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Preparation of Docetaxel-Anionic Nanoparticles, Galantamine (Reminyl) Gluco-oligosaccharides, Pergolide Mesilate (Permax) Gluco-oligosaccharides, α-Tocopherol Glycoside, Daidzein Glycoside, and Genistein Glycoside and Their Application for Treatment of Skin Cancer, Dementia, Parkinson's Disease and Allergy

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A B S T R A C T

Nanoparticles composed of anionic phospholipid of 1,2- dipalmitoyl- sn-glycero-3-phosphorylglycerol (DPPG), "anionic bicelles", or Technol phosphatidylglycerol (Technol PG), "anionic liposomes", and docetaxel were prepared by mixing them in water with cholic acid-based surfactants of SC through a subsequent heating/cooling/ultrasonicating process. Ultrasonic fragmentation at low temperature of 4°C prepared small-sized anionic DPPG nanoparticles ("anionic bicelles") (particle size: 15 nm) and small-sized anionic Technol PG nanoparticles ("anionic liposomes") (particle size: 5 nm). Through transdermal addition (*in vitro*) to rat skin tissue, resveratrol-anionic DPPG nanoparticles, "anionic bicelles" (size: 15 nm), infiltrated into the epidermis layer penetrating stratum corneum (intercellular space: ca. 100 nm). Docetaxel-anionic DPPG nanoparticles or docetaxel-anionic Technol PG nanoparticles showed high anti-cancer activity toward skin cancer A431 cells, SCL I cells, and KB cells in *in vitro* anti-skin cancer test. Additionally, during the *in vivo* anti-skin cancer test (anti-skin tumor test) using mouse model of skin cancer, our study revealed that the numbers of papillomas of the mouse applied with docetaxel-anionic DPPG nanoparticles, "anionic bicelles", or docetaxel-anionic Technol PG nanoparticles, "anionic liposomes", to mouse skin decreased, although those of the mouse applied with docetaxel itself to mouse skin (control) increased. These findings showed that docetaxel-anionic DPPG nanoparticles or docetaxel-anionic Technol PG nanoparticles could permeate stratum corneum and be incorporated into the epidermis layer of mouse, treating skin cancer. On the other hand, glycosylation of galantamine (reminyl) and pergolide mesilate (permax) was achieved by using enzymes as biocatalysts. Galantamine (reminyl) gluco-oligosaccharides and pergolide mesilate (permax) gluco-oligosaccharides showed high neuroprotective activity with enhancement of survival of TH-positive neurons in rat primary midbrain cultures in *in vitro* anti-dementia test. Galantamine (reminyl) gluco-oligosaccharides and pergolide mesilate (permax) gluco-oligosaccharides showed high *in vitro* neuroprotective activity toward Aβ treated rat hippocampal neurons. Galantamine (reminyl) gluco-oligosaccharides and pergolide mesilate (permax) gluco-oligosaccharides, which were intraperitoneally or orally injected to a mouse, could penetrate the blood-brain barrier (BBB) of mouse brain and be incorporated into the mouse's brain tissue (*in vivo*). Galantamine (reminyl) gluco-oligosaccharides enhanced spatial learning of mice in *in vivo* Y-maze test and *in vivo* novel object recognition test. Pergolide mesilate (permax) gluco-oligosaccharides, which were intraperitoneally or orally injected to 6-OHDA-induced hemi-parkinsonism mice, decreased the number of ipsilateral turns of mice (*in vivo*) and activated contralateral hind limb steps (*in vivo*), indicating that pergolide mesilate (permax) gluco-oligosaccharides could treat the Parkinson's disease (PD) improving the parkinsonian signs. In addition, maltoside of α-tocopherol showed high anti-allergic activity toward wheat-allergen, gliadin and glutenin. Maltoside of daidzein and genistein also had strong anti-allergic activity against soybean-allergen, globulin.

Introduction

Docetaxel is a taxane diterpenoid, which shows cytotoxic activity against leukemia cells and inhibitory action against a variety of tumors. It has been recognized as one of the most effective and widely used drugs for the treatment of ovarian, breast, and lung cancers. Despite its effective pharmacological activities, docetaxel has shortcomings such as low solubility in water and toxicity to normal tissues. (Nicolaou *et al.,* 1996; Uchida *et al.,* 2020a; Uchida *et al.,* 2020b; Uchida *et al.,* 2022). Skin is frequently exposed to oxidative stress from ultraviolet radiation, which presents a risk for the development of cancers such as melanoma, squamous cell carcinoma, and basal cell carcinoma. Efficient transdermal delivery of paclitaxel would be useful to cure these serious skin cancers. Skin tissue is composed of stratum corneum, epidermis, and dermis. However, the 10- to 40-μm-thick stratum corneum, consisting of densely packed cells, provides a barrier to protect the underlying tissue from infection, dehydration, chemicals, and mechanical stress. It is difficult to applicate docetaxel for treatment of skin cancer, because it cannot penetrate the stratum corneum.

Phospholipids are biologically friendly molecules to living body because they are synthesized in the body. Therefore, they are highly biocompatible. However, frequently utilized neutral phospholipids tend to form large-sized vesicles, which sometimes result in insufficient skin penetration. Nanotechnology has attracted biomedical attention for the usefulness of nanoparticles containing docetaxel, its opportunities, and also future perspective. Thus, preparation of phospholipid-based paclitaxel small-sized nanoparticles is still a challenging problem.

The blood–brain barrier (BBB) exists in the brain as a selective semipermeable border that prevents solutes in the circulating blood from non-selectively crossing the extracellular fluid of the central nervous system where neurons exist (Daneman *et al.,* 2015). It comprises endothelial cells of the capillary wall, astrocyte end-feet ensheathing the capillary, and pericytes fixed firmly in the capillary basement membrane (Ballabh *et al.,* 2004). While the BBB system allows the passage of some small molecules by passive diffusion, it also permits the selective transport of various nutrients, ions, organic anions, and macromolecules, such as glucose and amino acids, crucial to neuronal functioning (Ballabh *et al.,* 2004).

Here, we report nanoparticles, “anionic bicelles”, of docetaxel stabilized with anionic phospholipids of DPPG. Also, their applications for treatment of skin cancer are reported. Additionally, we report the therapeutic effects of galantamine (reminyl) gluco-oligosaccharides, pergolide mesilate (permax) gluco-oligosaccharides, α-tocopherol glycosides, daidzein glycosides, and genistein glycosides for dementia and allergy.

