *inhibits the migration of uterus cervix cancer cells*

As cancer cells' migration play a key role in the spread of cancer tumors and contribute to metastatic dissemination from primary tumor to secondary sites, we determined the effect of RCE on cervical cancer cells migration. In order to proceed, we studied the effect of (0, 31.25, 62.5, 125 µg/ml) of RCE on HeLa cells migration using wound healing assay (Fig. 2A,B). Compared to control, RCE induced a significant reduction by nearly (15–35%) on cell migration after 24 h of incubation (Fig. 2B). We showed that 31.25, 62.5 and 125 µg/ml concentrations of RCE had no effect on cell viability according to MTS viability test (Fig. 1A). We further confirmed this result by evaluating the total cell counts along with the percentage of viable cells at the end of the migration assay after 24 h of incubation with RCE using trypan blue staining. We showed that there is no significant difference; neither in the percentage of viable cells nor in the total cell counts at 31.25, 62.5 and 125 µg/ml concentrations when compared to control (Fig. 2C,D). Taken together, these results demonstrate that RCE has an inhibitory effect on uterus cervix cancer cell migration.

Phytochemical compounds identification by LC-MS

We then intended to identify new bioactive compounds potentially involved in sumac effect on cancer cells. The used methodology has been useful for the analysis and the identification of thirteen major compounds present in the hydro-alcoholic extract of sumac. Two flavonoid derivatives (quercitrin at *m/z* 447.1, and myricetin glucuronide at *m/z* 493.1) were identified based on their acceptable data obtained from ESI-MS. Both compounds presence is being reported in sumac fruit for the first time. Using this procedure and examining ions that contain derivatives of gallic acid, the following compounds were identified: the gallicin for the ion at *m/z* 183.1, glucogallic acid (*m/z* 331.1), tri-galloyl-hexoside (635.1), penta-galloyl-hexoside (939.1). These gallic derivatives with their aglycone have been reported as bioactive compounds with different biological activities either in *in vivo* or *in vitro* assays (Choubey et al., 2015). Worth mentioning that peak 2 and 10 have displayed higher peaks in the MS chromatogram (Fig. 3). Peak 2 (*Rt* 4.20 min) showed (220, 295) in the UV spectrum and the MS spectrum it showed the molecular ion at *m/z* 169.0. Based on the above data, 2 was labelled as gallic acid. Otherwise, peak 10 (*Rt* 10.02 min) showed the molecular ion at *m/z* 241.1 in the ESI-MS analysis and in the UV spectrum it displayed a maximum absorption at 220 nm. Compounds 6 and 9 showed the same fragment ion at *m/z* 317.0 (indicating myricetin in the structure). Therefore 6 and 9 were assigned as myricetin glucuronide and myricetin rutinoside, respectively. β-Sitosterol-hexoside was characterized for peak 11, relying on the data from ESI-MS which showed the main ion at *m/z* 575.1 and the fragment ion at *m/z* 413.7 [M-H]- after losing a hexose moiety.

Discussion

In this study, we have identified new phytochemicals present in *Rhus coriaria* fruits' extract for the first time. The phytochemical analysis was conducted using DAD spectra and MS acceptable data. Characteristic UV chromatographic profile sumac aqueous-alcoholic extract is shown in Fig. 3. On the other hand, in Table 1, a list of the major identified compounds is described, together with their UV maximum absorption and MS spectrum in the negative ESI ionization mode. The characterized compounds were numbered according to their elution order. Some of these compounds have been already identified but in the other parts of *Rhus coriaria*. For instance, quercitrin (4) was already described in the sumac leaves (Regazzoni et al., 2013), but firstly noted in the fruits. Myricetin rutinoside (9) was identified here in the sumac fruits for the first time. However, it was recently noticed in same botanical family: Anacardiaceae (Kirollos et al., 2018). The presence of: dihydroxy-methyl xanthone (10), β-sitosterol-hexoside (11), α-tocopherol (12), and linoleic acid (13) are being reported in *Rhus coriaria* for the first time in the plant fruits.

