scientific reports

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Editorial Board Highlights

Interviews

Read exclusive interviews with some of our board members and learn about their research and their experience as a *Scientific Reports* board member.

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Dr Carlo Cannistraci

Dr Carlo Cannistraci is a Theoretical Engineer and Editorial Board Member for Scientific Reports.

1. What is your current research focused on?

I am a Theoretical Engineer; my research interests include subjects at the interface between physics of complex systems, complex networks and machine intelligence, with particular interest in brain/bio-inspired computing for Big Data analysis, and applications in precision biomedicine and neuroscience.

2. What has been your biggest challenge and your greatest achievement in your career so far?

Mapping complex networks to their latent geometric spaces helps to investigate, understand and predict the structure and function of complex systems. My biggest challenge and greatest achievement was to recently propose a class of intelligent machines for efficient embedding of large real networks to the hyperbolic space, with future impact on big-network-data analysis in biology, medicine and social science. This work was proposed in the article: Machine learning meets complex networks via coalescent embedding in the hyperbolic space, A Muscoloni, JM Thomas, S Ciucci, G Bianconi, CV Cannistraci. Nature Communications 8 (1), 1, 2017.

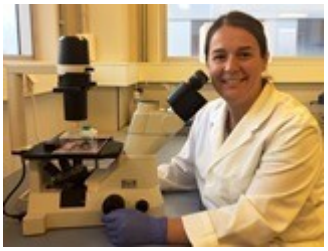
3. Why did you decide to become a board member?

I love to support other colleagues to improve their studies and to achieve high standards in their publications. This is the spirit of the review process: to offer feedback that improves science and its dissemination with a clear benefit for all of the scientific community.

4. What do you like most about being a board member for *Scientific Reports*?

Being an Editor for *Scientific Reports* for me is something more than being a normal Editor. The spirit of *Scientific Reports* is the spirit of 'freedom and equal opportunity' in science. I like the fact that *Scientific Reports* accept articles according to the only requirement that they should be technically correct. This ensures that the article selection is not biased by the opinion of a 'group of experts' that, in my opinion, can be also risky, because very innovative ideas that are against the mainstream in science might be rejected. I feel that being an editor for *Scientific Reports* allows me to sponsor the freedom to publish new scientific ideas which are technically correct but might not be recognised by a conservative establishment of experts.

Dr Joana Maria Ramis



Dr Joana Maria Ramis is a Miguel Servet Researcher at the Balearic Islands Health Research Institute (IdISBa), as well as Adjunct Lecturer at the University of the Balearic Islands, Spain.

1. What is your current research focused on?

My research is focused on the development of new therapies and biomaterials for restorative and regenerative medicine and its translation to clinical practice. My newest research line focus on the approach to cell-free regenerative medicine through the use of extracellular vesicles derived from different cells types.

2. What has been your biggest challenge and your greatest achievement in your career so far?

My biggest challenge and greatest achievement has been, and keeps being, reconciling family life and my research career.

3. Why did you decide to become a board member?

I considered the offer to become a board member as a great opportunity to deepen in the knowledge of the review process and to be an active part of it. Publication of our results is an important part of our work as researchers, and before becoming a board member for *Scientific Reports*, I have only acted as author or as reviewer, thus, to act as editorial board member was a role I was interested in exploring.

4. What do you like most about being a board member for *Scientific Reports*?

Being a board member for *Scientific Reports* allows me to be updated in the ongoing research in my areas of expertise and to really deepen in the technical aspects of the manuscripts I handle. On top of that, the most positive aspect of being a board member is how much I learn from the interaction with the reviewers and the authors and how manuscripts improve from it.

5. You are leading one of our Guest Edited Collections. What interested you about becoming a Guest Editor? What is your Collection focused on?

Yes, I am leading the Special Collection entitled "Extracellular vesicles in cell biology and medicine". The collection is focused on extracellular vesicles (EV), cell-derived membranous structures known as intercellular communicators exerting their function by exchanging their cargo. EV research is a burgeoning field with a high number of researchers from different disciplines working in this field. This Special Collection intents to deliver an up-to-date overview on some of the current developments in the field.
To increase my interaction with other researchers of the field is what most interested me about becoming a Guest Editor for the Collection.

6. Which is your favourite *Scientific Reports* paper?

It is really difficult to select one single paper! I will list you some:

Cells release subpopulations of exosomes with distinct molecular and biological properties.
Willms, E.; Johansson, H. J.; Mäger, I.; Lee, Y.; Blomberg, K. E. M.; Sadik, M.; Alaarg, A.; Smith, C. I. E.; Lehtiö, J.; El Andaloussi, S.; Wood, M. J. A.; Vader, P.

Size-Exclusion Chromatography-based isolation minimally alters Extracellular Vesicles' characteristics compared to precipitating agents.
Gámez-Valero, A.; Monguió-Tortajada, M.; Carreras-Planella, L.; Franquesa, M. la; Beyer, K.; Borràs, F. E.

Labeling Extracellular Vesicles for Nanoscale Flow Cytometry.
Morales-Kastresana, A.; Telford, B.; Musich, T. A.; McKinnon, K.; Clayborne, C.; Braig, Z.;

Rosner, A.; Demberg, T.; Watson, D. C.; Karpova, T. S.; Freeman, G. J.; DeKruyff, R. H.; Pavlakis, G. N.; Terabe, M.; Robert-Guroff, M.; Berzofsky, J. A.; Jones, J. C.

Bone marrow stromal/stem cell-derived extracellular vesicles regulate osteoblast activity and differentiation *in vitro* and promote bone regeneration *in vivo*.
Qin, Y.; Wang, L.; Gao, Z.; Chen, G.; Zhang, C.

Exosomes derived from human adipose mensenchymal stem cells accelerates cutaneous wound healing via optimizing the characteristics of fibroblasts.
Hu, L.; Wang, J.; Zhou, X.; Xiong, Z.; Zhao, J.; Yu, R.; Huang, F.; Zhang, H.; Chen, L.

Professor Xiaochun Li

Professor Xiaochun Li is the Raytheon Endowed Chair in Manufacturing Engineering at the Departments of Mechanical and Aerospace Engineering & Materials Science and Engineering at UCLA, USA. He is also a Guest Editor for the Nanotechnology enabled metallurgy Collection, which is currently welcoming submissions.

1. What has been your biggest challenge and your greatest achievement in your career so far?

The biggest challenge has been to bridge science and manufacturing for long term impact. The greatest achievement in my career so far is the discovery of the nano-particle self-dispersion and stabilisation mechanism in molten metals, which establishes a scientific foundation for nanotechnology enabled metallurgy.

2. Why did you decide to become a board member?

Being a board member is a good opportunity to provide a valuable service to the technical community.

3. What do you like most about being a board member for *Scientific Reports*?

My greatest pleasure is to help make the review process better, while having the opportunity to Guest Edit a special Collection.

4. You are leading one of our Guest Edited Collections. What interested you about becoming a Guest Editor? What is your Collection focused on?

I really like the opportunity to promote an important emerging field, Nanotechnology enabled metallurgy.

5. Which is your favourite *Scientific Reports* paper?

Core-shell nanoparticle arrays double the strength of steel

J.-B. Seol et al.

Professor Luciano Bosso

Professor Luciano Bosso is an Assistant Professor of Ecology at the University of Naples Federico II.

1. What is your current research focused on?

I am an ecologist expert in ecological modelling and GIS analysis. My main research interests include conservation biology, global change ecology, biogeography and invasion ecology and the application of species distribution models, niche analysis, risk mapping, conservation gap analysis, landscape ecology, spatial analysis, species connectivity and corridor network simulation.

2. What have been your biggest challenge and your greatest achievement in your career so far?

My biggest challenge is to make scientific research more accessible and comprehensible to a wider non-scientific audience. I am particularly devoted to increasing the ecological knowledge of non-experts. Several of my studies have informed policy makers about best management strategies of protected areas in Italy and Europe, and I consider this use of my research as my greatest achievement.

3. Why is *Scientific Reports* one of your favourite journals?

Scientific Reports is a multidisciplinary journal that publishes scientifically valid primary research from all areas of the natural sciences and beyond. I have always admired the quality and rigour of the scientific studies published in this prestigious journal.

4. Why did you decide to become a board member?

Considering the crucial role that editors have in scientific communication, I was looking for an opportunity where I can apply and especially improve/broaden my editorial skills as well as find professional and personal satisfaction both as an editor and a scientist. I am very grateful to *Scientific Reports* for this exciting opportunity.

5. What do you like most about being a board member for *Scientific Reports*?
I am particularly satisfied by the opportunity to enrich my background, collaborate in an international context, and contribute to the journal's high-quality publication standards.

6. Which is your favourite *Scientific Reports* paper?
It is really difficult to select a single paper! I was really impressed by these recent publications:

Integrating experimental and distribution data to predict future species patterns.
Kotta et al. (2019).

Risk of biodiversity collapse under climate change in the Afro-Arabian region.
Soultan et al. (2019).

Climate change-driven range losses among bumblebee species are poised to accelerate.
Sirois-Delisle and Kerr (2019).

Modeling the distributions of tegu lizards in native and potential invasive ranges.
Jarnevich et al. (2018).

Assessment of the effect of climate changes in the Late Pleistocene and Holocene on niche conservatism of an arvicolid specialist.
Castellanos-Frías et al. (2018).

Can Niche Modeling and Geometric Morphometrics Document Competitive Exclusion in a Pair of Subterranean Rodents (Genus Ctenomys) with Tiny Parapatric Distributions?
Kubiak et al. (2017).

Dr Ryoung Shin

Dr. Ryoung Shin is a Unit Leader at RIKEN Center for Sustainable Resource Science.

1. What is your current research focused on?

Potassium is one of major nutrients for plant growth, and lack of it in the soil environments has led to the increased use of fertilizers. However, such increased fertilizer usage does not necessarily result in a comparable production increase, and excess fertilizer run-off creates soil pollution. To address these issues, we elucidate the components of plant potassium sensing and deficiency signaling in plants using various approaches. In parallel, we are also using a marine red macroalgae *Pyropia yezoensis* in order to understand the mechanisms that enable seaweeds to survive in high salt conditions and to compare these mechanisms with those of the land plants in terms of Na^+/K^+ homeostasis. In addition, we identify and characterize chemicals which affect cesium and heavy metals uptake in plants to establish new methods of phytoremediation.

2. What has been your biggest challenge and your greatest achievement in your career so far?

My biggest challenge was starting the radiocesium phytoremediation research after the accident of Fukushima nuclear power plants following the big earthquake in Japan. It was a very challenging project (see here and here); and we are still actively working on this. One of my greatest achievements was that I have found and proven for the first time that Reactive Oxygen Species (ROS) is a key signal molecule of potassium-deficient signal transduction in plant roots.

3. Why did you decide to become a Board Member?

When I got the offer of being a Board Member, I recalled the time when we published two papers in *Scientific Reports*. It was an interesting and unique experience. *Scientific Reports* publishes articles from a variety of scientific backgrounds, including interdisciplinary research. Additionally, the editorial criteria for decision are different from other journals. I wanted to know more about this, and to be involved in *Scientific Reports* as a Board Member.

4. What do you like most about being a Board Member for *Scientific Reports*?

When I review the manuscript as a reviewer or handle the manuscripts as an editor, the manuscripts are usually from the specialised fields. At *Scientific Reports* I have really

enjoyed reading the interdisciplinary manuscripts. These are not easy because I should know many different fields to handle these manuscripts, but handling these papers gives me opportunity to learn about the various aspects and I can then see and appreciate the different angles.

5. Which is your favourite *Scientific Reports* paper?

One of my favourite *Scientific Reports* paper is "The antifungal plant defensin AtPDF2.3 from Arabidopsis thaliana blocks potassium channels" by Virens et al. Previously we found the link between Jasmonic acid signalling, including PDF genes and potassium/cesium signalling. This particular paper provides much more detailed insights into the relationship between PDFs and potassium channels. I really enjoyed reading this article. Recently, I have also had a pleasure of reading and handling a later published article "Effects of green seaweed extract on Arabidopsis early development suggest roles for hormone signalling in plant response to algal fertilisers" by Ghaderiardakani et al. This one was well balanced between the practical and basic scientific approaches using seaweeds. Ideas are attractive and the logical flow through was clear.

Dr. Alberto G. Fairén

Alberto G. Fairén is an Astrobiologist at the Centro de Astrobiología in Madrid, Spain, a Visiting Scientist at the Department of Astronomy, Cornell University, and Editorial Board Member for Scientific Reports.

1. What is your current research focused on?

My research is focused on helping to understand the nature of the early Martian environments using a variety of tools from different disciplines: geomorphology, sedimentology, paleohydrology, geochemistry, aqueous mineralogy, and environmental microbiology. My research interests in Martian science are broad, spanning from surface evolution and habitability, to robotic exploration and mission design and operation. My research activities include a combination of theoretical modeling, laboratory experiments, field work and spacecraft data analysis.

2. What has been your biggest challenge and your greatest achievement in your career so far?

The biggest challenge has been keeping focus while moving among institutions, countries and continents, during my postdoc years. As soon as I got my PhD in Spain, I moved to NASA Ames in California for my postdoc, and later I worked for the SETI Institute also in California, and Cornell University in New York. After 8 years in the US, I returned to my home country and joined Centro de Astrobiologia, where I have recently got tenure. The journey has been challenging, but it also had its rewards, because the interaction with a wide variety of colleagues with different expertise and backgrounds allowed me to significantly grow in my career, and to reach my greatest achievements in publications, grants and awards.

3. Why did you decide to become a board member?

One of the most important tasks for a scientist is communicating the results of your investigations to the community. We, as researchers, should help to disseminate the scientific outcomes of our work. These responsibilities are essential for authors and reviewers indeed, but also for editors contributing to achieve high standards in publication quality, ethics, and fairness.

4. What do you like most about being a board member for *Scientific Reports*?

Being a board member for *Scientific Reports* is a good opportunity to provide a valuable service to the Mars community, helping to improve the review process facilitating the interactions between authors and reviewers, while contributing to Scientific Reports's high-quality publication standards. In addition, the only requirement for the publication of a paper in *Scientific Reports* is that they must be "technically correct original contributions", and they don't need to have a subjective significance as perceived by the editors, which may very well be erroneous and most likely biased.

