# Bukti Publikasi Artikel
# di Royal Society Open Science

## Febdian Rusydi, S.T., M.Sc., Ph.D.
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Daftar Bukti:

1. Dewan Editorial Jurnal
2. Daftar Isi Volume 8, Issue 2
3. Submit dan Draf Manuskrip
4. Review Manuskrip
    - Komentar Reviewer
    - Pertanyaan dan Jawaban
    - Revisi Draf Manuskrip
5. Manuskrip Diterima
6. Artikel Terbit
    - Persiapan Terbit
    - Artikel

# 1. Dewan Editorial Jurnal

# ROYAL SOCIETY OPEN SCIENCE

## Editorial Board

### Editor-in-Chief

Professor Dame Wendy Hall DBE FREng FRS

### Registered Reports and Replications

#### Subject Editor

Professor Chris Chambers

More details on Registered Reports can be found here.

### Astronomy

#### Subject Editor

Professor Rob Ivison

**Dr Michelle Collins**
University of Surrey

*Keywords: Stellar populations and dynamics of nearby galaxies*

**Professor Asantha Cooray**
University of California, Irvine

*Keywords: Large-scale structure, galaxy surveys, IR surveys, instrumentation and new methods in astrophysics, cosmology, cosmic microwave background*

**Professor Charles Cockell**
University of Edinburgh

*Keywords: Astrobiology, microbiology, geobiology, space and planetary sciences*

**Professor Sofia Feltzing**
Lund University

*Keywords: Elemental abundancies in FGK stars, galactic archaeology, The Milky Way as a glaxy, stellar populations, galactic surverys and survey design, galaxy formation and evolution*

**Professor Alan Fitzsimmons**
Queen's University Belfast

*Keywords: Asteroids, comets, Kuiper-belt, trans-neptunian objects*

**Dr Thomas Kitching**
UCL

*Keywords: Large-scale structure, gravitational lensing, dark energy, dark matter*

**Dr. John McKean**
Netherlands Institute for Radio Astronomy

*Keywords: Radio astronomy, gravitational lensing, galaxy evolution, dark matter, galaxies, active galaxies*

**Professor Mark McCaughrean**
European Space Agency's Directorate of Science

*Keywords: Heliophysics, planetary physics, fundamental physics*

**Dr Elaine Sadler**
University of Sydney

*Keywords: Galaxy evolution, active galaxies, radio galaxies*

**Professor Ian Smail**
Durham University

*Keywords: Galaxies-evolution, formation, interaction, starburst, clusters, infrared, submillimetre, quasars*

**Dr Leonardo Testi**
European Southern Observatory

*Keywords: Star and planet formation, pre-main sequence evolution, protoplanetary disks, interstellar medium, radio, millimetre and infrared observational techniques*

**Professor Mark Wyatt**
University of Cambridge

*Keywords: Debris disks, planetary system dynamics, protoplanetary disks, planey formation, asteroids/comets*

**Professor Stephen Smartt**
Queen's University Belfast

*Keywords: Stars, transients, supernovae, stellar evolution, wide field surveys*

**Professor Kim-Vy H. Tran**
Texas A&M University

*Keywords: Galaxy evolution, galaxy formation, star formation histories, high redshift universe, surveys*

**Professor Catherine Heymans**
University of Edinburgh

*Keywords: Cosmology, gravitational lensing, optical/NIR surveys*

**Dr Celine Peroux**
European Southern
Observatory

*Keywords: Circumgalactic Medium ; Evolution of metals, gas and dust ; galaxy kinematics ; high-resolution & 3D spectroscopy ; millimetre astronomy*

**Professor Geraint F. Lewis**
The University of Sydney

*Keywords: Cosmology (observational and computational), large-scale structure, non-standard models of dark matter and dark energy, gravitational lensing, galactic archaeology*

**Dr Martin Hewitson**
Institute for Gravitational
Physics at Leibniz University
Hannover

*Keywords: Gravitational Waves, LISA, LISA Pathfinder, GEO600, detector characterisation, calibration, mission performance, interferometry*

## Biochemistry, Cellular and Molecular Biology

### Subject Editor

Professor Malcolm White

**Professor Alex Costa**
Università degli Studi di
Milano

*Keywords: Plant biology, calcium signaling, imaging and microscopy, environmental sensing, ions’ transport*

**Dr Payam A. Gammage**
CRUK Beatson Institute &
Institute of Cancer
Sciences, University of
Glasgow

*Keywords: mtDNA, mitochondria, cancer*

**Professor John Dalton**
National University of
Ireland, Galway

*Keywords: Infectious diseases, parasitology, vaccines, immunology, biochemistry, molecular biology, proteases*