Materials and Methods

General

Ultrasonication was performed by using a QSonica model ultrasonic homogenizer. The sizes of anionic nanoparticles were measured by using a Horiba model LA-960 laser diffraction particle size analyzer (SALD) or a Malvern model Zetasizer Nano ZSP zeta potential analyzer (DLS).

Preparation of DPPG-docetaxel, DPPG-fluorescent resveratrol, and Technol PG-docetaxel

Nanoparticles composed of anionic phospholipid of 1,2-dipalmitoyl- sn-glycero-3-phosphorylglycerol (DPPG), “anionic bicelles”, and docetaxel were prepared by mixing them in water with cholic acid-based surfactants of SC through a subsequent heating/cooling/ultrasonicating process. Docetaxel was mixed with DPPG powder (5.0 wt%) in water and sonicated for 2 minutes to disperse homogeneously, and then heated at 60°C for 15 minutes where the solution turned clear (Uchida *et al.,* 2020a). The resulting mixture (DPPG-paclitaxel) was kept stand at room temperature for 1 hour before use. DPPG-Oregon Green-labelled resveratrol (DPPG-fluorescent resveratrol) was prepared in the same method as DPPG-docetaxel except for using Oregon Green-labelled resveratrol instead of docetaxel. To prepare small-sized DPPG-Oregon Green-labelled docetaxel nanoparticles (DPPG-fluorescent resveratrol nanoparticles), the samples were ultrasonicated at 50 W for 3 hours with keeping the temperature at 4°C.

Nanoparticles composed of anionic phospholipid of Technol PG, “anionic liposomes”, and docetaxel were prepared by mixing them through a subsequent heating/cooling/ultrasonicating process. For the

preparation of Technol PG nanoparticle, "anionic liposomes", Technol PG (5 wt%) and docetaxel were mixed with cholic acid based surfactants of SC (0.5-5 wt%), CA (5 wt%), or CHAPSO (5 wt%) via a subsequent heating/cooling/ultrasonicating process in water and ultrasonicated at 4°C for 2 min.

In vitro transdermal delivery of resveratrol incorporated in "anionic bicelles" (anionic DPPG-fluorescent resveratrol nanoparticles) to epidermis layer

In vitro skin permeation tests were performed using a vertical Franz diffusion cell with an effective diffusion area of 0.95 cm^2 (Uchida *et al.,* 2022a; 2020b). Skin tissues were obtained from the abdominal hair of rats. The subcutaneous fat and other extraneous tissues of rat skin were trimmed and removed. A piece of excised skin (area 3.14 cm^2) was mounted on the Franz diffusion cell with the stratum corneum facing the donor compartment, in which DPPG-fluorescent resveratrol nanoparticles (DPPG-Oregon Green-labelled resveratrol nanoparticles) located. One circular SS Nikasol or SS HGA patch (area 0.785 cm^2) was applied to the stratum corneum side of the skin. The receptor compartment was filled with 3 mL of water and maintained at 32°C using a circulating water bath stirred with magnetic bars. For microscopic observations, skin tissue was embedded into OCT compound, frozen, and cryosectioned.

In vitro anti-cancer activity of docetaxel incorporated in "anionic bicelles" (anionic DPPG-docetaxel nanoparticles) or docetaxel incorporated in "anionic liposomes" (anionic Technol PG-docetaxel nanoparticles) against skin cancer A431 cells, SCL I cells, or KB cells

The sensitivity of A431 (SCL I, or KB) cells to docetaxel incorporated in DPPG (docetaxel incorporated in "anionic bicelles") or docetaxel incorporated in Technol PG (docetaxel incorporated in "anionic liposomes") was determined as follows. Cells were diluted with culture medium to the seeding density, suspended in 96-well tissue culture plates, preincubated at 37°C for 4 h, and then treated for 24 h with docetaxel incorporated in DPPG of Technol PG at various concentrations. After incubation, MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, yellow tetrazole) solution was added to each well and the plates were further incubated for 4 h. Absorbance at 570 nm was measured with a microplate reader model 450 (BIO-RAD).

In vivo anti-cancer (anti-tumor) activity of docetaxel incorporated in "anionic bicelles" (anionic DPPG-docetaxel nanoparticles) or docetaxel incorporated in "anionic liposomes" (anionic Technol PG-docetaxel nanoparticles) against skin cancer

All animals were housed individually in cages under specific pathogen-free conditions during the experiments. Age- and sex-matched mice were used for the experiments. 8-Week-old male C57BL mice were used. Skin tumors were induced by two-step application of DMBA and 12-*O*-tetradecanoylphorbol-13-acetate. First, 25 µg of DMBA in 100 µL of acetone was applied onto the shaved dorsal skin of the mice on day 7 (1 week). On day 0, topical application of 30 µg of 12-*O*-tetradecanoylphorbol-13-acetate in 100 µL of acetone was initiated and was continued for 20 weeks with a frequency of twice a week. Tumor development was monitored on a weekly basis and lesions greater than 2 mm in length were counted as positive. DPPG-docetaxel, docetaxel incorporated in "anionic bicelles" (0.2 g/kg), or Technol PG-docetaxel, docetaxel incorporated in "anionic bicelles" (0.2 g/kg), was applied to the rostral part of the back of mice five times a week. In the control experiment, docetaxel itself was administrated in the same method as described above.

In vitro neuroprotective effect of galantamine (reminyl) gluco-oligosaccharides or pergolide mesilate (permax) gluco-oligosaccharides on DA neurons in rat primary midbrain cultures

cDNA of glucosyltransferase from *P. americana* (*Pa*GT) was cloned into pQE30, and the resulting plasmids were transformed into *E.coli* M15 cells. The purified enzyme solution was dialyzed with 50 mM Tris-HCl (pH 7.2) containing 5 mM dithiothreitol, and stored at –80 °C. Glucosylation reactions were performed at 35 °C for 24 hours in 5 mL of 50 mM potassium phosphate buffer (pH 7.2) supplemented with galantamine (reminyl) (or pergolide mesilate (permax)), UDP-glucose, and enzyme *Pa*GT. The incubation was stopped by adding 1.5% trifluoroacetic acid; the reaction mixture was analyzed by HPLC. The resulting galantamine (reminyl) glucoside (or pergolide mesilate (permax) gluco-sides) was applied for further glycosylation by CGTase to give galantamine

(reminyl) gluco-oligosaccharides (or pergolide mesilate (permax) gluco-oligosaccharides).