Importantly, we found that non-cytotoxic concentrations of *Rhus coriaria* modulated HeLa cells migration capacities via reducing the migrated area using wound healing assay. Interestingly, we showed that increased concentrations of RCE reduce HeLa cells' viability after 48 h of incubation. However, RCE showed no effect on cell viability at 24 h. It has been reported that RCE inhibited cell migration of MDA-MB-231, a breast cancer cell line in a concentration- and time-dependent manner using both wound healing and boyden chamber techniques (El Hasasna et al., 2016). Compared to our results, we have a similar inhibitory effect of RCE on cell migration uterus cervix cancer cells using wound healing assay (Fig. 2). In addition, our results strongly indicate that the RCE concentrations used are gradually inhibiting the migration capacity of HeLa cells (Fig. 2b). Finally, those results together confirm that RCE has an anti-migratory effect on at least two different cancer cell lines. It has been also previously shown that sumac extract is rich in hydrolysable tannins ((Abu-Reidah et al., 2015), (Farag et al., 2018)). Tannins were shown to have a potent migratory-reducing effect on vascular smooth muscle cells (VSMC) that help

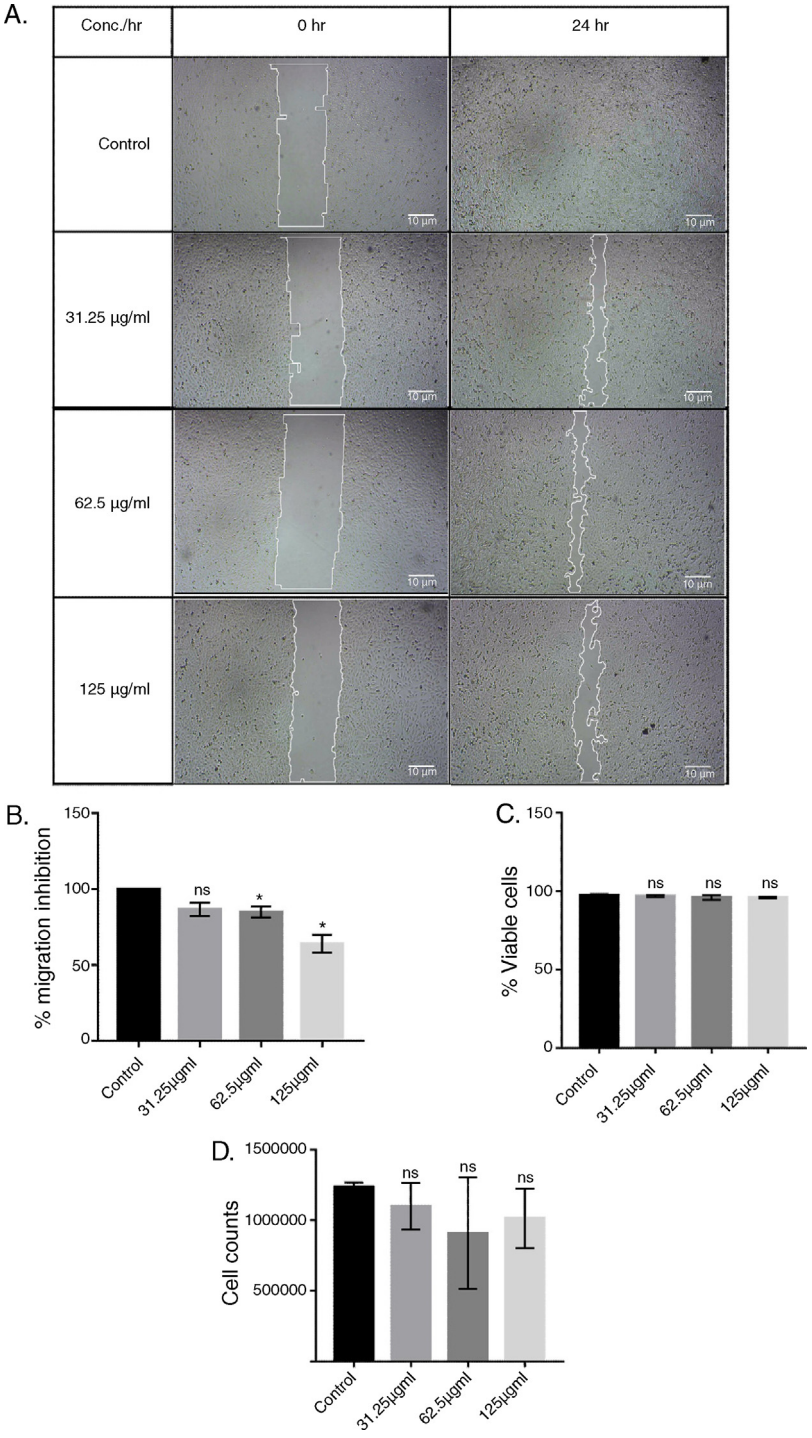

Fig. 2. *Rhus coriaria* inhibits the migration of uterus cervix cancer cells. (**A**) Visualization of HeLa cells at confluence incubated without or with 31.25, 62.5 and 125µg/ml concentrations of RCE during 24 h. The wound was photographed at 0 h and 24 h with an inverted