**Professor Paul J Lehner FMedSci FRS**
University of Cambridge

*Keywords: Viral evasion of the immune system, viruses, immune system, virus latency, Herpesvirus, genetic screens in mammalian systems, ubiquitin, HIV*

**Professor David Wales FRS**
University of Cambridge

*Keywords: Theoretical chemistry, energy landscapes, atomic and molecular clusters, statistical mechanics, global optimisation, thermodynamic sampling,*

**Dr Shaked Ashkenazi**
University of Oxford

*Keywords: molecular biology, biochemistry, protein-protein interaction, inflammation, innate immunity, host-pathogen interaction, host response to pathogen, cell biology, TNFalpha, NFkappaB, drug discovery.*

*rare event dynamics, machine learning*

**Dr Susana Santos Lopes**
NOVA University of Lisbon

*Keywords: Cilia, motile cilia, flow patterns created by motile cilia, ciliopathies, sensory cilia, Primary Ciliary Dyskinesia, zebrafish left-right development*

**Professor Diwakar Shukla**
University of Illinois at Urbana-Champaign

*Keywords: Molecular Modelling & Simulations, Molecular Dynamics, Markov State Models, Membrane proteins, Machine Learning, Protein Structure & function, Photosynthesis*

**Professor Xinguang Zhu**
Shanghai Institute of Plant Physiology and Ecology, Chinese Academy of Sciences

*Keywords: Photosynthesis, source sink interaction, photosynthesis efficiency, system modelling, global climate change, mesophyll conductance*

**Professor Alan J Warren**
University of Cambridge

*Keywords: Ribosome assembly, cryo-electron microscopy, X-ray crystallography, translation, ribosomopathy, bone marrow failure, leukaemia*

**Dr Simon Cook**
The Babraham Institute

*Keywords: Signal transduction, cell cycle, cell death, senescence, autophagy, cell:cell contacts and EMT, cancer, oncogenes, kinase inhibitors as cancer therapeutics, drug resistance*

**Dr Robson da Costa**
Federal University of Rio de Janeiro

*Keywords: Neuropharmacology, pain, analgesia and neurological disorders, animal models, cell culture, chronic pain, itch, TRP channels, GPCRs and inflammation.*

**Dr Nitin Baliga**
Institute for Systems Biology

*Keywords: Gene regulatory networks, extremophiles, halophiles, tuberculosis, host-pathogen interactions*

**Dr Marco Di Antonio**
Imperial College London

*Keywords: DNA secondary structures, biochemistry, chromatin, transcription regulation*

**Professor Anthony J Wilkinson**
University of York

*Keywords: Structural biology, protein structure and function, leishmaniasis, malaria, post-translational modification, gene control*

**Professor Joanna Parish**
University of Birmingham

*Keywords: Molecular and cellular virology, papillomavirus, cancer, virus-host interactions, viral persistence*

**Dr Karen Polizzi**
Imperial College London

*Keywords: Synthetic biology, genetically-encoded biosensors, bioprocess engineering, recombinant protein expression, therapeutic proteins, biologics, vaccines, Pichia pastoris, Chinese Hamster Ovary cells, glycosylation*

**Dr Ed Bolt**
University of Nottingham

*Keywords: Molecular biology, protein biochemistry, microbiology*

**Dr Seth B. Coffelt**
University of Glasgow, Institute of Cancer Sciences & Cancer Research UK Beatson Institute

*Keywords: Cancer immunology, tumor microenvironment, metastasis, immune evasion*

**Dr Juliane Liepe**
Max Planck Institute for Multidisciplinary Sciences

*Keywords: Systems biology, antigen processing and presentation, computational mass spectrometry, proteasome catalysed peptide splicing*

**Dr Julie A. K. McDonald**
Imperial College London

*Keywords: Gut microbiome, microbial ecology, colonisation resistance, antimicrobial resistance*

**Professor Haitao Lu**
Shanghai Jiao Tong University

*Keywords: Metabolomics, microbial metabolism, systems pharmacology, pancreatic cancers, gut microbiota, proteomics, lipidomics, mass spectrometry*

**Professor Richard Marais FRS**
Cancer Research UK Manchester Institute

*Keywords: Cancer biology, cell signalling, cell proliferation, oncogenes, melanoma, mouse models, drug discovery, clinical trials, targeted therapies, immunotherapy,* *translational research, biomarkers*

## Chemistry

### Subject Editor

Professor Anthony Stace FRS

For more details of our Chemistry section and our collaboration with the Royal Society of Chemistry, please see here.