In the presence of galantamine (reminyl) gluco-oligosaccharides (0.1, 1, 3, 10 μM) (or pergolide mesilate (permax) gluco-oligosaccharides), DA neurons were recognized with the polyclonal antibody against TH in rat primary midbrain cultures, and microglia were detected with the OX-42 antibody against CR3 receptor. Nine representative areas per well of the 96-well plate were counted under the microscope at 100 magnifications, for visual counting of TH-positive neurons. Counting was performed in a double-blind manner by two individuals, and conclusions were drawn only when the difference was within 5%.

In vitro neuroprotective effect of galantamine (reminyl) gluco-oligosaccharides or pergolide mesilate (permax) gluco-oligosaccharides on rat hippocampal neurons treated by Aβ

The effect of galantamine (reminyl) gluco-oligosaccharides (or pergolide mesilate (permax) gluco-oligosaccharides) on rat hippocampal neurons treated by Aβ was investigated. Aβ was administrated to the culture of rat hippocampal neurons at a dose of 2 μM. The living hippocampal neurons were treated with galantamine (reminyl) gluco-oligosaccharides (or pergolide mesilate (permax) gluco-oligosaccharides) at a single dose of 50 μM for 24 h in this study. The number of apoptotic cells was determined by double staining with Hoechst 33258 and propidium iodide.

In vivo BBB penetrating ability of galantamine (reminyl) gluco-oligosaccharides and pergolide mesilate (permax) gluco-oligosaccharides

The mice were orally injected once with galantamine (reminyl) glucoside, galantamine (reminyl) gluco-oligosaccharides, or galantamine (reminyl) (control) to test their BBB penetration abilities. Also, the BBB penetration abilities of pergolide mesilate (permax) gluco-oligosaccharides or pergolide mesilate (permax) (control) were examined.

One hour later, they were sacrificed by cervical dislocation, after which their brain tissue samples were quickly processed by rinsing with cold sodium phosphate buffer, then frozen and stored at −20°C. Subsequently, curcumin was extracted, after which its concentration in the brain sample was determined using HPLC. Tissue samples were first homogenized in sodium acetate buffer, and tissue homogenates were ultrasonicated in 0.1% Triton X-100.

Then, in a flask containing the homogenate mixture, α-glucosidase, β-glucosidase, and β-glucuronidase were added and incubated at 36°C for one hour. Organic compounds were finally extracted with ethyl acetate. After three extraction steps, ethyl acetate was evaporated. Samples were dissolved in methanol to give brain extracts sample. Finally, the extracted galantamine (reminyl) or pergolide mesilate (permax) was quantified by HPLC. The mice, which were intraperitoneally injected once with these compounds, were tested in the similar method with orally injected mice.

In vivo Y-maze test of galantamine (reminyl) gluco-oligosaccharides

A Y-maze with three arms was constructed with gray plastic, then it was equipped with a partition that isolates an arm. The experiment involved a 5-min trial 1, separated by a 40-min interval, followed by a 5-min trial 2. During the familiarization phase (trial 1), one arm (arm C: novel arm) of the Y-maze was closed with a partition. Then, while we placed one SAMP8 in one arm (arm A) of the two remaining arms (arms A and B) and the mouse allowed to explore the maze for five minutes, the partition was removed after a 40-min interval. Afterward, for five minutes, the mouse had free access to all three arms during the retrieval phase (trial 2). The time of the novel arm (arm C) exploration was only counted when the mouse put his hind feet in that arm. Then, the percentage of time spent in the novel arm C was calculated. Finally, galantamine (reminyl) was orally injected every day for five days to mouse (one injection per day) (the control), whereas galantamine (reminyl) gluco-oligosaccharides were orally injected every day for five days to mouse (one injection per day (200 mg/kg)) (the galantamine (remiry)-oligosaccharides-treated mouse). In case of intraperitoneal injection of the gluco-oligosaccharides to mice, injection and Y-maze test were demonstrated in the same method as described above.

In vivo novel object recognition test of galantamine (reminyl) gluco-oligosaccharides

The C57BL mouse, which was administered

galantamine (reminyl) gluco-oligosaccharides orally, was used in novel object recognition test. Galantamine itself was administrated to the mouse. The C57BL mouse was first introduced to two identical sample objects for 20 min for free exploration. The objects were fixed to the cage bottom and placed in the cage at one end near the corners, so that the mouse was able to move around the objects. The time was taken with a stopwatch when the mouse was exploring an object, placing the nose within 2 cm of either object. Climbing or biting the objects were not counted as exploration. A copy of the sample object and a new object were placed, 3-4 h later, at one end of the cage as earlier. The 5-min test started when the mouse approached either object for the first time. The exploration time of each object and the novelty preference index (NPI) in % (time exploring the novel object×100/ total exploration time) were counted. Mice that explored the objects in the test less than 3 s were discarded. The C57BL mouse, which was injected galantamine (reminyl) gluco-oligosaccharides or galantamine (reminyl) itself intraperitoneally, was tested in the same manner as described above.

In vivo rotation test of pergolide mesilate (permax) gluco-oligosaccharides

Drug-induced rotation was validated in the 6-OHDA-induced hemi-parkinsonism mice. Apomorphine-induced rotation test was performed to study the hypersensitivity of the lesioned striatum. Pergolide mesilate (permax) was orally injected every day for five days to mouse (one injection per day). On the other hand, pergolide mesilate (permax) gluco-oligosaccharides were orally injected every day for five days to mouse (one injection per day (10 mg/kg)) (the pergolide mesilate (permax)-oligosaccharides-treated mouse).

In case of intraperitoneal injection of the gluco-oligosaccharides to mice, injection and test were demonstrated in the same method as described above. Mice were placed in a clear plexiglass cylinder and ipsilateral and contralateral turns were relative to the site of the lesion. Full turns were counted in the ipsilateral and contralateral directions during a 20 min window of peak rotational response and data are expressed as net rotations. As for 6-OHDA-induced hemi-parkinsonism mice, to which sample was administrated orally or intraperitoneally, total number of spontaneous turns and contralateral turns was counted. Turns in the ipsilateral directions were indicated as % of total turns.