5. Which is your favourite *Scientific Reports* paper?

It is very difficult to single one paper out, but I was really impressed by "Perchlorates on Mars enhance the bacteriocidal effects of UV light", by Wadsworth and Cockell, because of its significant implications to our current search for life on Mars. In addition, I recently had the pleasure of handling "The fate of lipid biosignatures in a Mars-analogue sulfur stream", by Tan et al., "A record of igneous evolution in Elysium, a major martian volcanic

province", by Susko et al., and "Seasonal deposition and lifting of dust on Mars as observed by the Curiosity Rover", by Vicente-Retortillo et al., three very impressive papers dealing with different aspects of Mars exploration.

Professor Xuyang Lu

Professor Xuyang Lu is an Associate Professor at the Institute of Mountain Hazards and Environment at the Chinese Academy of Sciences. He is an Editorial Board Member for Scientific Reports *and is currently Guest Editing a Collection on Mountain surface processes and regulation, which is currently welcoming submissions until the end of September 2019.*

1. What is your current research focused on?

My academic research interests focus on the biogeochemical cycle and its microbial mechanism in mountain ecosystems. My recent work focuses on the effect of litter and soil organic matter chemistry on soil N transformation and its microbial function molecular ecological networks by comparing the China (Tibetan Plateau) and U.S. (Rocky Mountains) alpine ecosystems.

2. What has been your biggest challenge and your greatest achievement in your career so far?

I think my biggest challenge is the collection of soil and plant samples from alpine ecosystems, especially in the Tibetan Plateau. The plateau is considered to be the third "pole" of the world with an average elevation of 4 km above sea level. The natural environment is extremely harsh which characterized by high altitude, strong solar radiation, low temperatures and thin air. In this extreme environment, human survival is a challenge in itself, not to mention taking samples. In present, the greatest achievement in my career was that I discovered the influence extent and pattern of litter chemical composition and diversity on soil C, N transformation, which the related researches have

been published in Scientific Reports, Soil Biology & Biochemistry, Biology and Fertility of Soils.

3. Why did you decide to become a board member?

The first motivation is to learn how to become a qualified editor the academic journals. I feel a sense of accomplishment when a paper could reach the high-quality publication standard for *Scientific Reports* through the process of peer review and feedback with the authors.

4. What do you like most about being a board member for *Scientific Reports*?

I particularly like the criteria for publication in *Scientific Reports*, assessing an original article on the basis that they are technically sound and scientifically valid rather than innovation and importance, which provides the opportunity for more research works to be published. In addition, the Guest Edited Collection "Mountain surface processes and regulation", which I served as Guest Editor, supplies a high-quality publication platform for interdisciplinary studies of mountain surface processes and their responses to climate change and human activities. I sincerely appreciate *Scientific Reports* for this exciting opportunity.

5. Which is your favourite *Scientific Reports* paper?

Here I list three of my favourite *Scientific Reports* papers:
"A transnational perspective of global and regional ecosystem service flows from and to mountain regions", by Schirpke et al. (Article number: 6678, 2019).
"Altitudinal, temporal and trophic partitioning of flower-visitors in Alpine communities", by Lefebvre et al. (Article number: 4706, 2018).
"Planting increases the abundance and structure complexity of soil core functional genes relevant to carbon and nitrogen cycling", by Wang et al. (Article number: 14345, 2015).

Professor Matjaž Perc

Matjaž Perc is a Professor of Physics at the University of Maribor, Slovenia and Editorial Board Member for Scientific Reports.

1. What is your current research focused on?

Climate inaction, the overexploitation of natural resources, and a harrowing gap between rich and poor are some of the most pressing issues of our time. Since these problems can't even be fully understood, let alone solved, from a perspective of a single scientific discipline, the future prospects of our societies will be determined by interdisciplinary and cross disciplinary research that cuts across different domains of science. We are working hard to make physics, particularly methods of statistical physics, together with network and data science, a key piece of this puzzle. Social physics enables us to theoretically describe and understand collective social phenomena that are due to the interactions among individuals, groups, and governments. From the responsible use of antibiotics and vaccination, to the mitigation of social crisis and inequalities, we aim to develop better social systems and more efficient policies for a sustainable and better future by synergizing physics with the social sciences.

2. What has been your biggest challenge and your greatest achievement in your career so far?

One of my career goals has always been to stay at my home university, and ultimately to get a permanent position there. This has turned out to be the biggest challenge, as well as the greatest achievement of my career. Slovenia is a small country. Research funding is scarce, and vacant tenure track positions are basically nonexistent. A consistently impressive research output is needed, along with some luck and sponsorship from senior colleagues, to finally make it. For me it worked out great, but for many talented researchers in Slovenia this reality means being forced to go work abroad.

3. Why did you decide to become a board member?

Being a *Scientific Reports* board member is for me a way to give back to the research community, and to promote and support the research field in which I am active. *Scientific Reports* always stood for high quality, but also for freedom and opportunity, which together with the open access policy make it a perfect outlet for the most innovative research. Such research is often difficult to publish in journals that judge impact and novelty because it often challenges the mainstream in science.

4. What do you like most about being a board member for *Scientific Reports*?

The role puts you right in the center of research that is close to your heart. It feels a little bit like having reserved the finest seats in the theater of science, getting to learn about fascinating new discoveries before they are officially published. I also very much enjoy good cover letters, where authors usually explain the gist of their research in simpler terms, discussing its broader implications, and pondering about potential impact and directions for the future.

5. Which is your favourite *Scientific Reports* paper?

My favorite *Scientific Reports* paper remains to be the first paper I have handled after joining the editorial board, titled "Flavor network and the principles of food pairing" published in 2011. The paper generated a lot of attention at the time, both in the scientific community and in the media, and it stands precisely for the type of avant-garde research I was hoping Scientific Reports would encourage. In this particular case opening new avenues towards a systematic understanding of culinary practice across the world. From my own publications in *Scientific Reports* my favorite is "Self-organization of progress across the century of physics" published in 2013, for its collaboration with the American Physical Society and the resulting n-gram viewer for physics that is akin to Google's version for books.

Professor Yu Xin Zhang

Professor Yu Xin Zhang is a Professor at the College of Materials Science and Engineering, Chongqing University, China. He is also a Scientific Reports *Editorial Board Member and a Guest Editor for the Nanomaterials for energy and environmental applications Collection.*

1. What is your current research focused on?

My current research is mainly focused on the self-assembly of nanostructures with various morphologies, involving MnO_2 and diatomite-based nanocomposites, and their applications in energy storage and environmental fields.

2. What has been your biggest challenge and your greatest achievement in your career so far?

In my career, the biggest challenge was teaching Chinese students Technical Writing using English, which is my second language, while striving in materials science and engineering in Chongqing University. Indeed, it is highly important that teachers keep an eye on the learning process and abilities of students. Fortunately, my advisor, Prof. Hua Chun Zeng gave me a strict supervision in National University of Singapore, molding me to be a well-trained researcher and independent lecturer. In addition to being the biggest challenge in my career, teaching this course is also my greatest achievement. More than 5000 students who have had a direct or indirect contact with this course through me, have been able to improve their writing ability and some of them have even published their first article, which is a great motivation and confidence booster in scientific research, and nudged them to embark on the path of scientific research. I take pride in this.

3. Why did you decide to become a board member?

Becoming a board member is not only an endorsement of oneself, but also a means of staying abreast of the latest developments in scientific research, and actively communicating with international counterparts. Being a board member avails me these opportunities.

4. What do you like most about being a board member for *Scientific Reports*?

Scientific Reports is an outstanding journal, which publishes high quality articles with enormous future development prospects. I enjoy being able to make profound suggestions for the development of the journal, accepting excellent articles, and being able to learn substantially, even while doing something I love, and this is possible for me as a board member for *Scientific reports*. I like the rate at which the journal is developing in all aspects, it gets better and better.

Professor Z. Altounian

Professor Z. Altounian is a Professor in the Physics Department at McGill University, Montreal, Canada and Editorial Board Member for Scientific Reports.

1. What is your current research focused on?

My current research is mainly focused on studies of magnetic properties of materials.

2. What has been your biggest challenge and your greatest achievement in your career so far?

Challenges always occur if one enters a new field of study. My first challenge started in the winter of 1979 when I got interested in metallic glasses. This was also my greatest achievement as our group at McGill University became a world famous centre in this field. I still contribute to this field, but mainly through editorial/reviewing responsibilities for journals and conferences. My second, and more recent challenge occurred when I got involved in the studies of magnetic properties of hard magnetic materials. It is worth to mention that there was a very close relationship between my two challenges as we used the technique of rapid solidification, which is commonly used to prepare metallic glasses, to manufacture rare-earth based magnets. This also brought us to worldwide recognition in this particular field.

3. Why did you decide to become a board member?

One of the aspects that drew me to become an EBM was the problems that I had encountered while reviewing manuscripts. Mostly the poor quality of some of the reviewers which in many cases did not agree on the evaluation of the same submission. In those cases, I was asked to make the final decision. As an EBM, I hoped to improve the reviewing protocol.

4. What do you like most about being a board member for *Scientific Reports*?

Prior to becoming an EBM, I was a very active reviewer for a number of publications in the above-mentioned fields. When *Scientific Reports* invited me to join their editorial team, I accepted the offer as I had always enjoyed reviewing journal submissions.

5. Which is your favourite *Scientific Reports paper*?

My favorite paper is SR 7, 646 (2017), "The magnetic and crystal structure of MnxGa (1.15 ≤ x ≤ 1.8) Alloys". This was our first publication in *Scientific Reports* as well as the first introduction to this fascinating material. Even-though we have been studying magnetic materials for more than two decades, this publication finally put us on the world map in this field.

Dr Lena Ciric

Lena Ciric is Associate Professor in Environmental Engineering at the Department of Civil, Environmental and Geomatic Engineering of University College London, UK. She is also a Scientific Reports *Editorial Board Member and a Guest Editor for the Microbes in the built environment Collection.*

1. What is your current research focused on?

I am an environmental microbiologist. The environment I study is the built environment. My group works on two themes. The first is how microbes behave in the built environment. We have been studying the microbial communities and the horizontal gene transfer of antibiotic resistance genes in slow sand filtration, a commonly used drinking water treatment process. The other theme we study is how we can use engineering solutions to reduce the numbers of harmful microbes in our environment. We have been manufacturing water and air filters with antimicrobial nanoparticles embedded in them which are capable of killing bacterial and viral pathogens.

2. What has been your biggest challenge and your greatest achievement in your career so far?

I would say being an academic is both the biggest challenge and the biggest achievement of my career. The job can be extremely challenging as there are huge demands on your time. There is frequent failure – rejected grant applications, experiments that don't work, papers that are difficult to publish. But these challenges are also what motivates me. The job of an academic is so varied. We have the freedom to pursue our research ideas, we get to write, we get to read, collaborate, travel, interact with young people through teaching and speak to the public about our work. All of these experiences are extremely rewarding.

3. Why did you decide to become a board member?

I am naturally nosey, so I was curious to see what research is going on out there. As an editorial member you have the opportunity to reach out to experts in the field to help you scrutinise manuscripts and help the authors improve their work.

4. What do you like most about being a board member for *Scientific Reports*?

Scientific Reports has a novel approach. Instead of looking for the next big thing, it is happy to publish any scientific work that is technically sound. This is extremely useful to the scientific community. It means that we have a less biased view of the research going on around the globe.

5. Which is your favourite *Scientific Reports* paper?

Patterns in the skin microbiota differ in children and teenagers between rural and urban environments

I am fascinated by how the microbes that live on and in our bodies shape us physically and, some studies say, psychologically. I think it's wonderful to know that our body as an ecosystem rather than just one organism.

Professor Kah-Wee Ang

Prof. Kah-Wee Ang is Associate Professor in the Department of Electrical and Computer Engineering at the National University of Singapore.

1. What is your current research focused on?

I am an experimentalist and my current research focuses on the development of both electronic and photonic devices based on two-dimensional (2D) materials, which include field-effect transistor and integrated circuit, non-volatile memory, artificial intelligence synapse for neuro-inspired computing, as well as electro-optic modulator and photodetector for mid-infrared sensing applications.

2. What has been your biggest challenge and your greatest achievement in your career so far?

I started off my research career exploring the use of beneficial strain effect to modify the carrier transport properties in the conduction channel for enhancing the mobility and drive current performance of nanoscale field-effect transistors (FETs). Specifically, I pioneered a novel concept in employing lattice-mismatched stressor made of silicon-carbon (Si:C) alloy in the source and drain regions of metal-oxide-semiconductor FETs,

which was widely evaluated by major semiconductor foundries worldwide. The technology was eventually adopted in high volume manufacturing, which gave me a sense of satisfaction and achievement.

Since five years ago, I started investigating two-dimensional materials for electronic and photonic device applications. As a new comer to this emerging field, many technical challenges were encountered which spanned across material synthesis, device fabrication to large-scale circuit and system integration. Through conscientious efforts, several advancements have been made in addressing module and process integration issues on flexible substrates, which allow energy-efficient logic gates, memories and sensors to be realized. Going forward, we aim to demonstrate a transformative 3D monolithic system via van der Waals integration of new logic and memory devices built on atomic-scale 2D materials, which can deliver a remarkable improvement in computational energy efficiency over traditional system architecture.

3. Why did you decide to become a board member?

Today the research landscape is dynamically changing where new exciting fields are emerging rapidly. Being an editorial board member allows me to not just keep up with the latest progress made in my field, but also gives me the opportunity to keep abreast of the new development that takes place across multidisciplinary fields. Getting to know the experts often helps me in assigning appropriate reviewers to assess the submitted manuscripts, and make constructive recommendations to improve the quality.

4. What do you like most about being a board member for *Scientific Reports*?

Scientific Reports' approach in publishing technically sound work and let the wider scientific community determine the impact of the work is well received by like-minded researchers including myself. This allows board member to avoid making subjective decisions on rejecting manuscripts which are perceived with little immediate interests but may grow in importance over time.

Dr Pedro Oliveira

Dr Pedro Oliveira is a Senior Scientist at Mount Sinai School of Medicine, USA.

1. What is your current research focused on?

My current interests are on identifying emerging challenges in the fast-evolving research field of epigenomics, and on better understanding the epigenetic regulation mechanisms affecting gene expression and cellular processes in Bacteria. On a broader perspective, I seek to elucidate key biological insights that can translate into more accurate disease diagnosis and more effective treatment for certain bacterial pathogens.