---

**Dr Andrew M. Harned**
Deciphera Pharmaceuticals

*Keywords: Organic chemistry, Medicinal chemistry, Green chemistry*

**Dr Dattatray Late**
CSIR-National Chemical Laboratory

*Keywords: Synthesis of 1D and 2D nanomaterials, sensors, supercapacitors, light emitting diodes, photodetectors, nano-switches, non-volatile memory devices, lithium ion batteries, catalysts for water splitting application, field emission, transistors*

**Professor Darren Walsh**
The University of Nottingham

*Keywords: Electrochemistry, electrochemical energy storage and conversion, physical chemistry*

**Professor Ya-Wen Wang**
Southwest Jiaotong University

*Keywords: Fluorescence probes, chemosensor, molecular recognition*

**Dr Annette Trunschke**
Fritz Haber Institute of the Max Planck Society

*Keywords: Inorganic chemistry, catalysis*

**Dr. Debashree Ghosh**
Indian Association for the Cultivation of Science

*Keywords: Hybrid QM/MM, stochastic multireference methods, machine learning, force fields, photo-processes in DNA, melanin, Green fluorescent proteins*

**Dr Nadia Valentina Martínez Villegas**
San Luis Potosí Institute of Scientific Research and Technology

*Keywords: Hydrogeochemistry, soil science, soil chemistry, environmental soil science, soil pollution, surface and groundwater contamination, environmental risk assessment, trace element geochemistry, trace element mobility, trace element retention, trace element bioavailability, trace element speciation, environmental geochemistry, biogeochemistry, clays, peloids, arsenic, urban dust, hydrogeology*

**Dr Chaohua Cui**
Soochow University

*Keywords: Photoconductivity/photovoltaic effect; conductivity; Semiconductivity; Photoelectrochemistry; Solar energy; Electronic materials; Electrical properties of materials; Energy applications; Optical properties of materials; Organic materials*

## Computer Science and Artificial Intelligence

### Subject Editor

Professor Marta Kwiatkowska FRS

---

**Professor Ion Petre**
University of Turku

*Keywords: Systems biology, network science, biocomputing, theory of computing, natural computing*

**Professor Yulan He**
University of Warwick

*Keywords: Natural language understanding, sentiment analysis and opinion mining, information extraction, machine reading comprehension*

**Dr François Fages**
Inria Paris-Rocquencourt

*Keywords: Computational biology, theory of computing, bioinformatics, computational modelling, optimisation, constraints, logic*

**Professor Sabrina De Capitani di Vimercati**
Università degli Studi di Milano

*Keywords: Data protection; privacy; access control models, policies, mechanisms; cloud computing*

**Professor Mirella Lapata**
University of Edinburgh

*Keywords: Generation, summarization, semantic parsing, vision and language*

**Professor Bart De Moor**
KU Leuven

*Keywords: System identification and time series modelling, (generalized) eigenvalue problems, machine learning, neural networks, applications in Health 2.0 and Industry 4.0 (monitoring, control and automation, forecasting, anomaly and fraud detection, clustering and classification, etc.)*

**Professor Mirco Musolesi**
University College London and University of Bologna

*Keywords: Ubiquitous computing; human-centred artificial intelligence/machine learning; computational models of human behaviour and social systems (and their applications to systems design); reinforcement learning and multi-agent systems*

**Dr Sebastian Stein**
University of Southampton

*Keywords: Multi-agent systems, smart transportation, smart energy, mechanism design, crowdsourcing*

**Professor Theo Damoulas**
University of Warwick and The Alan Turing Institute

*Keywords: Probabilistic machine learning, Bayesian non-parametrics, robustness, causality, spatio-temporal modelling and approximate Bayesian inference*

**Professor Mahesan Niranjan**
University of Southampton

*Keywords: Machine learning, computational biology, signal processing*

# Earth and Environmental Science

## Subject Editor

**Professor Peter Haynes FRS**

---

**Dr Michael J. Ryan**
Carleton University

*Keywords: Vertebrate palaeontology; dinosaurs, taphonomy, systematics, evolution*

**Dr Philip M Benson**
University of Portsmouth

*Keywords: High-pressure deformation, rock physics, acoustic emission, permeability, fluid-triggered seismicity, tensile fracture mechanics, earthquake mechanics, rock friction*