In vivo hind limb steps test of pergolide mesilate (permax) gluco-oligosaccharides

Drugs were injected to the 6-OHDA-induced hemi-parkinsonism mice orally or intraperitoneally. Pergolide mesilate (permax) was orally injected every day for five days to mouse (one injection per day). On the other hand, pergolide mesilate (permax) gluco-oligosaccharides were orally injected every day for five days to mouse (one injection per day (10 mg/kg)) (the pergolide mesilate (permax)-oligosaccharides-treated mouse). In case of intraperitoneal injection of the gluco-oligosaccharides to mice, injection and test were demonstrated in the same method as described above. Total count of spontaneous hind limb steps and that of contralateral steps were investigated in a 5-min test. Steps of the contralateral hind limb were indicated as % of total counts.

Anti-allergic activity of α-tocopherol glycoside, and daidzein glycoside and genistein glycoside against glutenin, gliadin, and globulin

Glucosylation reactions were performed at 35 °C for 24 hours in 5 mL of 50 mM potassium phosphate buffer (pH 7.2) supplemented with α-tocopherol, daidzein, or genistein, UDP-glucose, and enzyme *Pa*GT and CGTase. When using a biocatalyst, the mixture of acetonitrile and water was used for a solvent. The incubation was stopped by adding 1.5% trifluoroacetic acid; the reaction mixture was analyzed by HPLC. The yield of the glucoside products was calculated on the basis of the peak area from HPLC using the calibration curves prepared by the HPLC analyses of authentic glycosides. The glucosides were applied for further glycosylation by CGTase to give the corresponding maltosides.

Effects of compounds on O_2^- generation from rat neutrophils were examined as follows. Male Wistar rats, each weighing 250 g, were used. Under ether anesthesia, whole blood was collected from the carotid artery and diluted twice with Hanks' balanced salt solution (HBSS). Neutrophils were purified by Percoll density gradient centrifugation. O_2^- generation from rat neutrophils was measured by the cypridina luciferin analog-dependent chemiluminescence. Neutrophil suspensions were incubated for 3 min in HBSS containing cypridina luciferin analog and sample at 37°C in the dark. Five seconds later, fMLP was added into the assay mixture.

Cypridina luciferin analog-dependent chemiluminescence was monitored. The results are expressed in terms of the percentage reduction of the O_2^- generation from rat neutrophils at 5 min after the administration of fMLP by test compounds.

The effects of test compounds on compound 48/80-induced histamine release from rat peritoneal mast cells were examined as follows. Peritoneal mast cells were collected from the abdominal cavities of rats (Male Wistar rats, Nippon SLC) and purified to a level higher than 95%. The purified mast cells were suspended in a physiological buffered solution (PBS) containing NaCl, KCl, $CaCl_2$, glucose, and 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) to give approximately 10^4 mast cells/mL. Cell viability was always greater than 90% as judged by the trypan blue exclusion test. Mast cells were preincubated with the test compound for 15 min at 37°C, and subsequently exposed to compound 48/80. Histamine release was determined by a fluorometric assay, and was expressed as a percentage of total histamine.

The inhibitory action of test compounds on IgE antibody formation was examined as follows. Glutenin, gliadin, or 7S-globulin was used as the antigen, and $Al(OH)_3$ and pertussis toxin were used as the adjuvants. Sensitization was made by injection of a mixture of the antigen and the adjuvant into the paws of each rat (male). Paw edema was measured 24 h after injection and the treated rats were divided in groups with an equal average swelling volume. Each sample was dissolved in physiological saline containing 10% Nikkol and the solution containing test compound was injected daily into each rat for 11 d starting on the day of grouping. Hydrocortisone was used as the positive control. The amount of IgE was measured on the 15th day. The results were expressed as plasma IgE levels.

Results and Discussion

Preparation of anionic nanoparticles

Nanoparticles composed of anionic phospholipid of 1,2-dipalmitoyl- sn-glycero-3-phosphorylglycerol (DPPG), “anionic bicelles”, or Technol phosphatidylglycerol (Technol PG), “anionic liposomes”, and docetaxel were prepared by mixing them in water with cholic acid-based surfactants of SC through a subsequent heating/cooling/ultrasonicating process. When size-controlled nanoparticles composed of fluorescent Oregon Green-labelled resveratrol (standard compound) stabilized with DPPG (DPPG-fluorescent resveratrol) were added to rat skin tissue, fluorescent Oregon Green-labelled resveratrol molecules infiltrated into epidermis layer penetrating stratum corneum. DPPG molecules are expected to form kinetically stable nanoparticles maintaining the assemblies in physiological conditions because bilayer melting temperature of DPPG is higher than body temperature. When docetaxel was mixed with DPPG or Technol PG, a highly transparent dispersion was observed after the preparation. Tuning particle size is important for designing drug delivery systems. Especially, small-sized nanoparticles are preferable for the transdermal drug delivery system. For this purpose, we next tried to create small-sized DPPG-docetaxel nanoparticles. When we performed an ultrasonication treatment to the sample for 3 hours, the anionic DPPG-docetaxel nanoparticles were fractionated to 15 nm-sized nanoparticles as confirmed by a particle size distribution analysis. On the other hand, the anionic Technol PG-docetaxel nanoparticles were fractionated to 5 nm-sized nanoparticles.

In vitro transdermal delivery of resveratrol incorporated in “anionic bicelles” (anionic DPPG-fluorescent resveratrol nanoparticles) to epidermis layer

We investigated the skin permeability of anionic DPPG-resveratrol nanoparticles, “anionic bicelles”. For the evaluation of skin permeation capability, we prepared small-sized DPPG-resveratrol nanoparticles, “anionic bicelles”. The small-sized DPPG-fluorescent resveratrol nanoparticles were obtained in the same method as small-sized DPPG-resveratrol nanoparticles and were incubated with rat skin tissue placed on Franz diffusion cells. We prepared a histological section of the skin sample and performed fluorescent microscopic observation. Surprisingly, strong fluorescence was successfully observed due to the penetration of fluorescent paclitaxel molecules not only to the stratum corneum but also to the epidermis layer (Fig. 1B), as compared with the sample without DPPG-fluorescent resveratrol (Fig. 1A). Although the molecular structure of fluorescent resveratrol is not exactly as same as that of resveratrol, we expected that anionic DPPG-resveratrol nanoparticles, “anionic bicelles”, would have rather high skin permeation capability because the molecular structure of resveratrol is much smaller than that of fluorescent resveratrol.