2. What has been your biggest challenge and your greatest achievement in your career so far?

My biggest challenge has been in embracing some of the downsides of a career in academia, such as frequent failure and rejection, and being able to transform such missteps and roadblocks into an opportunity for something new. My greatest achievement as a researcher has been in help propelling the field of bacterial epigenomics. Such field has been attracting increased attention for its exciting potential to transform our knowledge on gene regulation, virulence, and adaptation. As an example, we recently performed the first large-scale comprehensive epigenomic analysis in *Clostridioides difficile*, known to be one of the leading causes of nosocomial antibiotic-associated disease in the developed world. We found evidence for epigenetic regulation associated with sporulation (a key step in *C. difficile* disease transmission), cell length, biofilm formation, and host colonization. For more information, please check: Oliveira *et al*. Epigenomic characterization of *Clostridioides difficile* finds a conserved DNA methyltransferase that mediates sporulation and pathogenesis. *Nature Microbiology*.

3. Why did you decide to become a board member?

Essentially, it was a great opportunity to become an active part of the decision-making process, while simultaneously helping the authors to achieve a higher quality standard in their publications. I am very thankful to *Scientific Reports* for this opportunity.

4. What do you like most about being a board member for *Scientific Reports*?

I particularly enjoy contributing to a journal that seeks high quality standards in its publications, focusing primarily on research robustness and validity, and less on subjective

editorial decisions. In this sense, *Scientific Reports* makes a distinctive contribution when compared with other journals. Furthermore, being a Board Member has given me the opportunity to learn and keep myself up to date on the latest research in my areas of expertise, while simultaneously delving into the multiple aspects of the manuscripts I handle.

5. Which is your favourite *Scientific Reports* paper?

It's difficult to highlight one single paper. I particularly enjoyed reading a recent publication describing a portable epigenetic switch for bistable gene expression in bacteria based on the *opvAB* operon of *Salmonella enterica*.

Dr Ciria C. Hernandez

Dr. Ciria C. Hernandez is an Assistant Research Scientist at the Life Sciences Institute, University of Michigan, USA. She is an Editorial Board Member for Scientific Reports *and currently Guest Editing a Collection on Channelopathies, which is welcoming submissions on a rolling basis.*

1. What is your current research focused on?

The focus of my research has always been to understand the fine regulation of ion channels in physiological and pathological states. Thus, I have been fully immersed in the study of the molecular determinants of the interaction of small peptides, G-protein coupled receptors (GPCRs) and both voltage and ligand gated ion channels, whether they are defective or not, by carrying mutations in their structure that prevents them from normal function. Most recently, I have been working on the elucidation of the structural determinants of the interaction of GPCRs that mediate a variety of physiological processes critical for energy homeostasis, and potassium channels known to be involved in a novel G protein independent signaling pathway in a brain region that controls hunger. We are tackling the idea of bias agonism as a therapeutic approach to overcome defective GPCR-channel coupling in conditions where the rheostats of energy homeostasis are defective.

2. What has been your biggest challenge and your greatest achievement in your career so far?

My biggest challenge and my greatest achievement merge at the same point. Be competitive and remain relevant in the face of the unstoppable and continuing flow of new technologies. While this is true for any electrophysiologist, as a woman, coming from a developing country, there is a bigger challenge considering the general perception that you have about making a career in science, and still being able to respond to the demands of academia. Scientifically perhaps the biggest challenge is to understand how to fit every discovery I make, however small and trivial it may seem, in the greater puzzle we are helping to complete. We merge these pieces when we write the discoveries we made in the scientific articles, when we guide the youngest, and when we collaborate with peers from different fields. This is at the essence of science and my career has fundamentally been learning how to "put the pieces together" ever since I started my career. Although I have managed to break many barriers and be in a privileged position, I have not stopped learning and growing scientifically, and honestly, I will never stop doing it. This is my greatest achievement as a scientist.

3. Why did you decide to become a board member?

Being part of the editorial board of *Scientific Reports* implies transforming and transferring knowledge beyond critical thinking. We have to be not only the best scientists, but the best communicators. Being a board member of *Scientific Reports* made me realize how to communicate the passion that we scientists have for discovering the smallest molecular interactions and chats between receptors, channels, proteins, and bring them to public light. My passive voice became a strong megaphone through the publications of all the authors who contribute to making the best science in the world. By realizing that through my contribution, I am shaping the science that is read and at the same time inspiring me to be the best scientific communicator.

4. What do you like most about being a board member for *Scientific Reports*?

Each manuscript submitted is a challenge of new knowledge and unexpected creativity. The diversity of topics within our area of expertise is tremendous. It shows the high quality of science that is translated from the bench and witnessing that is unmatched and novel in many ways. At the same time, we are the role models for the challenges imposed in the current era, where the disparity of world economies challenges science in the quest for new discoveries.

5. Which is your favourite *Scientific Reports* paper?

Without reservations I invite you to read part of my work published in 2017 describing the defects on GABAA receptor function caused by deleterious mutations in cases with catastrophic epileptic encephalopathies, and many other fascinating studies on the special Collection dedicated to Channelopathies.

Professor Claudia RC Moreno

Prof. Claudia RC Moreno is Head of Department at the School of Public Health, University of Sao Paulo, Brazil and is currently an Editorial Board Member for Scientific Reports.

1. What is your current research focused on?

The process of urbanization, as well as the use of electricity and its technology, has changed the way of life of society. The possibility of extending the waking period through the use of electric light changed working, sleeping, eating and leisure hours. I have been studying communities with and without access to electricity with the focus on lifestyle, working hours, sleep and eating behavior.

2. What has been your biggest challenge and your greatest achievement in your career so far?

The biggest challenge was to run a study in the Amazon forest, collecting data from rubber tappers and having to freeze saliva samples to send to Sao Paulo, many kilometers away. It is hard to say my greatest achievement, but there are two things that I would like to highlight, first, the success of my former PhD students, and second, my participation on a monograph at the IARC-WHO regarding night shift work and cancer.

3. Why did you decide to become a board member?

Scientific Reports is a quite interesting journal due to its policy to evaluate papers technically sound. Moreover, I think it is important to have board members from Latin America.

4. What do you like most about being a board member for *Scientific Reports?*

It is a very dynamic task, and help me to keep myself updated.

5. Which is your favourite *Scientific Reports* paper?

My favorite paper is from an international group of researchers with focus on sleep in a rural cohort study. Timing and quality of sleep in a rural Brazilian family-based cohort, the Baependi Heart Study

Professor Jimin Zhao

Professor Jimin Zhao currently works in the Institute of Physics at the Chinese Academy of Sciences (CAS), Beijing, and is an Editorial Board Member for Scientific Reports.

1. What is your current research focused on?

I currently work on ultrafast spectroscopy and ultrafast dynamics of correlated quantum materials.

2. What has been your biggest challenge and your greatest achievement in your career so far?

The biggest challenge in my career so far is to convince my colleagues outside of my specific area that what I have done is reliable. This is especially challenging when our manuscripts are being reviewed, whereby very simple questions and unreasonable doubts come in by renowned yet non-experts in the field. I have investigated the ultrafast dynamics in novel iron-based superconductors and Weyl semimetals, I have also achieved SSPM and all-optical switching in 2D materials. I am currently a full professor at IOP-CAS and I am also an OSA senior member.

3. Why did you decide to become a board member?

Being a board member will open a new venue that I can do service to the community. Optical spectroscopy of solids is not a big area, and I feel my colleagues may need me to objectively judge on works using sophisticated optical means to investigate condensed matter physics.

4. What do you like most about being a board member for *Scientific Reports*?

Handling works in slightly different areas is interesting. My own experience can make a decisive contribution, whereas I can also enlarge my horizon through the handling process.

5. Which is your favourite *Scientific Reports* paper?

There are many. I remember one very good theoretical paper called Anomalous isotope effect in iron-based superconductors. I should say another one is one of our works. Out of the 6 papers I have published in *Scientific Reports*, our work Coherent Generation of Photo-Thermo-Acoustic Wave from Graphene Sheets, *Scientific Reports* 5, 10582 (2015) is my most favorite one. This work is highlighted in Chinese magazine *Physics*. It is a phenomenon parallel to photoluminescence. After we publish, I got to know that Alexander Graham Bell also worked on this topic and had filed a patent, and he thought it was one of his greatest achievements. Dr. Bell was a great scientist, and knowing this is wonderful. Nonetheless, before us, there are no serious and solid experimental proofs that cleanly removed other very possible mechanisms. We have also achieved remote coherent control of acoustic sound.

Professor Amy Peterson

Professor Amy Peterson is Associate Professor of Plastics Engineering at the University of Massachusetts Lowell, USA and is an Editorial Board Member for Scientific Reports.

1. What is your current research focused on?

My current research is focused on multilayered polymer structures – these range from nanometer-scale polyelectrolyte multilayers for cell culture coatings, to packaging materials, to additively manufactured structures. As engineers, we use experimental and computational approaches to probe what happens at interfaces and surfaces in these systems, and use this knowledge to guide creation/selection of improved materials and processes.

2. What has been your biggest challenge and your greatest achievement in your career so far?

This past week has been the most intensely challenging of my career. It ended with shutting down our laboratory on Saturday, but the lead up to that final act included figuring out what critical experiments were needed for each group member, attempting to get them approved as access to labs became increasingly restricted by my university, trying to keep my group up to date on the status of their possible experimental work, and doing all of this in a dynamic situation via phone, email, and videoconference. I feel fortunate because we have substantial modelling efforts as well as experimental ones, so we'll be able to continue to make progress on our research. However, my group meets weekly in person for group as well as one-on-one meetings, and I am concerned about how we will all fare being isolated in our homes.

My proudest moments are when I see my students succeed, whether it's at graduate, a defense, an award, a paper, or a presentation.

3. Why did you decide to become a board member?

Being a board member gives me an opportunity to give back to my broader research community and learn at the same time.

4. What do you like most about being a board member for *Scientific Reports*?

The same reasons I became a board member.

5. Which is your favourite *Scientific Reports* paper?

Clogging transition of many-particle systems flowing through bottlenecks – I like how it makes connections between systems of large numbers of people, flocks of sheep, and colloidal suspensions.

Dr Jagadeesh Bayry

Dr. Jagadeesh Bayry is Director of Research at the Institut National de la Santé et de la Recherche Médicale, Centre de Recherche des Cordeliers, Paris, France and is an Editorial Board Member for Scientific Reports.

1. What is your current research focused on?

Our current research is focused on the mechanisms by which regulatory T cells and circulating immunoglobulins maintain immune homeostasis and deciphering the host-pathogen interaction.

2. What has been your biggest challenge and your greatest achievement in your career so far?

Though we identify mechanisms of various biological processes in the experimental systems, translation of these results to humans is always challenging. For that matter, I am proud of many achievements of my team and myself that include:

- Demonstration that regulatory T cells in contrast to central dogma on them as universal immunosuppressor cells, induce activation of human basophils (Science Immunology 2018. doi: 10.1126/sciimmunol.aan0829)
- Demonstration that surface hydrophobin protein layer prevents immune recognition of airborne fungal spores (Nature 2009. doi: 10.1038/nature08264)
- Demonstration of molecular mechanisms by which therapeutic normal immunoglobulin G expands regulatory T cells (Blood 2013. doi: 10.1182/blood-2012-11-468264) and induces induction of IL-4 in human basophils (J Allergy Clin Immunology 2019. doi: 10.1016/j.jaci.2018.10.064)
- Identification and validation of small molecule antagonists to CCR4 that function as molecular adjuvants in vaccination by transiently inhibiting the migration of regulatory T cells (Proc Natl Acad Sci USA 2008. doi: 10.1073/pnas.0803453105)
- Activation signal-dependent regulation of human dendritic cell functions by B lymphocytes (Nature Communications 2014. doi: 10.1038/ncomms5092)

3. Why did you decide to become a board member?

For me, it is a service to scientific community. Though it demands my time, I feel that it is a highly privileged position. In addition, it gives visibility to myself, team and institute.

4. What do you like most about being a board member for *Scientific Reports*?

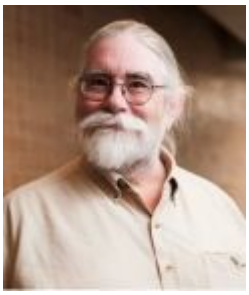
'Open Access' journals have been misinterpreted by some people as 'journals that can publish anything'. As an editorial board member, I ensure that low-quality studies are not published in Scientific Reports. One should not forget that currently there is huge demand

for external reviewers. Therefore, being a board member of journal, I can allow only original and technically sound articles for peer review. It will reduce burden on the reviewers.

5. Which is your favourite *Scientific Reports* paper?

It is difficult to pick a single paper. I have many favourite *Scientific Reports* papers.

Professor Timothy Geary



Prof. Timothy Geary is a Professor in the Institute of Parasitology in the Faculty of Agricultural and Environmental Sciences at McGill and is an Editorial Board Member for Scientific Reports.

1. What is your current research focused on?

I do research in two areas: the pharmacology of antiparasitic drugs (including drug target identification, mechanisms of action and resistance, and development), and understanding the molecular language of the host-parasite interface, with an emphasis on nematodes. The primary focus of this work is the identification and characterization of parasite-derived proteins, metabolites and miRNAs that have immunomodulatory activity in the mammalian host, enabling the establishment of chronic infections.

2. What has been your biggest challenge and your greatest achievement in your career so far?

It's always hard to rank an event as #1 in these areas. Certainly, a major challenge was transitioning from a 20-year career in the pharmaceutical industry to a 15-year career in academia at McGill and now also QUB. The switch was made possible by the Canada Research Chairs programme, which enabled me to get started at McGill, and by support from the Bill and Melinda Gates Foundation, which enabled me to use some of the technology I had developed in the industry to conduct an innovative drug discovery program with partners in Africa. The greatest achievement may have been research that provided a plausible explanation for how the anthelmintic ivermectin removes larval stages of filariid nematodes (microfilariae) from hosts, a key action that makes the drug of value in filariasis control programmes. In another sense, my greatest achievement has

been to work with enormously talented colleagues around the world in fascinating areas of research.

3. Why did you decide to become a board member?

It is an honour to be asked to contribute to the success of one of the Nature family of journals, and I was flattered to be invited. I am on the editorial boards of a number of journals in parasitology, and am glad to serve in that capacity, but *Scientific Reports* addresses broader topics; I wanted to make sure that parasite-related manuscripts submitted here would be fairly and rigorously evaluated.

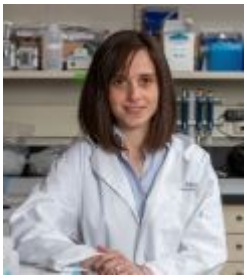
4. What do you like most about being a board member for *Scientific Reports*?

I enjoy the breadth of manuscripts sent to me to consider as board member. Also – and importantly – the staff assistance is exceptional and makes the tasks associated with securing reviews much easier. It is a pleasure to work with them.