**Professor Quazi K. Hassan**
University of Calgary

*Keywords: Optical/thermal remote sensing in: (i) forecasting and monitoring of natural hazards/disasters, such as forest fire, drought, and flooding; (ii) comprehending the dynamics of natural resources, such as forestry, agriculture, and water; and (iii) modelling issues related to boreal environment.*

**Dr Riccardo Avanzinelli**
Università degli Studi di Firenze

*Keywords: Magma genesis and differentiation, mantle metasomatism and melting, element cycling at subduction zones, conditions and timescales of magma storage and eruption, application of traditional and non-traditional isotopic tracers to igneous petrology.*

**Professor Graham E. Budd**
Uppsala University

*Keywords: Palaeobiology, Cambrian explosion, patterns of evolution, evo-devo*

**Dr Nicola Allison**
University of St. Andrews

*Keywords: Biomineralisation, palaeoproxy development, carbonate formation and geochemistry, environmental change, ocean acidification*

**Professor Wolfgang D Maier**

**Dr Hywel Griffiths**
Aberystwyth University

**Dr Michelle Alexander**
University of York

Cardiff University

*Keywords: Layered intrusions, mafic-ultramafic igneous rocks, anorthosites, basalts, komatiites, magmatic ore deposits, platinum-group elements, nickel, copper, chromium, vanadium*

*Keywords: Geomorphology, fluvial systems, palaeohydrology, floods, river erosion, coastal systems, environmental change, ecosystem services*

*Keywords: Biomolecular archaeology, archaeology, isotope analysis, palaeodiet, historical ecology, collagen*

**Dr Chunqing Sun**
Chinese Academy of Sciences

*Keywords: Tephrochronology, Volcanic ash, Tephra, Explosive volcanic eruption, Volcanology, Quaternary Science*

**Dr Pablo J Gonzalez**
Estación Volcanológica de Canarias (IPNA-CSIC)

*Keywords: Satellite geodesy, tectonics, earth observation, satellite radar interferometry, earthquake cycle, volcanic deformation*

## Ecology, Conservation, and Global Change Biology

### Subject Editor

Professor Peter Smith FRS

---

**Dr Joachim Mergeay**
Research Institute for Nature and Forest, Belgium; KU Leuven

*Keywords: Conservation genetics, conservation genomics, landscape genetics, Habitats Directive, Biodiversity policy, population genetics theory*

**Dr Roberto Carlucci**
University of Bari

*Keywords: Marine mammals, sharks and rays, food web modelling, management fisheries, ecosystem functioning, consumption flows, fishery sustainability, spatial distribution modelling, cetaceans, assessment of species of*

**Dr Emily L. Lindsey**
La Brea Tar Pits – Natural History Museum of Los Angeles County

*Keywords: Paleoecology, Conservation Paleobiology, Quaternary Extinctions, South American Mammals, Radiocarbon Dating, Taphonomy* *conservation interest, invasive species*

**Dr Luis Daniel Llambí C.**
Universidad de Los Andes, Venezuela; CONDESAN

*Keywords: Plant ecology, alpine ecosystems, vegetation dynamics, community assembly, plant-plant interactions, climate change, land use, adaptive strategies, species invasions, plant succession, long-term monitoring, adaptation, Tropical Andes*

**Dr Krijn Paaijmans**
Arizona State University

*Keywords: Infectious disease vectors, mosquitoes, malaria, arboviruses, surveillance, global change, control, prevention, elimination*

**Dr Agnieszka Latawiec**
Pontifical Catholic University of Rio de Janeiro (PUC-Rio) and International Institute for Sustainability and University of Agriculture, Krakow

*Keywords: Ecosystem services, integrated land management, modelling, environmental decision making, biochar, applied soil science, impact evaluation, participatory approach*

**Professor Brian J. Reid**
University of East Anglia

*Keywords: Soil, carbon, chemicals, pollutants, restoration, remediation, ecosystem-services*

**Dr Melita A. Samoilys**
CORDIO East Africa

*Keywords: Tropical marine ecology, coral reef biodiversity, fishes, climate change, marine conservation, fisheries, community-based approaches*

**Dr Enrico Bertuzzo**
University of Venice Ca’ Foscari

*Keywords: Ecohydrology, stream biogeochemistry, population dynamics, ecological modelling, metapopulation/metacommunity dynamics, epidemiological modelling, waterborne diseases*