In vitro anti-cancer activity of decetaxel incorporated in "anionic bicelles" (anionic DPPG-docetaxel nanoparticles) or in "anionic liposomes" (anionic Technol PG-docetaxel nanoparticles) against skin cancer A431 cells, SCL I cells, or KB cells

The cytotoxic activity of docetaxel incorporated in DPPG (or Technol PG) nanoparticles toward human A431 (or SCL I) cells was examined. A431 (or SCL I) cells were diluted, suspended in 96-well tissue culture plates, preincubated, and then treated with docetaxel incorporated in DPPG (or Technol PG) nanoparticles. After incubation, MTT solution was added to each well and the plates were further incubated. Absorbance at 570 nm was measured. The cytotoxic activity of docetaxel incorporated in DPPG nanoparticles (IC_{50}=35 μM for A431 cells, IC_{50}=30 μM for SCL I cells, IC_{50}=28 μM for KB cells) was higher than docetaxel itself (control) (IC_{50}=50 μM for A431 cells, IC_{50}=56 μM for SCL I cells, IC_{50}=40 μM for KB cells). Also the cytotoxic activity of docetaxel incorporated in Technol PG nanoparticles (IC_{50}=30 μM for A431 cells, IC_{50}=27 μM for SCL I cells, IC_{50}=25 μM for KB cells) was higher than docetaxel itself (control) (IC_{50}=50 μM for A431 cells, IC_{50}=56 μM for SCL I cells, IC_{50}=40 μM for KB cells).

In vivo anti-cancer (anti-tumor) activity of docetaxel incorporated in "anionic bicelles" (anionic DPPG-docetaxel nanoparticles) or in "anionic liposomes" (anionic Technol PG-docetaxel nanoparticles) against skin cancer

Mice started to develop papillomas later than 10 weeks after initial 12-*O*-tetradecanoylphorbol-13-acetate treatment. At 14 weeks after initial 12-*O*-tetradecanoylphorbol-13-acetate treatment, mice developed three papillomas and were used for the in vivo transdermal delivery experiment. The numbers of papillomas in anionic DPPG-docetaxel nanoparticles-treated mouse (docetaxel incorporated in "anionic bicelles"-treated mouse) were decreased, although those in docetaxel-treated mouse (control) were increased (Fig. 2). Also, the numbers of papillomas in anionic Technol PG-docetaxel nanoparticles-treated mouse (docetaxel incorporated in "anionic liposomes"-treated mouse) were decreased, although those in docetaxel-treated mouse (control) were increased (Fig. 3). These observations would explain that anionic docetaxel nanoparticles (docetaxel incorporated in "anionic bicelles" or "anionic liposomes") may contribute as chemo-preventive and anti-skin cancer agents. Total procedures have been done twice. And the two experiments showed almost the same results. The representative one is reported here.

In vitro neuroprotective effect of galantamine (reminyl) gluco-oligosaccharides or pergolide mesilate (permax) gluco-oligosaccharides on DA neurons in rat primary midbrain cultures

Incubation of glucosyltransferase from *Phytolacca americana* (*Pa*GT) with galantamine (reminyl) (or pergolide mesilate (permax)) gave glucoside as the sole product. Glucosylation of galantamine (reminyl) (or pergolide mesilate (permax)) with *Pa*GT described here is considerably efficient method to give galantamine (reminyl) glucoside (or pergolide mesilate (permax) glucoside) rather than chemical glucosylation. Biocatalytic glycosylation of galantamine (reminyl) glucoside (or pergolide mesilate (permax) glucoside) with CGTase was attempted to synthesize galantamine (reminyl) gluco-oligosaccharides (or pergolide mesilate (permax) gluco-oligosaccharides).

In the previous report, DA uptake assay was used as a functional index, and immuno-cytochemical staining for TH-positive (a marker for DA neurons) neurons was used for both morphometric analysis and cell count to assess the viability of DA neurons in rat primary midbrain neuron-glia cultures (Wu *et al.,* 2009). To cultures were added various concentrations of galantamine (reminyl) gluco-oligosaccharides (or pergolide mesilate (permax) gluco-oligosaccharides) (0.1-30 μM) or vehicle seven days after seeding. DA uptake assay was performed one week later. Galantamine (reminyl) gluco-oligosaccharides (or pergolide mesilate (permax) gluco-oligosaccharides) in the range of 3-10 μM enhanced the capacity of DA uptake in a dose-dependent manner (Wu *et al.,* 2009). That galantamine (reminyl) gluco-oligosaccharides (or pergolide mesilate (permax) gluco-oligosaccharides) increased (0.1, 1, 3, and 10 μM) the number of TH-positive neurons (DA neurons) in a dose-related manner (320, 340, 545, and 795) (310, 335, 550, and 798 for pergolide mesilate (permax) gluco-oligosaccharides) was found by cell count analysis. These results indicated that galantamine (reminyl) gluco-oligosaccharides (or pergolide mesilate (permax) gluco-oligosaccharides) enhanced survival of DA neurons in rat primary midbrain cultures. Galantamine (reminyl) gluco-

oligosaccharides (or pergolide mesilate (permax) gluco-oligosaccharides) showed high neuroprotection of DA neurons.

In vitro neuroprotective effect of galantamine (reminyl) gluco-oligosaccharides or pergolide mesilate (permax) gluco-oligosaccharides on rat hippocampal neurons treated by Aβ

The effect of galantamine (reminyl) gluco-oligosaccharides (or pergolide mesilate (permax) gluco-oligosaccharides) on the relative numbers of rat hippocampal neurons treated by Aβ was examined. The ratio of the relative numbers of cells with signs of apoptosis in the culture of rat hippocampal neurons with the addition of 2 μM Aβ and 50 μM galantamine (reminyl) gluco-oligosaccharides (or pergolide mesilate (permax) gluco-oligosaccharides) was 9% (15% for pergolide mesilate (permax) gluco-oligosaccharides). In case of addition of 2 μM Aβ to the culture of rat hippocampal neurons (control), the ratio of the numbers of apoptotic cells in rat hippocampal neurons was 28%. Galantamine (reminyl) gluco-oligosaccharides (or pergolide mesilate (permax) gluco-oligosaccharides) showed strong neuroprotective effects toward Aβ treated rat hippocampal neurons.