5. Which is your favourite *Scientific Reports* paper?

This I cannot answer….there have been too many to rank. I am confident that they have all been valuable additions to the literature.

Dr Leyla Soleymani



Dr. Leyla Soleymani is a Professor and Canada Research Chair at McMaster University and an Editorial Board Member for Scientific Reports.

1. What is your current research focused on?

My current research is focused on creating new hierarchical materials and applying these to biosensors and antimicrobial surfaces.

2. What has been your biggest challenge and your greatest achievement in your career so far?

I guess my greatest achievements and greatest challenges are related. I have found it challenging to balance the needs of an industry relevant product with the required novelty

for successful scientific publication. Some of my proudest achievements have been on technology development activities that are in the process of being translated to knowledge users.

3. Why did you decide to become a board member?

I highly respect the peer-review process and I find it critically important for advancing science. Being an editorial board member at *Scientific Reports* allows me to take part in overseeing the peer review process and work in ensuring that a fair and transparent process is followed, to get the first scoop on new and exciting papers, and to contribute to the publication of high quality papers, not just as an author or a peer reviewer but also as an editorial board member.

4. What do you like most about being a board member for *Scientific Reports*?

I get to read new papers in more diverse areas that I would normally read, which gives me inspiration and insight.

5. Which is your favourite *Scientific Reports* paper?

It is tough to choose an all time favourite, but recently I came across this paper "Logistic growth of a surface contamination network and its role in disease spread" and found it eye-opening in the context of the COVID-19 pandemic.

Dr Ruth Blasco

Dr Ruth Blasco is Taphonomy researcher at Centro Nacional de Investigación sobre la Evolución Humana (CENIEH), Burgos, Spain and is an Editorial Board Member for Scientific Reports.

1. What is your current research focused on?

My current research explores human subsistence strategies during the Pleistocene using a taphonomic approach. I am trying to determine several aspects of human behaviour from the faunal record and contribute to evolutionary anthropology by developing several research sub-areas, such as butchery patterns and hominid–carnivore interactions.

2. What has been your biggest challenge and your greatest achievement in your career so far?

Documenting an intentional delayed consumption of some animal resources (specifically bone marrow from fallow deer metapodials) with implications that affect the subsistence systems of more than 300 thousand years ago.

Food storage is considered a "risk-reducing mechanism" designed to offset downturns in resource availability. The deliberate accumulation of some bones for later marrow consumption implies an anticipation of and concern for future needs. This fact marks a threshold for new modes of Palaeolithic adaptation because the foresight capacity surpasses the "here and now" as a means of subsistence. This study was published last year in Science Advances [Blasco, R., Rosell, J., Arilla, M. ,Margalida, A.,Villalba, D., Gopher, A., Barkai, R., Bone marrow storage and delayed consumption at Middle Pleistocene Qesem Cave, Israel (420 to 200 ka). Sci. Adv. 5, eaav9822 (2019)].

3. Why did you decide to become a board member?

I think that the peer-review process is a fundamental tool for generating quality scientific production. Participating in this process not only as an author or a reviewer but also as an editorial board member allows me to ensure that these processes are objective and transparent and that rigorous, novel and exciting studies are released. I consider it to be a highly privileged position as well as a way of serving the scientific community.

4. What do you like most about being a board member for *Scientific Reports*?

Beyond reading papers from very diverse areas that continuously broaden my knowledge and inspire my future work, being a board member for *Scientific Reports* has allowed me to lead and handle a special collection on "Quaternary Taphonomy" that involves trans- to pluri-disciplinary approaches, such as archaeology, palaeontology, geology, biology and ecology, with a wide array of methodologies. The number of researchers working on taphonomy is steadily increasing, and their contributing to high-ranked scientific journals is becoming a regular trend. This collection is gathering some of the most relevant current studies within this field in the attempt to become a reference source for further studies.

5. Which is your favourite *Scientific Reports* paper?

It is difficult to choose a specific paper, but I will highlight "Deep learning and taphonomy: high accuracy in the classification of cut marks made on fleshed and defleshed bones

using convolutional neural networks", which is a clear example of how the recent application of machine learning algorithms to the taphonomic discipline is achieving higher accuracy in the identification of bone surface modifications and the agents and/or processes that produce them.

Dr. Feng Gao

Dr. Feng Gao is a Professor in the Department of Physics, School of Science, at Tianjin University, Tianjin, China and an Editorial Board Member for Scientific Reports.

1. What is your current research focused on?

I am engaged in bioinformatics research, currently focusing on microbial replication origins.

2. What has been your biggest challenge and your greatest achievement in your career so far?

In the last semester, how to balance teaching, research, editorial activities, and family life has been my biggest challenge, especially during the COVID-19 pandemic. The greatest achievement in my career is the systematic prediction of microbial replication origins using bioinformatics methods, some of which have been confirmed experimentally. The related web server Ori-Finder and online database DoriC have been gradually recognized by researchers in this field.

3. Why did you decide to become a board member?

A Nature Research journal launched in 2011, *Scientific Reports* is really a rising star with an experienced Chief Editor and renowned Editorial Board Members, and an editorial ethos unlike those of other Nature Research journals. This attracted me to become a board member in 2013.

4. What do you like most about being a board member for *Scientific Reports*?

I really enjoy the process of handling manuscripts from all over the world, which report the latest findings from the scientific community. I pick qualified manuscripts using rapid,

high-quality peer review, and present them to the readers in a timely manner. It's an excellent experience to see that the handled manuscripts were well-received by a wide audience or highly cited, which gives me a great sense of achievement.

5. What is your favourite *Scientific Reports* paper?

My favourite *Scientific Reports* paper is: 'RASTtk: A modular and extensible implementation of the RAST algorithm for building custom annotation pipelines and annotating batches of genomes', which has already been cited 570 times according to Web of Science. In fact, I often use the RAST server, which is a very popular genome annotation tool, to annotate our newly sequenced genomes. I was very glad to handle this manuscript and accept it for publication in *Scientific Reports* as quickly as possible.

Professor Kenji Kansaku

Professor Kenji Kansaku is a Professor and Chair at the Department of Physiology, Dokkyo Medical University School of Medicine, Japan. He is also an Editorial Board Member for Scientific Reports *and Guest Editor for the 'Neuroprosthetics in systems neuroscience and medicine' Collection.*

1. What is your current research focused on?

I am a Systems Neuroscientist. I began my career as a neurosurgeon and, therefore, my research interests include both understanding brain functions and applying neuroscientific knowledge to medical practice. I am more specifically focused on practical neuroprosthetics, as well as neural mechanisms of body image and sense of self.

2. What has been your biggest challenge and your greatest achievement in your career so far?

Over the past 15 years, I have mainly focused on the brain–machine interface, which is a neuroprosthetic for patients with neurological disorders. Five years ago, I co-edited a book entitled "Clinical Systems Neuroscience" (Springer), which gathered chapters authored by researchers from various fields, including systems neuroscience, rehabilitation, neurology, psychology, and engineering.

3. Why did you decide to become a board member?

I felt that it would be an opportunity to contribute to various research fields worldwide.

4. What do you like most about being a board member for *Scientific Reports*?

Scientific Reports is unique in that it accepts articles with the only requirements being that they should be technically sound original contributions, and there is no focus on perceived importance and significance. Although the strategy may make it difficult for the journal to set research trends, it provides fair opportunities for papers that would otherwise potentially remain hidden for various reasons.

5. You are leading one of our Guest Edited Collections. What interested you about becoming a Guest Editor? What is your Collection focused on?

I am editing the Guest Edited Collection: Neuroprosthetics in Systems Neuroscience and Medicine. This Collection provides a platform for interdisciplinary research in neuroprosthetics, and gathers studies investigating medical applications of systems neuroscience, informatics, and engineering in the development of neuroprosthetic devices. As mentioned above, I edited a book 5 years ago entitled "Clinical Systems Neuroscience," in which all authors of the provided chapters were assigned by the editors. Here, the free submission style of the Collection has successfully gathered wonderful papers from various research fields. I would be happy for it to contribute to the development of a new special interest group worldwide.

Scientific Reports (*Sci Rep*) | ISSN 2045-2322 (online)

scientific reports

Research articles

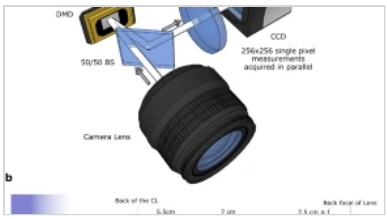
Article Type

All

Year

2022 (21849)

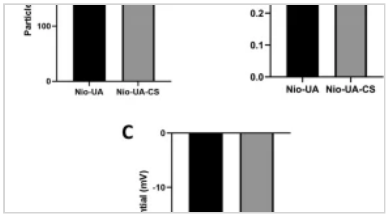
Computational version of the correlation light-field camera



Thomas Gregory, Matthew P. Edgar ... Paul-Antoine Moreau

Article | Open Access | 10 Dec 2022

The effectiveness of ursolic acid niosomes with chitosan coating for prevention of liver damage in mice induced by n-nitrosodiethylamine



Andang Miatmoko, Amelia Anneke Faradisa ... Esti Hendradi

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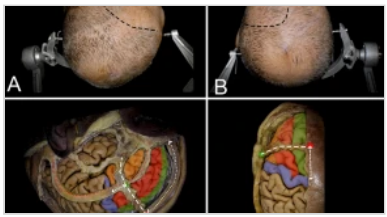
Cortical and white matter anatomy relevant for the lateral and superior approaches to resect intraaxial lesions within the frontal lobe



Tomasz Andrzej Dziedzic, Aleksandra Bala ... Andrzej Marchel

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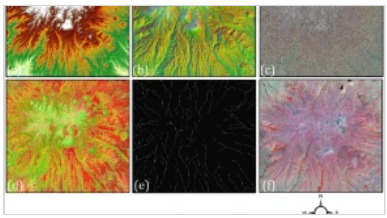
Developing an integrated approach based on geographic object-based image analysis and convolutional neural network for volcanic and glacial landforms mapping



Mohammad Kazemi Garajeh, Zhenlong Li ... Vahid Hossein Haghi

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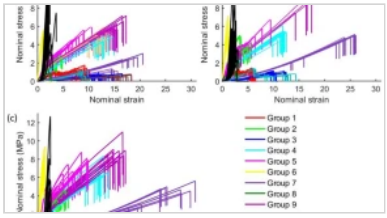
Synthetic tissues lack the fidelity for the use in burn care simulators



Vanessa Hannay, F. N. U. Rahul ... Suvranu De

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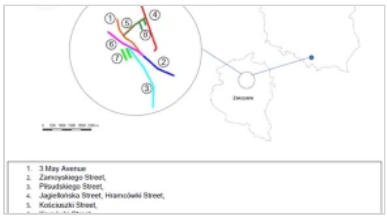
Potential hazard characteristics of trees with hollows, cavities and fruiting bodies growing along pedestrian routes



Marzena Suchocka, Magdalena Wojnowska-Heciak ... Hazem M. Kalaji

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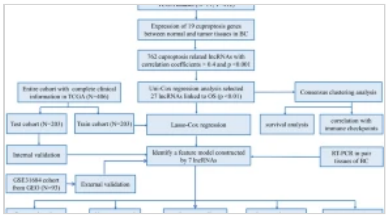
Identification of cuproptosis-related long noncoding RNA signature for predicting prognosis and immunotherapy response in bladder cancer



Gaomin Huang, Yawei Huang ... Xiaoqing Xi

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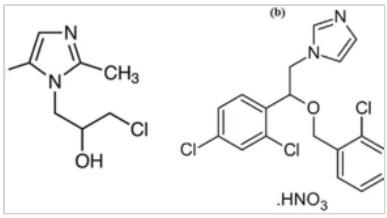
Green synthesis, characterization, and antimicrobial applications of silver nanoparticles as fluorescent nanoprobes for the spectrofluorimetric determination of ornidazole and miconazole



Galal Magdy, Eman Aboelkassim ... Fathalla Belal

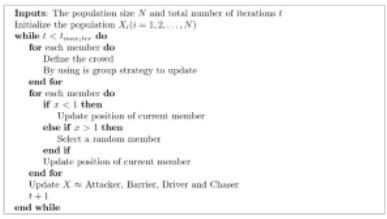
Article | Open Access | 10 Dec 2022

Larvicidal and repellent potential of *Ageratum houstonianum* against *Culex pipiens*

Doaa El Hadidy, Abeer M. El Sayed ... Doaa R. Abdel Haleem

Article | Open Access | 10 Dec 2022

Enhanced chimp optimization algorithm for high level synthesis of digital filters



Mandeep Kaur, Ranjit Kaur & Narinder Singh

Article | Open Access | 10 Dec 2022

scientific reports

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The effectiveness of ursolic acid niosomes with chitosan coating for prevention of liver damage in mice induced by n-nitrosodiethylamine

Andang Miatmoko[1,2]✉, Amelia Anneke Faradisa[1], Achmad Aziz Jauhari[1], Berlian Sarasitha Hariawan[3], Devy Maulidya Cahyani[3], Hani Plumeriastuti[4], Retno Sari[1] & Esti Hendradi[1]

Ursolic acid (UA) is a pentacyclic triterpene carboxylic acid which produces various effects, including anti-cancer, hepatoprotective, antioxidant and anti-inflammatory. However, UA demonstrates poor water solubility and permeability. Niosomes have been reported to improve the bioavailability of low water-soluble drugs. This study aimed to investigate the protective action of UA-niosomes with chitosan layers against liver damage induced by N-Nitrosodiethylamine (NDEA). UA niosomes were prepared using a thin layer hydration method, with chitosan being added by vortexing the mixtures. For the induction of liver damage, the mice were administered NDEA intraperitoneally (25 mg/kgBW). They were given niosomes orally (11 mg UA/kgBW) seven and three days prior to NDEA induction and subsequently once a week with NDEA induction for four weeks. The results showed that chitosan layers increased the particle sizes, PDI, and ζ-potentials of UA niosomes. UA niosomes with chitosan coating reduced the SGOT and SGPT level. The histopathological evaluation of liver tissue showed an improvement with reduced bile duct inflammation and decreasing pleomorphism and enlargement of hepatocyte cell nuclei in UA niosomes with the chitosan coating treated group. It can be concluded that UA niosomes with chitosan coating improved the efficacy of preventive UA therapy in liver-damaged mice induced with NDEA.