**Professor Leslie R. Brown**
University of South Africa

*Keywords: Terrestrial plant ecology, plant community classification,*

**Dr Nicole A. Hynson**
University of Hawaii at Manoa

*Keywords: Fungal Ecology, plant*

**Dr Christie Bahlai**
Kent State University

*Keywords: Population modelling, temporal ecology, community ecology, insects, data* *veld management, biodiversity, plant-animal interactions*

*ecophysiology, community ecology*

*integration, abrupt change, working landscapes*

**Dr Francisco Barros**
Federal University of Bahia

*Keywords: Benthic ecology, estuarine ecology, conservation, mangroves, human impacts, coastal ecology*

**Professor Eva Wollenberg**
University of Vermont and CGIAR

*Keywords: Climate change, mitigation, agroecology, agriculture, social justice, land use management*

**Dr Aileen Mill**
Newcastle University

*Keywords: Wildlife management, invasive species, marine foodwebs, stable isotope ecology, adaptive management, structured decision making, disease modelling, vertebrate population modelling, human wildlife interactions*

**Dr Elsa Youngsteadt**
North Carolina State University

*Keywords: Insect ecology, thermal ecology, urban ecology, pollination, plant-insect interactions*

**Dr Kazuo Isobe**
Peking University

*Keywords: Soil microbial ecology, nutrient cycling, plant-microbe interaction, soil development*

**Professor Beth Scott**
University of Aberdeen

*Keywords: Marine ecology, ecosystems and climate change, trophic interactions, oceanographic and anthropogenic effects*

## Engineering

### Subject Editor

Professor Kerry Rowe FREng FRS

---

**Dr Jagdish Telangrao Shahu**
Indian Institute of Technology

*Keywords: Foundations, soil mechanics, rock*

**Dr Hengky Chandrahalim**
The U.S. Air Force Institute of Technology

*Keywords: MEMS, NEMS, optics, microsystems, photonics, sensors,*

**Professor Weisi Guo**
Cranfield University

*Keywords: Telecommunication, wireless, 5G, natural language processing,* *engineering, slopes, waste materials, geosynthetics*

*optomechanics, optofluidics, microfabrication, microfluidics, nanofabrication, lasers, nonlinear optics, biophotonics, photoacoustics, radio frequency, microwaves*

*clustering, neural network, graph signal processing, complex network, molecular communication, Internet-of-Things, social analytics, conflict models.*

**Professor Nicole Metje**
University of Birmingham

*Keywords: Utility detection, buried infrastructure, quantum technology gravity sensing, geophysics, buried asset condition assessment, tunnelling, underground space*

**Professor Francesco Granata**
University of Cassino and Southern Lazio

*Keywords: Hydraulic engineering, machine learning, hydrology, water resources, deep learning, wastewater hydraulics, two-phase air-water flows, urban drainage*

**Professor Simon Schultz**
Imperial College London

*Keywords: Neural coding, computational neuroscience, two photon imaging, neural coding, information theory, cortical circuits*

**Professor Zach Agioutantis**
University of Kentucky

*Keywords: Mining systems, rock mechanics, ground control, subsidence.*

**Dr Iman Mohagheghian**
University of Surrey

*Keywords: Smart materials and structures, additive manufacturing, lightweighting, multifunctional structures, active structural control, metamaterials, 4D printing, composites, architectured materials, energy absorption material and structures, soft robotics*

**Dr Ramesh Rayudu**
Victoria University of Wellington

*Keywords: Solar power, wind power, geothermal energy, green hydrogen, DC grids, off-grid microgrids*

**Professor H. Daniel Wagner**
Weizmann Institute of Science

*Keywords: Composite materials, interface mechanics, carbon nanotubes, graphene, nanocomposites, biological materials mechanics*

**Dr Adil Al-Mayah**
University of Waterloo

*Keywords: Mechanical characterization of materials, biomechanics: properties of soft tissues and medical applications, biomechanical-based deformable image registration, composite materials applications in civil structures*

**Dr Omid Kavehei**
University of Sydney

*Keywords: Biomedical engineering, biomedical instrumentation, medical devices, neurotechnology, microsystems, retinal prosthesis, neural prosthesis, microelectronics, nanoelectronics, biomedical signal processing*

**Dr Xiaoli Guo Larsén**
Technical University of Denmark

*Keywords: Extreme wind, atmospheric turbulence, air-sea interaction, wind resource, wind farm wakes*

**Professor C.W. Lim**
City University of Hong Kong

*Keywords: Elasticity, theory of plates and shells, nonlinear dynamics, dynamics of metamaterials, symplectic elasticity*