In vivo BBB penetrating ability of galantamine (reminyl) gluco-oligosaccharides and pergolide mesilate (permax) gluco-oligosaccharides

Galantamine (reminyl) gluco-oligosaccharides (or pergolide mesilate (permax) gluco-oligosaccharides) were orally injected to the mouse. Mouse brain tissue samples were processed as described in the Materials and Methods. After homogenizing tissue samples in sodium acetate buffer, the homogenates were ultrasonicated and treated by hydrolysis with glycosidases. Afterward, the products were extracted with ethyl acetate to prepare brain extracts. The obtained galantamine (reminyl) (or pergolide mesilate (permax)) was subsequently quantified by HPLC analysis of the brain extracts. Thus, galantamine (reminyl) (or pergolide mesilate (permax)) was detected. The HPLC analysis results of the brain extracts sample indicated that galantamine (reminyl) gluco-oligosaccharides (or pergolide mesilate (permax) gluco-oligosaccharides) were incorporated into the mouse brain tissue. Investigations also revealed that the brain extracts sample of the mouse treated with galantamine (reminyl) (control) (or pergolide mesilate (permax) (control)) contained no galantamine (reminyl) (or no pergolide mesilate (permax)), indicating that it hardly migrated to the mouse brain tissue. These results suggest that galantamine (reminyl) gluco-oligosaccharides (or pergolide mesilate (permax) gluco-oligosaccharides), which were orally injected into mouse, could penetrate the BBB migrating to the mouse brain. In case of intraperitoneal injection with galantamine (reminyl) gluco-oligosaccharides (or pergolide mesilate (permax) gluco-oligosaccharides), galantamine (reminyl) (or pergolide mesilate (permax)) was detected. The brain extracts sample of the mouse treated with galantamine (reminyl) (control) (or pergolide mesilate (permax) (control)) contained no galantamine (reminyl) (or no pergolide mesilate (permax)), suggesting that it hardly migrated to the mouse brain tissue. These investigations indicate that galantamine (reminyl) gluco-oligosaccharides (or pergolide mesilate (permax) gluco-oligosaccharides), which were intraperitoneally injected into mice, could smoothly penetrate the BBB in the mouse brain.

In vivo Y-maze test of galantamine (reminyl) gluco-oligosaccharides

In the Y-maze test using SAMP8, time spent in the novel arm (arm C) by galantamine (reminyl)-oral-administrated mouse, galantamine (reminyl) gluco-oligosaccharide-oral-administrated mouse, galantamine (reminyl)-intraperitoneal-administrated mouse, and galantamine (reminyl) gluco-oligosaccharide-intraperitoneal-administrated mouse were 118, 160, 107, and 155. The time spent in the novel arm of the Y-maze by the mouse intraperitoneally injected with galantamine (reminyl) gluco-oligosaccharides, was longer than that spent by the control mouse, into which galantamine (reminyl) itself was intraperitoneally injected (control). In case of Y-maze test using SAMP8 mouse orally injected with galantamine (reminyl) gluco-oligosaccharides, the time spent in the novel arm of the Y-maze was longer than that spent by the galantamine (reminyl)-treated mouse (control). The ratio of time spent in the novel arm by galantamine (reminyl) gluco-oligosaccharides-treated mouse was higher than that of the time spent by the control mouse. These results suggest that galantamine (reminyl) gluco-oligosaccharides penetrated the BBB and were incorporated into the brain tissue of SAMP8, enhancing spatial learning of the mouse.

Figure.1 Fluorescent nanoscopic observation of skin sample (A) without and (B) with DPPG-fluorescent resveratrol nanoparticles, "anionic bicelles".

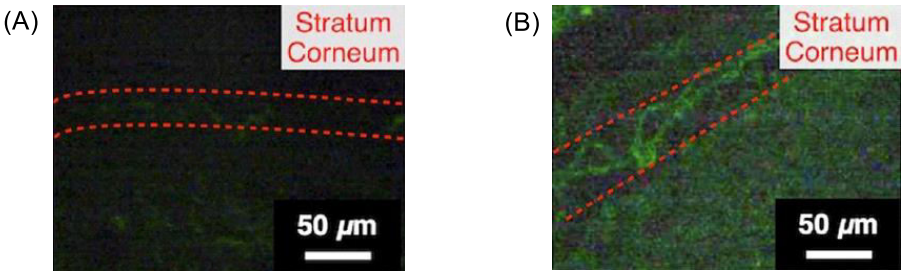


Figure.2 Numbers of papillomas of anionic DPPG-docetaxel nanoparticles (docetaxel incorporated in "anionic bicelles")-treated mouse (●) and docetaxel-treated mouse (control, □). ITT: initial 12-*O*-tetradecanoylphorbol-13-acetate treatment. Total procedures have been done twice. And the two experiments showed almost the same results. The representative one is reported here.