Liver damage is the leading global cause of death. In 2017, 1.32 million deaths worldwide or 2–4% of the annual total were due to liver cirrhosis[1,2]. Chemically-induced liver damage results from the metabolic transformation of chemicals into reactive intermediate compounds with the potential to change the structure and function of cellular macromolecules[3]. There are several causes of liver damage, one being exposure to carcinogenic chemicals such as N-nitrosodiethylamine (NDEA) which produces reactive oxygen species (ROS) causing oxidative stress and cellular destruction[4]. Reactive products and free radicals cause an increase in the serum index of liver function such as alanine transaminase (ALT) or serum glutamic-pyruvic transaminase (SGPT), aspartate aminotransferase (AST) or serum glutamic-oxaloacetic transaminase (SGPT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), and total bilirubin. In cases of severe histopathological lesions they cause neoplastic transformation[5].

UA, a natural pentacyclic triterpenoid compound, has various pharmacological properties including anti-cancer, hepatoprotective, anti-angiogenesis, apoptosis induction, antioxidant and anti-inflammatory[6,7]. As an antioxidant, UA reduces oxidative stress, modulates the Receptor for Advanced Glycation End Products (RAGE) and decreases NADPH oxidase to prevent the formation of ROS[8]. UA also produces a hepatoprotective effect by maintaining the structural integrity of the liver, reducing high levels of bilirubin, stabilizing serum protein

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concentrations, and suppressing oxidative stress, inflammation, and apoptosis in the liver[9,10]. Oral administration of a 500 mg/kgBW dose of UA to subjects resulted in a reduction in SGOT and SGPT as well as improvement in liver histopathology[11].

However, limitations on the oral use of UA, which belongs to class IV Biopharmaceutics Classification System (BCS)[12], result from poor solubility and absorption. An effective drug delivery system is required to increase its solubility and dissolution. Niosomes represent a vesicular bilayer system composed of non-ionic surfactants and cholesterol in the aqueous phase which can increase drug half-life, enhance stability, and deliver drugs to target organs in a controlled release[13].

Chitosan, a natural polysaccharide, is a product of alkaline deacetylation of chitin[14] derived from the exoskeleton of crustaceans[15] and is widely employed because of its intrinsic polycation properties, low toxicity, and excellent biocompatibility. Modification of UA liposomes with chitosan coating can increase bioavailability, slow drug release in tumor tissue and reduce both dose and side effects. Chitosan can open the tight junctions of epithelial cells, thereby enabling a drug to pass easily through the epithelial membrane via the paracellular pathway[15]. Chitosan also possesses mucoadhesive properties as a result of ionic interactions between positively charged amino groups and negatively charged functional groups on the surface of epithelial cells provide a controlled release while also enhancing absorption in the gastrointestinal tract and intestinal permeability[16]. Therefore, it is expected that the modification of chitosan on the niosomal surface will enhance absorption in the gastrointestinal tract, promote UA niosome accumulation in the liver and increase bioavailability.

In our previous study, optimization of the UA niosome formula found the optimum physical stability in the span 60-cholesterol-UA formula with a mol percent ratio of 3:2:10[17]. Characterization of UA reported that the presence of chitosan showed an increase in the physical stability of UA niosomes. Chitosan coating on UA niosomes affects their physicochemical properties which, in turn, causes an increase in particle size and a more positive zeta potential. Biodistribution evaluation with coumarin-6 labeling revealed that high fluorescence intensity of coumarin-6 indicates high levels of UA in plasma and liver, together with an increase in bioavailability.

In this study, the evaluation of the effectiveness of UA niosomes with chitosan coating as an orally administered in vivo therapy for the prevention of liver damage in NDEA-induced subjects was by means of serum levels of SGOT, SGPT, and liver tissue histopathology.

Results

Physical characteristics of UA niosomes. Characteristic UA niosomes parameters include particle size, polydispersity index, and ζ–potential. Measurements were taken from Nio-UA and Nio-UA-CS preparations. A graph of the characteristics of AU niosomes can be seen in Fig. 1A–C.

UA niosomes with chitosan coating (Nio-UA-CS) experienced an increase in particle size from 211.7 ± 1.7 nm (Nio-UA) to 257.4 ± 4.3 nm. A significant difference also occurred in the PDI parameters where the presence of chitosan coating increased the PDI from 0.337 ± 0.018 to 0.393 ± 0.021. The ζ-potential parameter of chitosan coating can also alter the charge from UA niosomes which was initially -26.6 ± 0.2 mV to -24.1 ± 0.4 mV. Based on a statistical analysis of the Independent T-Test conducted, the results were $p < 0.001$ on the particle size parameter, $p = 0.03$ on the PDI parameter, and $p = 0.001$ on the ζ-potential parameter, all three of which indicated a significant difference between Nio-UA and Nio.-UA-CS.

Evaluation of mice body weight. The weight of the subjects in the five groups was recorded every week prior to treatment commencing. The average differences in their weight gain and loss can be seen in Fig. 2.

The body weight profiles of the normal group subjects that had not been induced by NDEA were compared with those of the other four groups that were subjected to NDEA induction on four occasions. The normal group subjects were observed to have experienced the most significant weight gain, while those in the negative control group that had been administered NDEA, but did not undergo UA treatment, demonstrated the smallest difference in body weight. Previous studies of liver inflammation using an NDEA-induced subject model also yielded a weight loss profile[18]. NDEA metabolism in the liver can produce ROS that induce oxidative stress resulting in DNA damage[33].

Morphology and organ weight of mice induced with NDEA after administration of UA niosomes. Each organ was photographed post-surgery to determine the qualitative comparison of the morphological organs of subjects in the normal group, the negative control group, the group that received UA, Nio-UA, and Nio-UA-CS suspension treatment. Pictures of complete organs of the normal group subjects, the negative control group subjects induced by NDEA, and the group subjects that received the suspension treatment of UA, Nio-UA, and Nio-UA-CS can be seen in Fig. 3A–G. As it can be seen in Fig. 3A–E, qualitative organ observations confirmed differences in the organs of normal subjects and those which had undergone NDEA induction. In the normal group, the liver surface was bright red and shiny in appearance. Meanwhile, in the negative control group induced by NDEA, a slight color change occurred and several nodules were visible on the surface of the liver, as presented in Fig. 3F,G. This indicates that a 4-week period of NDEA induction damages liver cells.

Quantitatively, all the organs of each subject were weighed with each group members' results being subsequently compared to determine if there was a significant difference. Data on the absolute and relative weight of each organ post-UA treatment and total NDEA induction for 28 days can be seen in Fig. 4A–E. The results show that there were significant differences between groups in the normal group compared to the UA suspension and Nio-UA with regard to the liver and the UA suspension group compared to normal and Nio-UA-CS groups for the lungs.

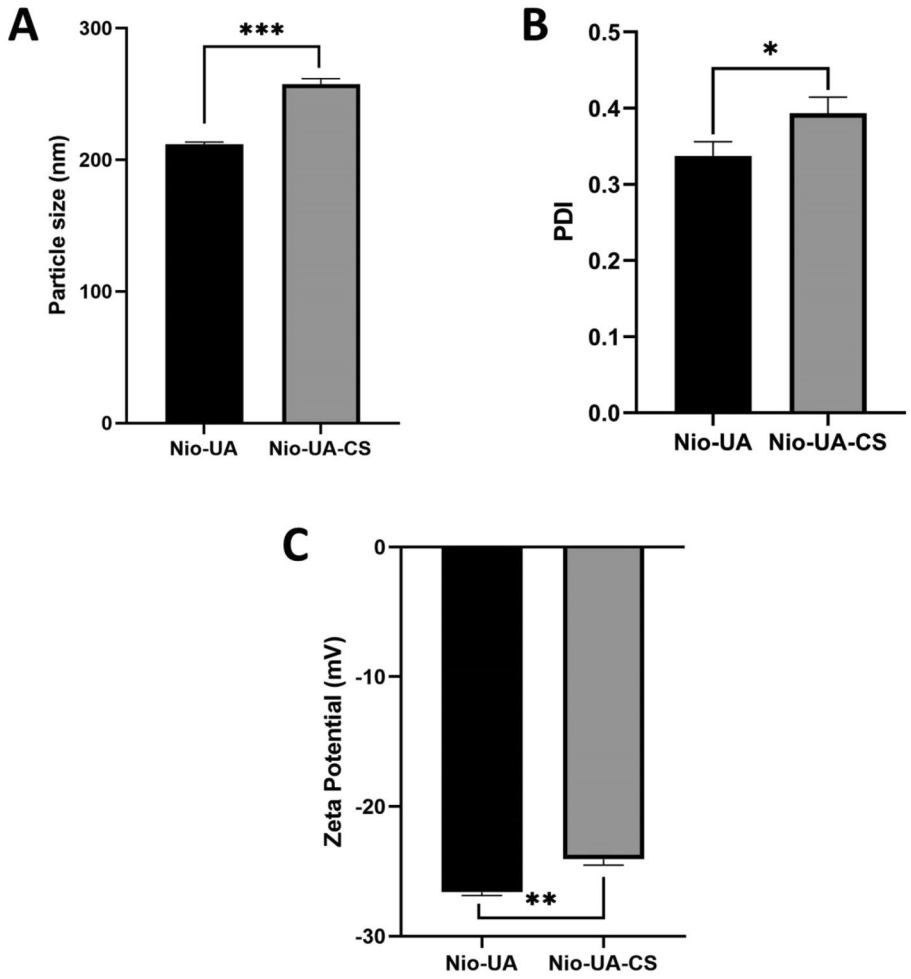

Figure 1. Average (**A**) particle size, (**B**) polydispersity index, (**C**) ζ -potential of Nio-UA and Nio-UA-CS. *p < 0.05; **p < 0.01; ***p < 0.001.

Evaluation of SGOT-SGPT levels of mice induced with NDEA after administration of UA niosomes. The results of measuring the levels of SGOT and SGPT in the blood serum of subjects in the normal group, negative control, UA suspension, Niosom UA (Nio-UA), and Niosom UA with chitosan coating (Nio-UA-CS) can be seen in Fig. 5. Based on these results, the administration of Nio-UA and Nio-UA-CS can be seen to restore relatively normal serum SGOT and SGPT levels.

Histopathology evaluation of liver and spleen mice induced with NDEA after administration of UA niosomes. The results of microscope observation of liver tissue can be seen in Fig. 6. In this study, in order to further develop the effectiveness of UA niosomes with or without chitosan coating, histopathological analysis of liver and spleen tissue was carried out. Prior to observations being conducted, the tissue was stained with H&E to turn the extracellular matrix and cytoplasm pink, while the cell nucleus was highlighted in blue. The results of observations of subjects' liver tissue preparations can be seen in Table 1.

Parameters observed in this liver tissue include lobulation, bleeding, neutrophil infiltration and dysplastic hepatocytes. Figure 6A, which relates to a normal group, contains normal lobules with normal hepatic plate, uniform cell nucleus size and normal chromatin distribution. No bleeding, neutrophil infiltration and dysplastic hepatocytes were detected. In Fig. 6B, the negative control experienced significant inflammatory cell infiltration, unclear hepatic plate, and erythrocytes outside the blood vessels which is a symptom of bleeding (green arrow). Moreover, pleomorphic nuclei and hyperchromatin, which are indicative of cancer cells, are present indicating that this group is at the initiation stage because the other cell nuclei remain normal. In Fig. 6C, the NDEA group induced with UA suspension treatment presented more portal veins, while darker nuclei thought to be due to necrosis, no proliferation of cells, swelling of cells, enlarged cell nuclei and cytoplasmic eosinophil granules, were indicative of it still being in the initiation phase. In Fig. 6D, the NDEA-induced group subjected to Nio-UA treatment was found to have normal recognizable liver architecture, while in some preparations hyperchromatin nuclei were observed, inflammation occurred around the bile ducts and hepatocyte degeneration ensued (ballooning degeneration). From Fig. 6E, containing the NDEA-induced group with Nio-UA-CS treatment, normal

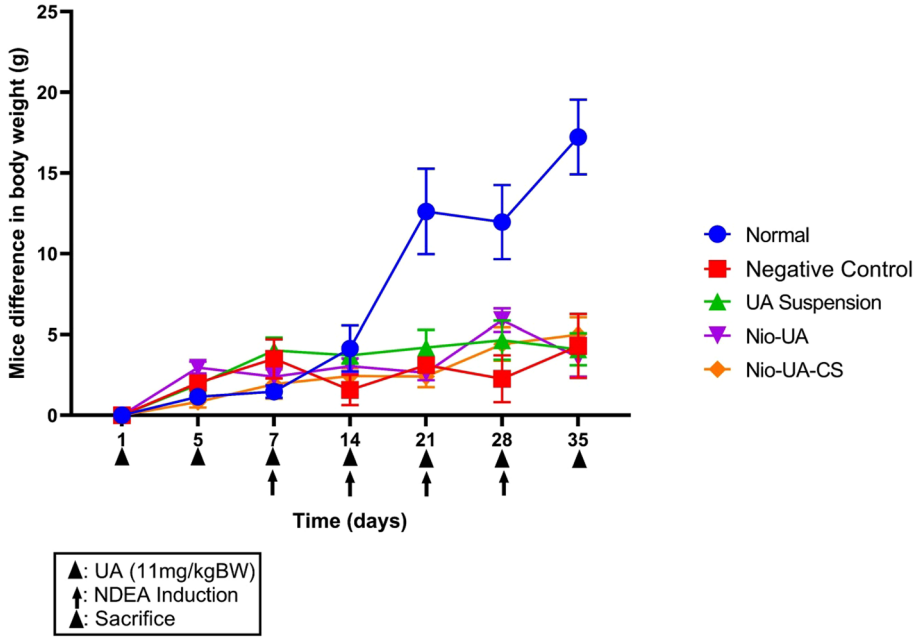

Figure 2. The average difference in body weight of subjects that were treated orally six times with the equivalent of 11 mg UA/kgBW simultaneously with NDEA intraperitoneal induction four times at a dose of 25 mg NDEA/kgBW after which they were sacrificed.