microscope. Scale bar equals 10µm. conc. stands for concentration. (**B**) Quantification of area migrated by cells treated without or with 31.25, 62.5 and 125µg/ml of RCE at 24 h. Control stands for Non-treated cells. Values represent the percentage of migration inhibition compared to control. (**C**) Quantification of the number of viable HeLa cells (represented as a percentage) and (**D**) the total cell counts using trypan blue staining after incubating cells with 0, 31.25, 62.5 and 125µg/ml of RCE during 24 h. Data are reported in SEM; n =3. ns = non-significant. *($p < 0.05$) indicates statistical difference from the control at each time point (Paired t-test).

in the treatment of atherosclerosis (Zargham and Zargham, 2008). These results together suggest that sumac extract possesses an anti-migratory effect on different cell lines.

We showed for the first time that RCE has a growth inhibitory effect on uterus cervix cancer cells after 48 h of incubation while it had no effect at 24 h (Fig. 1A and B). Previous work proves a similar time- and concentration-dependent effect of RCE on three different cell lines of breast cancer: MDA-MB-231, T47D and MCF-7 (El Hasasna et al., 2015) and two colon cancer cell lines: HT-29 and Caco-2 (Athamneh et al., 2017). Interestingly, MDA-MB-231 and T47D were more sensitive to RCE compared to MCF-7 (El Hasasna et al., 2015). Taken together, those results point out that RCE has a growth inhibitory effect on various cancer cell lines and that the extent of RCE effect is cancer cell line-dependent.