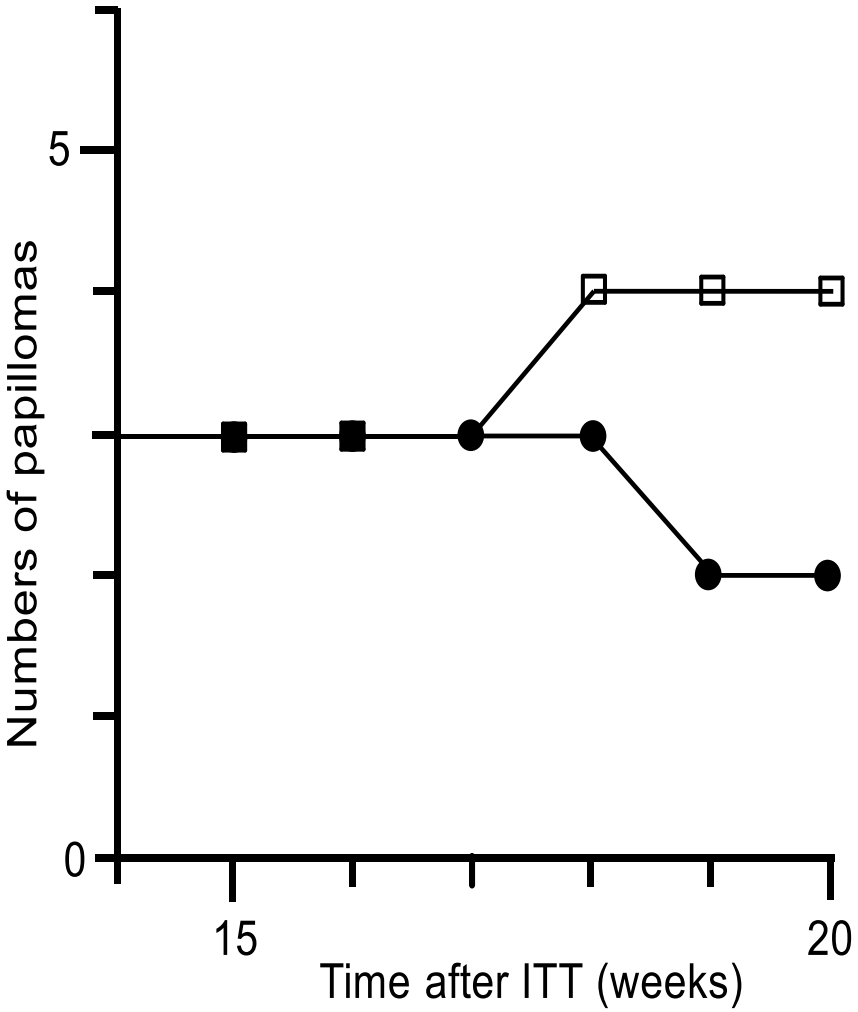
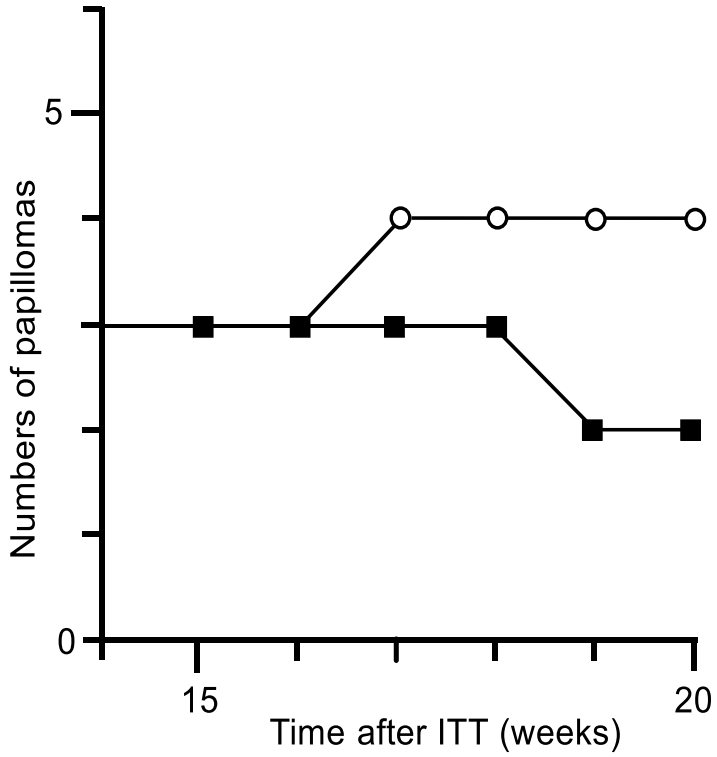


Figure.3 Numbers of papillomas of anionic Technol PG-docetaxel nanoparticles (docetaxel incorporated in "anionic liposomes")-treated mouse (■) and docetaxel-treated mouse (control, ○). ITT: initial 12-*O*-tetradecanoylphorbol-13-acetate treatment. Total procedures have been done twice. And the two experiments showed almost the same results. The representative one is reported here.



In vivo novel object recognition test of galantamine (reminyl) gluco-oligosaccharides

It is well known that the male mice use scent marking of their territory, including objects there. The substance for scent marking is long-lasting and insoluble to water. Nevertheless, many reports mentioned cleaning the samples objects with water before using them a second time in the test, but only a little reported using an extra copy of the sample object or cleaning the object with ethanol to remove the potential scent marks.

In all reports the time of exploration was the basis of the test readout. The novelty preference index (NPI) of the mouse, which was administered galantamine (reminyl) gluco-oligosaccharides orally, was 65%. On the other hand, the NPI of control mouse, that was administered galantamine (reminyl) itself orally, was 52%. Although the NPI of the mouse injected galantamine (reminyl) gluco-oligosaccharides intraperitoneally was 68%, the NPI of control mouse administered galantamine (reminyl) itself intraperitoneally was 53%. These results suggest that galantamine (reminyl) gluco-oligosaccharides enhanced spatial learning of the mouse in both cases of oral and intraperitoneal injection.

In vivo rotation test of pergolide mesilate (permax) gluco-oligosaccharides

The rotation test is a standard measurement of 6-OHDA lesion efficacy. After unilateral median forebrain bundle DA depletion, a postural bias towards the side of the lesion is exhibited. Ipsilateral rotation is driven by an imbalance of DA between hemispheres generating decreased movement on the side of lesion. Spontaneous rotations ipsilateral to the 6-OHDA-lesioned side of 6-OHDA-induced hemi-parkinsonism mice were represented as a percent of the total rotations. The group of PBS infusion was tested. Although its rate of ipsilateral turns resulted in 85%, that of intraperitoneally-pergolide mesilate (permax) gluco-oligosaccharides-treated 6-OHDA-induced hemi-

parkinsonism mice decreased to 48%.

The intraperitoneally injected pergolide mesilate (permax) experiment showed 76%. The rate of ipsilateral turns of orally-pergolide mesilate (permax) gluco-oligosaccharides-treated 6-OHDA-induced hemi-parkinsonism mice was 52%. The orally injected pergolide mesilate (permax) experiment showed 78%. This result indicated that pergolide mesilate (permax) gluco-oligosaccharides treated the Parkinson's disease (PD) improving the parkinsonian sign, i.e., drive of ipsilateral turns.