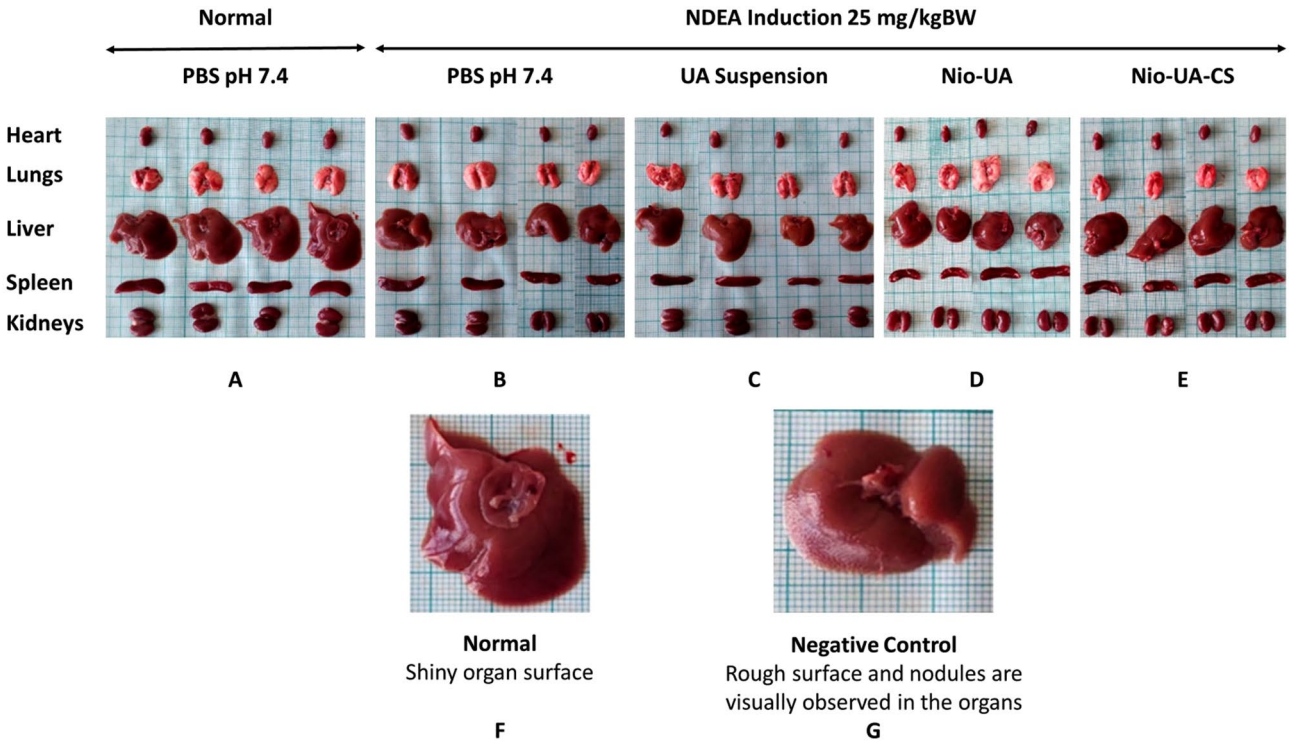

Figure 3. Morphology of the heart, lungs, liver, spleen, and kidneys in group (**A**) of normal subjects with PBS pH 7.4 and oral administration; (**B**) intraperitoneal-induced negative control 25 mg NDEA/kgBW with PBS pH 7.4; induced ip 25 mg NDEA /kgBW with (**C**) UA suspension (**D**) Nio-UA (**E**) Nio-UA-CS which is equivalent to 11 mg UA/kgBW. Differences in liver morphology in the (**F**) normal and (**G**) negative control groups induced by NDEA at a dose of 25 mg/kgBW.

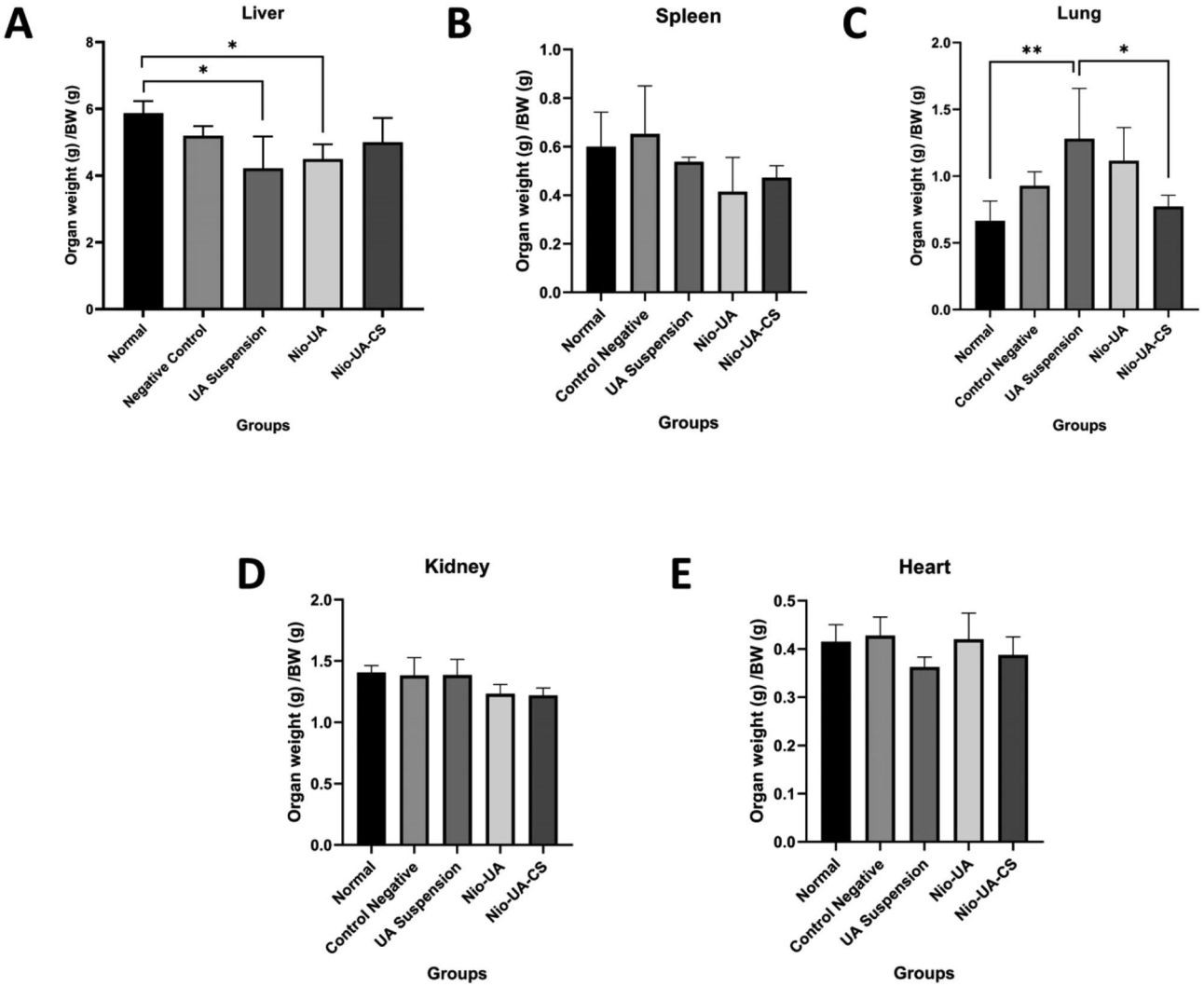

Figure 4. Graph of the relative weight of organs (**A**) liver, (**B**) spleen, (**C**) lungs, (**D**) kidney, (**E**) heart in the normal group and the group which had been NDEA induced with a dose of 25 mg/kgBW and UA suspension treatment, Nio -UA, and Nio-UA-CS which is equivalent to 11 mg UA/kgBW. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

liver architecture can clearly be recognized, several hyperchromatin nuclei, mild inflammation/neutrophil infiltration in the bile ducts, and hepatocyte degeneration (ballooning degeneration) can be observed.

The comparative observation results relating to spleen tissue viewed through a microscope of the normal group, the negative control group, suspensions of AU, Nio-UA, and Nio-UA-CS can be seen in Fig. 7. The observation results of spleen tissue preparations of the subjects can be seen in Table 2. The parameters observed in the spleen tissue include density, germinal center or white pulp, neutrophil infiltration, and trabeculae. In the normal group (Fig. 7A), under normal density conditions, the white pulp was clearly demarcated with red pulp, normal germinal centers and trabeculae and no neutrophil infiltration. In the negative control group (Fig. 7B), while a decrease in the number of follicles, but no germinal center, was observable, there was an increase in macrophages (giant cells). However, the continued absence of hyperplasia obviated significant damage to the spleen caused by NDEA induction. In group induced by NDEA with UA suspension treatment (Fig. 7C), an increase in the number of germinal centers and marginal proliferation of white pulp lymphoid occurred, indicating the possibility of activation in lymphoid tissue. In group induced by NDEA with Nio-UA treatment (Fig. 7D), a proliferation of white pulp lymphoid tissue was observed, indicating the additional possibility of activation in lymphoid tissue. In group induced by NDEA with Nio-UA-CS treatment (Fig. 7E), mild neutrophil infiltration, marginal proliferation of white pulp lymphoid and an increase in the number of germinal centers was observed indicating the possibility of lymphoid tissue activation.

Discussion

The increase in particle size of chitosan-coated UA niosomes was due to the fact that chitosan had formed a hydrophilic shell on the niosomal surface through electrostatic interaction[15,19]. Although the particle size increased, coating chitosan on UA niosomes can enhance its effectiveness. It is estimated that, in the presence of chitosan, drug transport can be effected through two pathways, namely; direct cell membranes and paracellular

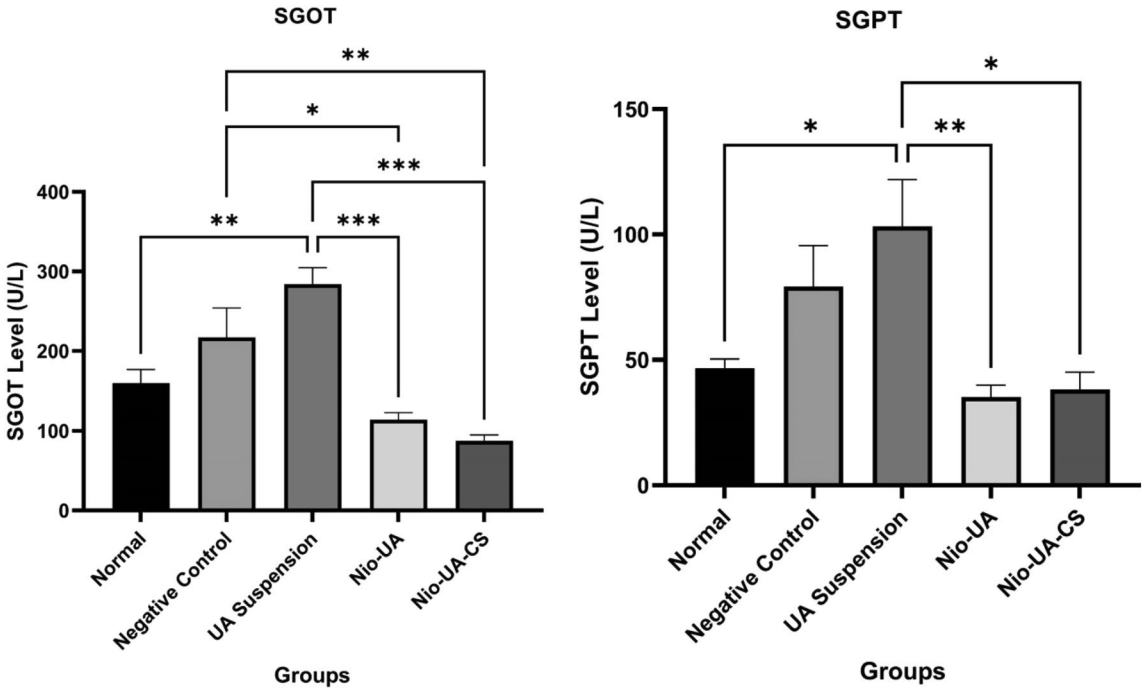

Figure 5. Graph of the average SGOT and SGPT levels in the normal group and the NDEA-induced group at a dose of 25 mg/kgBW with suspension UA, Nio-UA, and Nio-UA-CS treatments which were equivalent to 11 mg UA/kgBW. The data displayed is the mean ± SD (n = 4).

pathways[15]. However, with the addition of chitosan, the value of the polydispersity index (PDI) also increased. The homogeneity criteria for samples with lipid-based carriers was that of PDI < 0.3[20]. The PDI value of Nio-UA remained approximately 0.3 which indicated a relatively homogeneous size distribution. However, chitosan coating significantly increased the PDI value possibly due to the addition of chitosan forming a polymer layer on the surface of the random vesicles[19,21]. Zeta potential is a detection index of electric charge on the particle surface. In vivo, it can influence the distribution of niosomes, while it is thought that in vitro it might contribute to the physical stability of niosomes by reducing the rate of aggregation and fusion[15]. The addition of chitosan can significantly mitigate the negative properties of Nio-UA due to the electrostatic interaction between the positive charge on chitosan and the negative charge on UA[15,21]. Surface charge has been reported as affecting in vivo drug distribution. Several studies have revealed that positively charged nanoparticles show higher phagocytic and cellular uptake than negatively, neutrally charged, and PEGylated nanoparticles[22,23]. The positively charged nanoparticle will be endocytosized through clathrin receptors, while the negatively charged nanoparticles are primarily internalized via caveolin receptors[23]. However, other research into the bioavailability studies of nanoparticles has indicated that their negative charge increases the macrophage uptake more significantly than that of positively charged nanoparticles, thereby potentially reducing the effectiveness of nanodrug delivery[24]. Opsonin serum protein binding with negatively charged nanoparticles seems to occur to a higher degree than that of positively charged nanoparticles. Consequently, negatively charged nanoparticles are covered more extensively by opsonin proteins with greater stimulation of the phagocytosis by macrophages[25].

Data on the weight of each organ indicated a reduced mean relative weight of the liver in the members of the four NDEA-induced groups compared to those of the normal group. Induction of NDEA causes hepatic degeneration that generally reflects loss of function associated with hepatocellular atrophy and injury[18]. A significant difference in relative liver weight occurred in the normal group compared to the UA and Nio-UA suspensions. In previous in vivo studies, administration of UA was known to reduce liver weight. UA can effectively relieve hepatic steatosis and reduce adipocyte size in the epididymis and decrease total cholesterol and triglycerides in the liver and plasma of subjects[26,27]. In this study, NDEA-induced subjects did not present a difference in relative spleen weight compared to members of the normal group.

NDEA is a well-known carcinogen that induces cancer of various organs in experimental animal subjects. Inducing liver cancer, NDEA can also result in lung adenocarcinoma[28]. Moreover, positively charged nanoparticles are also more easily taken up by lung cells, compared to neutral or negatively charged nanoparticles with the result that they can accumulate extensively in the lungs[29]. This may underlie the significant differences in the pulmonary organs, while in the heart, no changes were observed possibly due to differences in cell types and characteristics. However, further analysis of these organs is required.