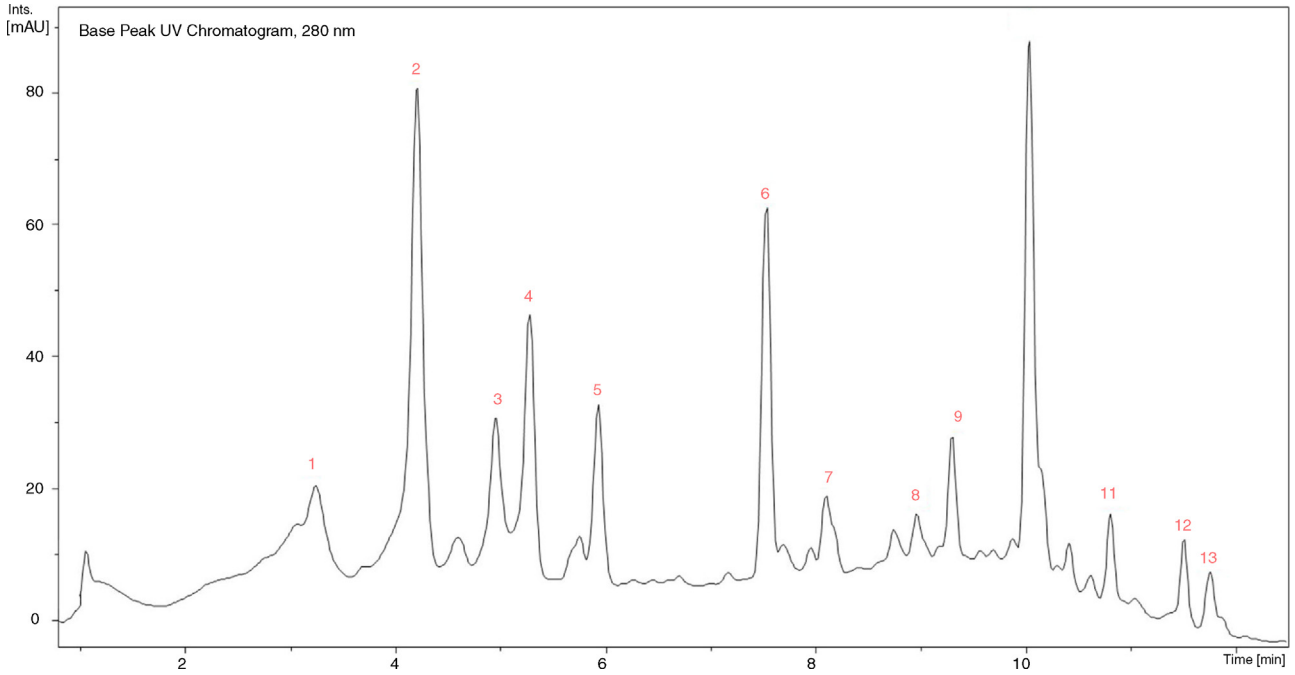

Fig. 3. UV spectrum detected (280 nm) of the major identified compounds in sumac. Ordered according to their elution time: (1) Gallicin, (2) Gallic acid, (3) Glucogallic acid, (4) Quercitrin, (5) Isohyperoside, (6) Myricetin glucuronide, (7) Tri-galloyl-hexoside, (8) Penta-galloyl-hexoside, (9) Myricetin rutinoside, (10) Dihydroxy-methyl xanthone, (11) β-Sitosterol-hexoside, (12) α-Tocopherol, (13) Linoleic acid.

Table 1
List of identified compounds in *Rhus coriaria* extract by using isotope distribution, exact mass, UV absorption.

Peak #	RT [min]	UV max	*m/z* [M-H]-*	MS^2 fragments	Identification
1	3.25	219, 240	183.1	169.0	Gallicin
2	4.20	220, 295	169.0	125.0	Gallic acid
3	4.95	270	331.1	169.0	Glucogallic acid
4	5.39	260, 300, 357	447.1	301.0	Quercitrin
5	5.91	257, 266sh, 358	463.2	301.0	Isohyperoside
6	7.73	261, 301sh, 353	493.1	317.0	Myricetinglucuronide
7	8.24	220, 265, 286sh	635.1	169.0	Tri-galloyl-hexoside
8	9.00	281	939.1	169.0	Penta-galloyl-hexoside
9	9.35	365	625.1	317.0	Myricetin rutinoside
10	10.02	220	241.1	195.2	Dihydroxy-methyl xanthone
11	10.85	204, 231	575.1	413.7	β-Sitosterol-hexoside
12	11.57	295	429.6	280	α-Tocopherol
13	11.86	215	279.1	280	Linoleic acid

Sh, shoulder; * = In the negative ion detection mode; RT, retention time.

Our data demonstrate that *R. coriaria* inhibits uterus cervix cancer cells migration capacity and possesses an inhibitory effect on their cell growth. Those results together suggest *R. coriaria* as a potent anti-migratory and anti-proliferative agent in cervical cancer treatment.

Authors contribution

SA developed ideas and concepts. SA designed cancer migration, viability experiments. SA, AM and TA performed cancer migration and viability experiments. IA designed, performed, and wrote extract analysis part. SA analyzed data and wrote the manuscript.

Ethical disclosures

Protection of human and animal subjects. The authors declarethat no experiments were performed on humans or animals forthis study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflicts of interest

The authors declare no conflicts of interest.

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