In vivo hind limb steps test of pergolide mesilate (permax) gluco-oligosaccharides

Total number of steps were counted with both ipsi-and contra-lateral hind limbs. Spontaneous contralateral hind limb steps were indicated as % of the total steps. The contralateral hind limb steps in the PBS infusion test resulted in 25%. On the other hand, the contralateral hind limb steps of intraperitoneally-pergolide mesilate (permax) gluco-oligosaccharides-treated 6-OHDA-induced hemi-parkinsonism mice increased to 50%. The intraperitoneally injected pergolide mesilate (permax) experiment showed 36%. The result of orally-pergolide mesilate (permax) gluco-oligosaccharides-treated 6-OHDA-induced hemi-parkinsonism mice was 46%. The orally injected pergolide mesilate (permax) experiment showed 30%. The findings obtained here indicated that pergolide mesilate (permax) gluco-oligosaccharides improved the movement of contralateral hind limb, showing that pergolide mesilate (permax) gluco-oligosaccharides treated the Parkinson's disease (PD) improving the parkinsonian sign, i.e., inhibition of contralateral hind limb steps.

Anti-allergic activity of α-tocopherol glycoside and daidzein glycoside and glycitein glycoside against glutenin, gliadin, and globulin

The inhibitory activities of α-tocopherol, daidzein, genistein α-tocopherol maltoside, daidzein maltoside, and genistein maltoside for O_2^- generation from rat neutrophils were 33%, 29%, 25%, 60%, 52%, and 50% inhibition, respectively. Compound 48/80-induced histamine release from rat peritoneal mast cells was inhibited by α-tocopherol maltoside with a %inhibition of 87%. Daidzein maltoside (65% inhibition) and genistein maltoside (60% inhibition) had strong inhibitory activity toward histamine release. The anti-allergic actions of the glycosides were caused by inhibition of histamine release with these compounds owing to their inhibitory aspects for O_2^- generation from rat neutrophils. The effects of α-tocopherol maltoside and α-tocopherol on immunoglobulin E (IgE) antibody formation were investigated by an in vivo bioassay using glutenin as an antigen. It was found that α-tocopherol maltoside showed stronger anti-allergic activity (IgE level 107) against glutenin than α-tocopherol (IgE level 192). When gliadin was used as the antigen, α-tocopherol maltoside showed stronger anti-allergic activity (IgE level 128) against gliadin than α-tocopherol (IgE level 192). On the other hand, IgE levels of daidzein maltoside and daidzein against 7S-globulin were 96 and 256. IgE levels of genistein maltoside and genistein against 7S-globulin were 107 and 213. Daidzein maltoside and genistein maltoside showed higher anti-allergic activity against 7S-globulin than the aglycons, daidzein and genistein, respectively; the suppression activity toward IgE formations of the glycosides was higher than that of the corresponding aglycons.

In conclusion, Nanoparticles incorporating docetaxel, stabilized by anionic phospholipids of DPPG, ("anionic bicelles": particle size=15 nm) or anionic phospholipids of Technol PG, ("anionic liposomes": particle size=5 nm), penetrated the skin barrier of stratum corneum (intercellular space: ca. 100 nm), when they were administered to rat skin tissue. Applications of docetaxel, which has no skin permeability, to anti-skin cancer materials have been still challenging because of its difficulty in transdermal delivery. The anionic DPPG-docetaxel nanoparticles, docetaxel incorporated in "anionic bicelles", or anionic Technol PG-docetaxel nanoparticles, docetaxel incorporated in "anionic liposomes", having skin permeability demonstrated in this study would be a new candidate as effective anti-skin cancer materials, which can infiltrate into epidermis layer decreasing numbers of papillomas.

Previous studies showed that anti-dementia drug such as memantine decreases β-amyloid levels via increase in secretion of amyloid precursor protein and activation of α-secretase (Niles *et al.,* 2006; Wu *et al.,* 2009; Shan *et al.,* 2014; Hashemi *et al.,* 2022). The hippocampus is a critical brain area for cognitive and memory functions, making it a sensitive area in Alzheimer's (Berardi *et al.,* 2009). Anti dementia drug has been shown to improve learning and memory in several pharmacological models of Alzheimer's disease. The investigation of the effects

of such drug on locomotor activity, social behavior, and spatial learning assessed in a transgenic mouse model of Alzheimer's disease indicated that it improves hippocampus-based spatial learning in a transgenic mouse model of Alzheimer's disease without producing nonspecific effects on locomotion/exploratory activity (Evers *et al.,* 2004; Minkeviciene *et al.,* 2004). These previous findings are consistent with our study, which suggests that galantamine (reminyl) gluco-oligosaccharides are chemopreventive agents that can protect neurons against the β-amyloid-induced disruption of spatial learning and memory in the hippocampus of SAMP8 and enhance spatial learning. Therefore, based on these results, our findings suggest that the gluco-oligosaccharide modification of neuroprotective chemicals, such as curcumin, enhances their crossing ability through the BBB in the brain, thus, proposing that the brain–drug-delivery technique of neuroprotective chemicals by glycoside (gluco-oligosaccharide) modification is useful for preparing new anti-dementia drugs.

In addition, this study indicates that pergolide mesilate (permax) gluco-oligosaccharides can treat the Parkinson's disease (PD) improving the parkinsonian signs, i.e., drive of ipsilateral turns and inhibition of contralateral hind limb steps.

It is known that glutenin, gliadin, and 7S-globulin are allergic compounds included in wheat flour and soybean, respectively. α-Tocopherol is a component in wheat and daidzein and genistein in soybean. α-Tocopherol maltoside, daidzein maltoside, and genistein maltoside would be potent anti-allergic food additives.

Our findings indicate that suppression of O_2^- generation caused inhibition of signal transduction of histamine release, resulting in reduction of IgE antibody formation.

Further studies on the anti-skin cancer property of anionic docetaxel nanoparticles, “anionic bicelles” or “anionic liposomes”, are now in progress in our laboratory.

Author Contributions

Hiroki Hamada: Investigation, formal analysis, writing—original draft. Yuya Fujitaka: Validation, methodology, writing—reviewing. Kohji Ishihara:—Formal analysis, writing—review and editing. Ryusuke Hosoda: Investigation, writing—reviewing. Kei Shimoda: Resources, investigation writing—reviewing. Yuya Kiriake: Validation, formal analysis, writing—reviewing. Daisuke Sato: Conceptualization, methodology, data curation, supervision, writing—reviewing the final version of the manuscript.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical Approval Not applicable.

Consent to Participate Not applicable.

Consent to Publish Not applicable.

Conflicting Interests

The authors declare no potential conflicts of interest regarding the research, authorship, and/or publication of this article.

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