The SGOT and SGPT levels in serum in the negative control group were recorded as higher than that in normal group. This indicates that the administration of NDEA 25 mg/kgBW to negative control group members on four occasions caused liver damage characterized by increased levels of SGOT and SGPT in blood serum. SGOT and SGPT are enzymes sensitive to liver cell damage which are predominantly contained in liver cells and, to a lesser extent, in muscle cells. Exposure to toxic substances causes a change in the permeability of the liver

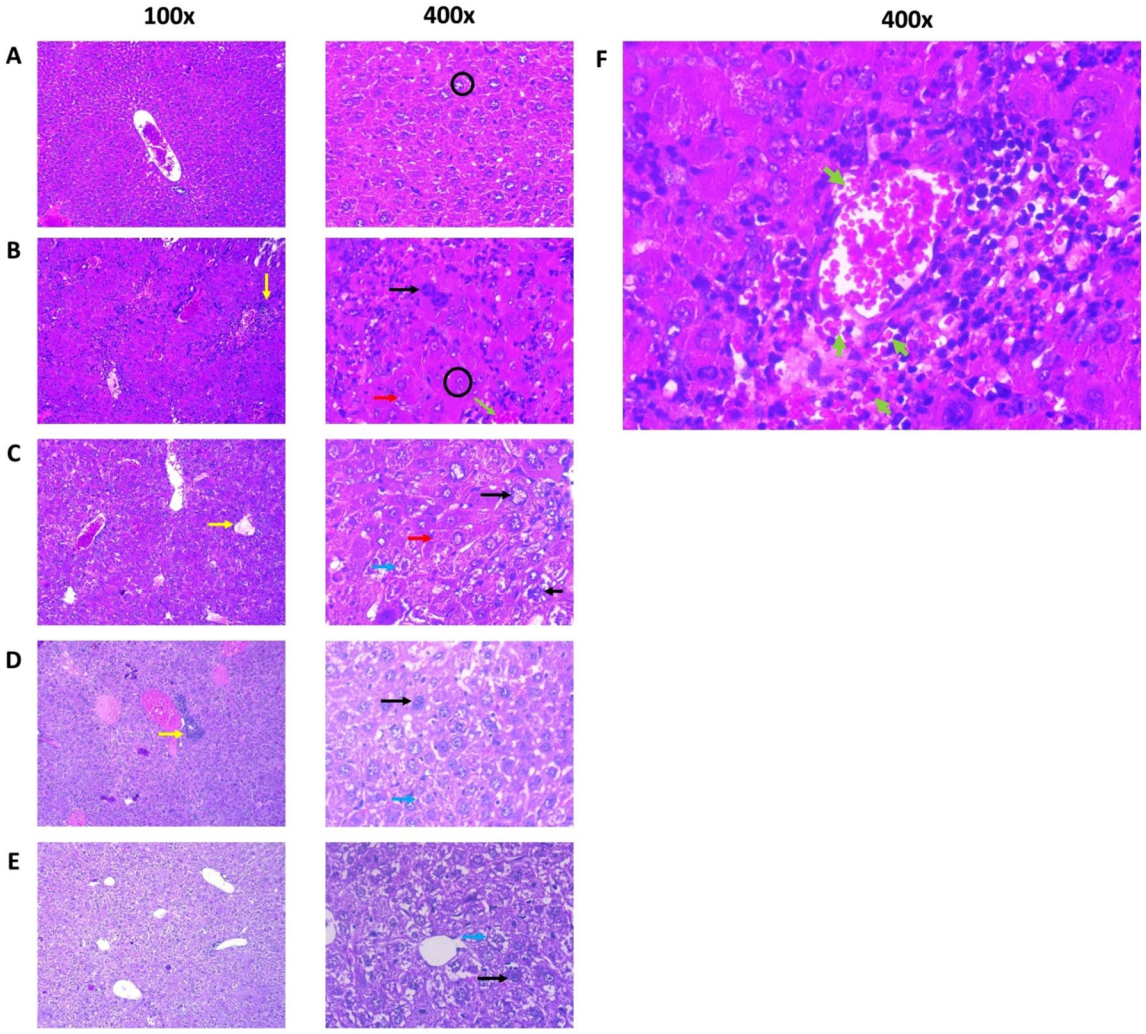

Figure 6. Histopathological picture of subjects' livers (**A**) Normal, (**B**) Negative control induced with 25 mg NDEA /kgBW ip; (**C**) UA suspension, (**D**) Nio-UA, (**E**) Nio-UA-CS at an equivalent dose of 11 mg UA/kgBW. Picture (**F**) shows the bleeding in the liver tissue of the Negative control group. Image magnification are 100 × and 400 × with H&E staining. Black circle = hepatic plate, black arrow = hyperchromatin and enlarged cell nucleus, yellow arrow = neutrophil infiltration, blue arrow = hydropic degeneration, red arrow = cytoplasmic eosinophilic granules, green arrow = hemorrhage.

cell membrane resulting in damage or leakage, as a result of which the liver cells will release the enzymes they contain into the blood circulation, thereby increasing the levels of SGOT and SGPT and signaling liver disease[30].

The levels of SGOT and SGPT in the negative control group were also higher than those in the Nio-UA and Nio-UA-CS groups. SGOT levels showed a significant difference ($P < 0.05$) while SGPT levels did not demonstrate a significant difference ($P > 0.05$) in the Nio-AU and Nio-UA-CS groups compared to the negative control group. This indicates that the administration of Nio-UA and Nio-UA-CS produces a hepatoprotective effect by reducing the release of SGOT and SGPT into the blood compared to UA suspension. A previous study of in vivo test results relating to paclitaxel niosomes indicated that the plasma drug concentration was higher in the paclitaxel niosome group than in the paclitaxel suspension group[31]. Oral use of niosomes can improve permeation and bioavailability, solubility of hydrophobic drugs, drug accumulation in the liver and controlled and targeted drug release[32].

The SGOT level in the Nio-UA-CS group was lower than that of the Nio-UA group. The presence of chitosan can induce a greater effect marked by the release of fewer SGOT enzymes. This finding supports those of previous studies regarding the modification of UA liposomes with chitosan coating increasing bioavailability, slowing drug release in tumor tissue, and reducing dosage and potential side effects. This can happen because chitosan opens tight junctions in epithelial cells and allows drug to pass freely through epithelial cells via paracellular pathways[15]. Chitosan also induces mucosal adhesion through ionic interactions between positively charged amino groups and negatively charged functional groups on the surface of epithelial cells, thereby providing controlled release and absorption in the gastrointestinal tract[16]. Chitosan has good mucoadhesive properties that can prolong the residence time of the drug in the gastrointestinal tract. Under acidic conditions, chitosan will trigger the opening of tight junctions between epithelial cells and facilitate paracellular transport of niosomes[15]. Therefore, the

Group	Parameter			
	Lobulation	Hemorrhage	Neutrophil infiltration	Dysplastic hepatocytes
Normal	Normal (approximately 40% experience mild degeneration/cloudy swelling)	Negative	Negative (approximately 40% present symptoms of mild port hepatitis)	Negative
Negative control	Enlargement of the hepatocellular plate Hepatic plate not clear Hepatocytes with severe hydropic degeneration (ballooning degeneration)	Mild to moderate around the central vein	Moderate porta hepatitis Several microabscess foci Giant cells	Visible enlargement and size of the nucleus varies and hyperchromatic nuclei Eosinophilic granule cytoplasm Proliferation of biliary duct epithelium
UA suspension	Enlargement of the hepatocellular plate Hepatic plate not clear Hepatocytes with moderate to severe hydropic degeneration Necrotic biliary ducts epithelium	Negative	Mild portal hepatitis was diagnosed (33%) intralobular neutrophil infiltration (50%)	Visible hepatocyte nucleus enlargement Eosinophilic granule cytoplasm Proliferation of biliary duct epithelium (17%)
Nio-UA	Normal liver architecture remains recognizable Mild-severe hydropic degeneration	Negative	Neutrophil infiltration around the bile ducts (pericholangitis)	Cells with hyperchromatic nuclei are observed
Nio-UA-CS	Normal liver architecture remains recognizable Hepatocytes with severe hydropic degeneration	Negative	Mild infiltration of the bile ducts (many are normal)	Several cells with large hyperchromatic nuclei were observed

Table 1. Observation of histopathological liver preparations of subjects in the normal group, negative control, suspension of UA, Nio-UA, and Nio-UA-CS equivalent to a dose of 11 mg UA/kgBW.

nanoparticle system in the presence of chitosan coating can effectively improve oral absorption. There is still no information regarding the effect of chitosan on tight junctions in hepatocytes.

The levels of SGOT and SGPT in the UA suspension group were higher than in the negative control group, although they did not differ significantly. This is possible because the dose of 11 mg UA/kgBW administered is less effective if in the form of a suspension. The use of niosomes can overcome the problem of low drug solubility in water, thereby reducing drug dosage[33]. Previous research into the use of UA in the prevention of liver fibrosis due to CCl_4 induction found optimal protection through the administration of UA at a dose of 50 mg/kgBW in distilled water containing 0.1% Tween 80[10,34]. Moreover, this is feasible due to the difference in the amount of UA taken because the UA suspension is insoluble. Consequently, there is a possibility that the preparation is not homogeneous, while the niosomes are more evenly dispersed than the suspension.

An analysis of the study results confirmed that the levels of SGOT and SGPT parameters in the Nio-UA and Nio-UA-CS groups were lower than in the normal group, although not significantly different. The lower the level, the healthier the condition of the liver[35]. In terms of further research, if experimental subjects are used, it is preferable to complete a sampling to check the levels of SGOT and SGPT before the subjects are treated to ensure that their initial condition is healthy.

It is evident from these observations that the administration of Nio-UA-CS can reduce inflammation, pleomorphism, dysplasia, and enlargement of hepatocyte cell nuclei in mice liver. These results indicate that the administration of chitosan to UA niosomes increases the anti-inflammatory and anticancer activity of UA[11]. This finding is consistent with those of previous studies regarding CS modification of liposomes which resulted in increased drug activity of UA liposomes and enhanced antitumor drug efficacy[15]. Liver histopathology observations were linear with the results of SGOT and SGPT levels indicating that the optimum repair of liver damage occurred in the Nio-UA-CS group followed by Nio-UA and, finally, UA suspension.

Spleen histopathology was also observed in the course of this study. Conventional nanoparticles are known to be trapped by RES, most of which will migrate to the liver and spleen[36]. Liposomes and lipid nanocarriers larger than 100–150 nm can be taken up by phagocytes. Monocytes, macrophages and neutrophils are phagocytes. The majority of these phagocytes reside in the liver and spleen for subsequent elimination[20].

The administration of Nio-UA-CS indicates lymphoid tissue activation. Such activation is correlated with an increase in immune system activity[37] which can protect the body from non-self-pathogens or cancer cells by destroying them[38]. In a previous study on UA nanoparticles with chitosan coating as folate-targeting, the preparation was shown to enhance tumor inhibition and promote an immune-boosting more effectively than free UA[39,40].

It has been reported that Chitosan induces transient tight junction opening by translocating the membrane's tight junction protein claudin-4 (Cldn4) into the cytoskeleton followed by its degradation in lysosomes[41,42]. Cldn4 has been recognised as a protein responsible for cell adhesion, polarity and paracellular permeability[43]. Intracelullar redistribution results in the weaking of the tight junction leading to the opening of the cells[41,42]. On the other hand, it has been reported that Cldn4 is not expressed in normal hepatocytes. However, its expression is increased due to fibrosis, rather than inflammatory condition, of severe liver injury[44], which this gene expression correlates with differentiation of progenitor cells into mature hepatocytes. This study also reported that its expression was not found in cases of hepatocellular carcinoma. Therefore, chitosan's effects on hepatocyte permeability and the drug's penetration into deeper damaged liver tissue are still questionable, need to be further explored. In addition, NDEA induction has been reported to increase serum bilirubin levels[45], and UA effectively reduced them, proving its potential efficacy for liver protection and promoting bile secretion[46,47]; however, this

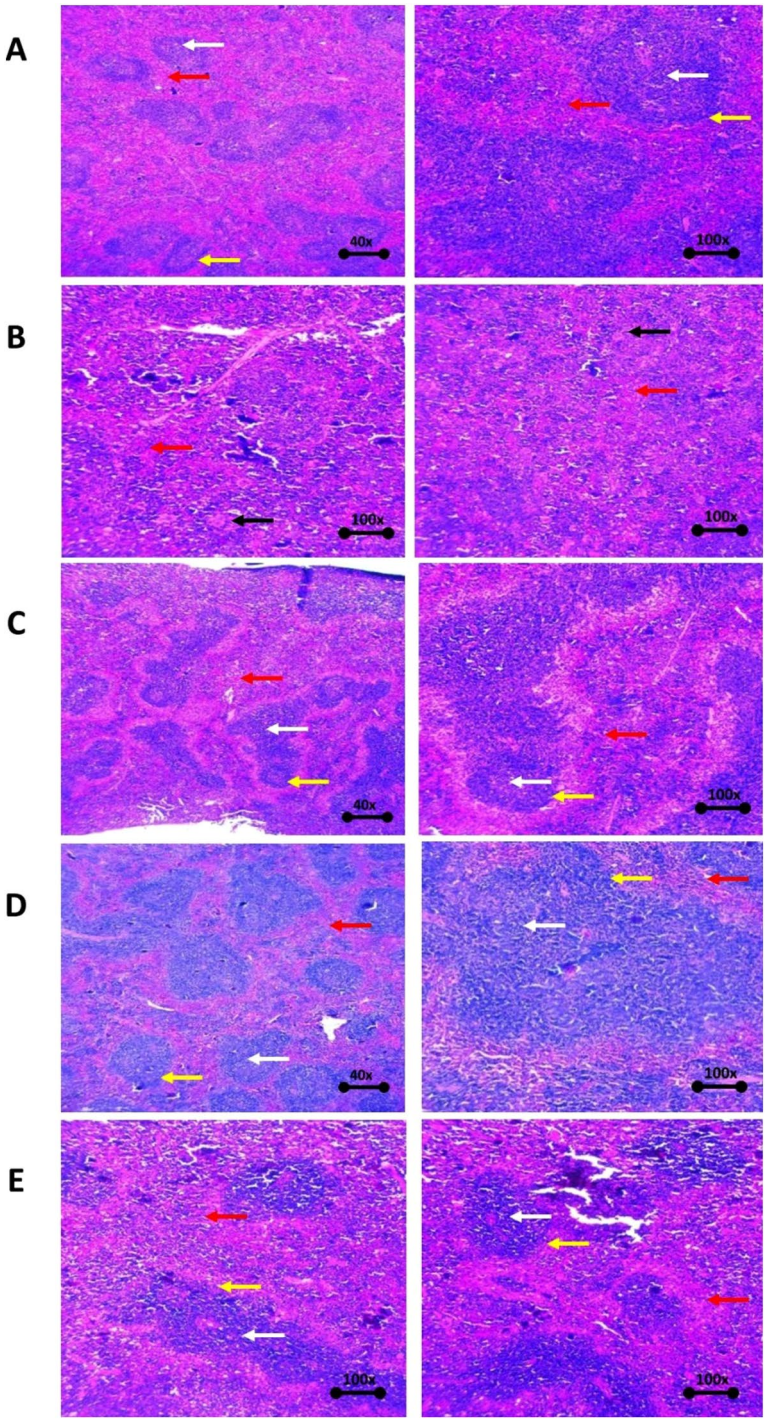

Figure 7. Histopathological picture of the spleen of mice (**A**) Normal, (**B**) Negative control induced with 25 mg NDEA/kgBW ip; (**C**) UA suspension, (**D**) Nio-UA, (**E**) Nio-UA-CS with an equivalent dose of 11 mg UA/kgBW with H&E staining. Red arrow = red pulp, white arrow = white pulp/germinal center, yellow arrow = marginal zone, black arrow = giant cell macrophage.

study was limited. Therefore, evaluating the serum bilirubin levels is vital to provide the information associated with the repair of liver damage and its dysfunctions[48].

Chitosan coating on UA niosomes can improve the physical morphology of the liver, resulting in the relative weight of the liver and lung organs which are relatively the same as the normal group and there is no significant difference in the difference in body weight. Chitosan coating on UA niosomes can increase the effectiveness of UA as a therapy to prevent liver damage in subjects induced by N-Nitrosodiethylamine in terms of histopathological parameters of liver tissue which are relatively more normal than negative controls. Chitosan coating

Group	Parameter			
	Density	White pulp/germinal center	Neutrophil infiltration	Trabecular
Normal	Normal	Normal	Negative	Normal
Negative control	Lymphoid tissue appears rather loose	Slight to no visible germinal center, observable increase in macrophages (giant cells)	Negative	Normal
UA suspension	Lymphoid tissue appears rather loose	Marginal proliferation of white pulp lymphoid, increased number of germinal centers	Negative	Normal
Nio-UA	Normal	Marginal proliferation of white pulp lymphoid, a dramatic increase in the number of germinal centers	Mild neutrophil infiltration	Normal
Nio-UA-CS	Lymphoid tissue appears rather loose	Marginal proliferation of white pulp lymphoid, significant increase in the number of germinal centers	Negative	Normal

Table 2. Observations of spleen histopathological preparations of mice in the normal group, negative control, UA suspension, Nio-UA, and Nio-UA-CS equivalent to a dose of 11 mg UA/kgBW.

Formulation	Component (mol ratio)			
	Span 60	Cholesterol	UA	Chitosan
Nio-UA	60	40	10	–
Nio-UA-CS	60	40	10	+

Table 3. Ursolic acid niosome formulation. *UA* ursolic acid, *CS* chitosan, (–) without chitosan addition, (+) with chitosan addition.

on UA niosomes can increase the effectiveness of UA as a therapy to prevent liver damage in mice induced by N-Nitrosodiethylamine in terms of decreasing serum levels of SGOT and SGPT.

Methods

Preparation of UA niosomes. Preparation of niosomes was conducted using a thin layer hydration method with a formula composition referred to previous studies as shown in Table 3[17]. UA (sigma-Aldrich, Tokyo, Japan) solution in methanol, span 60 (Wako Pure Chemical Industries, Ltd., Osaka, Japan), and cholesterol (Wako Pure Chemical Industries, Ltd., Osaka, Japan) in chloroform (Merck, Darmstadt, Germany) were mixed in a round bottom flask. The organic solvents were then heated in a rotary vacuum evaporator at a temperature of 60 °C until they had all evaporated and a thin lipid layer was formed. This layer was hydrated using 2 ml PBS solution pH 7.4 at 60 °C for 1 h[17]. Sonication was carried out with a water bath sonicator to form niosomes in order to reduce the size of the vesicles. Dissolving chitosan (Biotech, Cirebon, Indonesia) in 0.1 M acetic acid produced 0.1% chitosan solution which was subsequently diluted using distilled water to obtain a solution of 0.005% v/v chitosan which was added to the UA niosomal suspension. The addition was completed by mixing 40 µl of chitosan solution with 400 µl of niosomal samples before vortexing for ten seconds.

Physical characterizations of UA niosomes. Approximately 100 µL niosomes was diluted in 2 mL aqua demineralization with particle size and PDI measurements subsequently being completed by the Dynamic Light Scattering method using Malvern Zetasizer Instruments (Malvern Panalytical, UK). Furthermore, 100 µL niosomes were also taken diluted in 2 mL aqua demineralization ζ-potential measured using the Electrophoresis Light Scattering method with Malvern Zetasizer Instruments (Malvern Panalytical, UK). The evaluation was completed three times for each of the Nio-UA and Nio-UA-CS samples.

In vivo efficacy evaluation of UA niosomes in mice induced with NDEA. The use of experimental animals in this research was approved following an ethical feasibility test conducted on April 1, 2022 at the Faculty of Veterinary Medicine, Universitas Airlangga by the Faculty's Research Ethics Commission through the issuance of Certificate of Ethics Eligibility No. 2.KEH.035.04.2022**.** All methods were performed in accordance with ARRIVE guidelines and relevant regulations[49]. In this study, 6-week-old male mice (*Mus musculus*) Balb/c represented the subjects. Determination of the number of sample replications employed the Federer's Formula. Five randomly selected subjects formed the members of each treatment group. The negative control group was treated by means of NDEA i.p. injection for four weeks, while PBS pH 7.4 was administered orally during sample treatment.

Induction of liver damage of mice by NDEA injection. Induction of liver damage in subjects was achieved through the intraperitoneal administering of a 25 mg/kgBW dose of NDEA (sigma-Aldrich, Tokyo, Japan)[50] once a week for four weeks. Evaluation of the resulting liver damage was effected by recording the subjects' body weight on a weekly basis during the test period to identify any increase or decrease.

Administration of UA niosomes into mice induced with NDEA. Subjects were given drugs, including UA suspension in 0.5% CMC Na, Nio-UA, and Nio-UA-CS, according to whichever group they belonged. The UA dose was equivalent to 11 mg UA/kgBW[40]. The drug was administered orally using a needle probe seven and three days before NDEA induction and was continued once a week together the intraperitoneal induction of NDEA at a dose of 25 mg/kgBW for the subsequent four weeks.

SGOT and SGPT evaluation of mice induce with NDEA after administration of UA niosomes. After the final UA preparation had been administered, the subjects were left for seven days before their organs were surgically removed. Having been given intraperitoneal anesthesia in the form of a 10 mg/kgBW dose of ketamine, a blood sample was taken from the inferior vena cava, inserted into test tubes and centrifuged at 6000*g* × force for 15 min at 4 °C to obtain serum whose levels of SGOT and SGPT was then determined using the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) 37 method. The decrease in SGOT and SGPT levels was determined from comparisons between each treatment group and the control group. The SGOT and SGPT levels were determined by enzymatic reaction kinetic method. The reagents used were ready-to-use reagents consisting of AST (GOT) and ALT (GPT) reagents[51].

Histopathological evaluation of liver and spleen of mice induce with NDEA after administration of UA niosomes. Following extraction of the blood sample, the subjects' spines were dislocated. The subjects were dissected and their livers immediately removed, rinsed with normal saline, and dry wiped with a tissue or filter paper, before finally being weighed, photographed and morphologically examined. The liver sections were fixed in 10% neutral buffered formalin and then stained with haematoxylin and eosin (H&E staining) for further histological analysis of the differences in appearance between the livers of the normal and treated subjects[11]. Changes in lobular architecture, bleeding, neutrophilic infiltration, and dysplastic hepatocytes on histopathological preparations of liver tissue were observed by means of light microscopy[45,52]. To evaluate the organ weight of the subjects, quantitatively each organ of mice in each group was weighed. Because overall body weight affects the weight of individual organs, the relative weight of the livers was calculated using the formula[53]:

$$\text{Relative Weight} = \frac{Absolute\ organ\ weight(g)}{Body\ Weight(g)} \times 100\%.$$

The calculation results relating to the relative weight of the organs in the treatment group were then compared with those of the normal and negative control groups to determine whether significant differences existed.

Statistical analysis. The quantitative data represent the average and standard deviation of sample measured in replications. A statistical analysis was performed using the one-way variant analysis (ANOVA) method followed by a Post Hoc Tukey HSD test. The $P\ value < 0.05$ is considered as a significant difference between the results.

Ethical conduct of research statement. The animal study procedures were performed in accordance with the ethical clearance issued by The Ethics Commission of Faculty of Veterinary Medicine, Universitas Airlangga (Certificate number 2.KEH.035.04.2022 dated April 1, 2022).

Data availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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Author contributions

A.M.: (1) conception and design of the work, data acquisition, data analysis and interpretation; (2) critically revising the article for important intellectual content; (3) final approval of the version to be published; (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of the work are appropriately investigated and resolved. A.A.F.: (1) conception and design of the work, data acquisition, data analysis and interpretation; (2) drafting the article; (3) final approval of the version to be published; (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of the work are appropriately investigated and resolved. A.A.J.: (1) conception and design of the work, data acquisition, data analysis and interpretation; (2) drafting the article; (3) final approval of the version to be published; (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of the work are appropriately investigated and resolved. B.S.H.: (1) conception and design of the work, data acquisition, data analysis and interpretation; (2) Final approval of the version to be published; (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of the work are appropriately investigated and resolved. D.M.C.: (1) conception and design of the work, data acquisition, data analysis and interpretation; (2) Final approval of the version to be published; (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of the work are appropriately investigated and resolved. H.P.: (1) data analysis and interpretation; (2) critically revising the article for important intellectual content; (3) final approval of the version to be published; (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of the work are appropriately investigated and resolved. R.S.: (1) data analysis and interpretation; (2) critically revising the article for important intellectual content; (3) final approval of the version to be published; (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of the work are appropriately investigated and resolved. E.H.: (1) data analysis and interpretation; (2) critically revising the article for important intellectual content; (3) final approval of the version to be published; (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of the work are appropriately investigated and resolved.

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Competing interests

The authors declare no competing interests.

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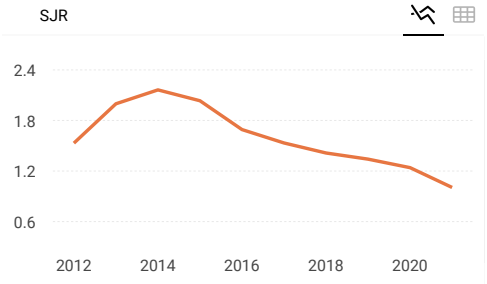

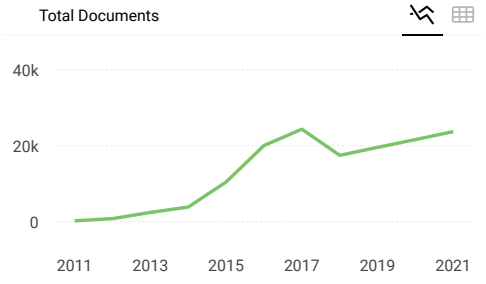

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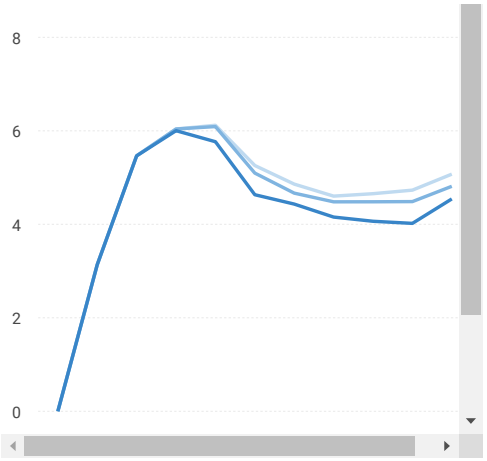

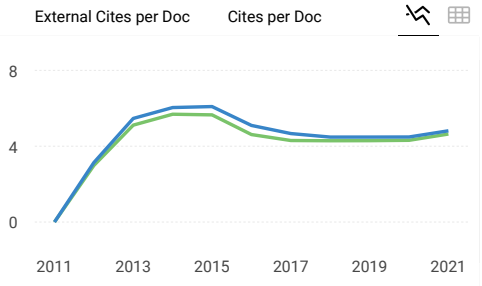

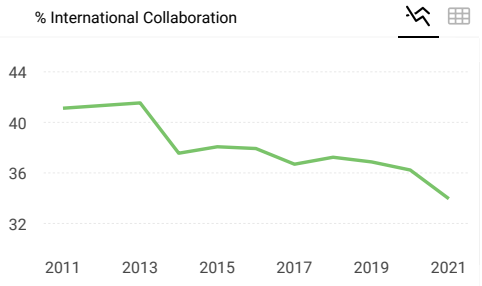

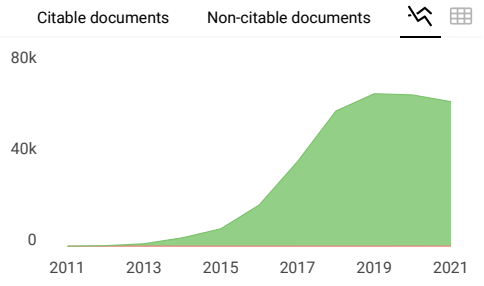

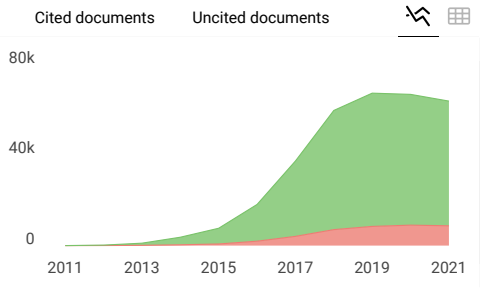

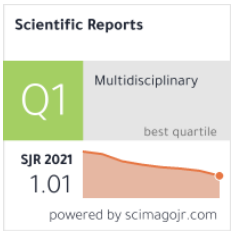

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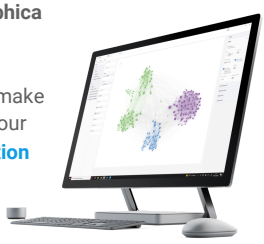

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