**Dr Deepak Pant**
Flemish Institute for Technological Research (VITO)

*Keywords: Electrosynthesis, CO2 conversion, resource recovery, bioelectrochemistry, microbial fuel cell*

## Genetics and Genomics

### Subject Editor

Professor Steve Brown FRS FMedSci

---

**Dr Paul Schofield**
University of Cambridge

*Keywords: Mammalian disease genetics, functional genomics, model organisms, bioinformatics, ontology*

**Dr Cheryl P. Andam**
University at Albany, State University of New York

*Keywords: Population genomics, comparative genomics, microbial evolution, genomic epidemiology of infectious*

**Professor Nicholas D.E. Greene**
University College London

*Keywords: Birth defects, neural tube, one-carbon metabolism, metabolomics, folate, mouse embryo, mouse genetics* *diseases, antimicrobial resistance, horizontal gene transfer, recombination*

**Professor Simon G. Sprecher**
University of Fribourg

*Keywords: Neurogenetics, sensory receptors, visual system, taste systems, Drosophila, Invertebrates*

**Professor Lluis Quintana-Murci**
Institut Pasteur and Collège de France

*Keywords: Human genetics, evolutionary genetics, genetic anthropology, genetics of gene expression, genetics of immunity and infectious diseases*

**Professor Laura A Johnston**
Columbia University

*Keywords: Developmental genetics, cell and tissue growth, cell competition, fitness sensing, Drosophila, regeneration*

**Dr James Locke**
University of Cambridge

*Keywords: Plant systems biology, gene-network models, circadian clocks, noise in gene expression, single cell time-lapse microscopy*

**Professor Andrew Teschendorff**
CAS-MPG Partner Institute of Computational Biology, Chinese Academy of Sciences; UCL Cancer Institute

*Keywords: DNA methylation, epigenomics, cancer, aging, networks, cell-type heterogeneity, single-cells, single-cell RNA-Seq, systems biology, stem-cells, EWAS*

**Dr Anu Bashamboo**
Institut Pasteur

*Keywords: Developmental biology, reproductive genetics, stem cell biology*

**Professor Ruth Arkell**
The Australian National University

**Professor Michael J Owen**
Cardiff University

*Keywords: Psychiatry, Schizophrenia, Genetics,*

**Professor Andrew Copp**
UCL GOS Institute of Child Health

*Keywords: Congenital Defects, Developmental Biology, Gene Expression, Molecular Mechanisms, Cell Signalling, Transcription factors*

*Genomics, GWAS*

*Keywords: Embryo, nervous system, neural tube, malformations, primary prevention*

## Mathematics

### Subject Editor

Professor Mark Chaplain FRSE

---

**Professor Françoise Tisseur**
The University of Manchester

*Keywords: Numerical analysis, numerical linear algebra, numerical algorithms and software, high performance computing, matrix analysis*

**Dr Jonathan Fraser**
University of St Andrews

*Keywords: Fractals, self-similarity, dynamical systems, real analysis, complex analysis, dimension theory*

**Professor Jose Antonio Carrillo de la Plata**
Mathematical Institute, University of Oxford

*Keywords: Kinetic equations, nonlocal equations, non-linear diffusions, analysis, modelling and applications*

**Dr Kenta Ishimoto**
Kyoto University

*Keywords: Fluid mechanics, biofluid mechanics, complex fluids, low-Reynolds-number flow, biomechanics, biophysics, soft and active matter, swimming, propulsion, stability*

**Professor Anotida Madzvamuse**
University of Sussex

*Keywords: Pattern formation, reaction-diffusion systems, coupled bulk-surface PDEs, cell motility, cell migration, finite elements, finite differences, transport mechanisms, cross-diffusion*

**Professor Joshua Ross**
University of Adelaide

*Keywords: Modelling in ecology and epidemiology, stochastic models, computational Bayesian statistics, outbreak analytics, operations research*

**Professor Dirk Drasdo**
INRIA

*Keywords: Bioinformatics, physical and mathematical biology, modelling of tumour growth, modelling of tissue formation and regeneration processes, sequence alignment, tissue folding and early animal development, reconstruction and modelling of gene regulation networks*

**Professor Robert S. MacKay FRS**
University of Warwick

*Keywords: Dynamical systems, control, complexity science, networks, interacting particle systems, dynamics, complex system*

**Professor Christine Currie**
University of Southampton

*Keywords: Simulation optimisation, stochastic modelling, healthcare, decision analysis, infectious disease modelling*

**Dr Vladimir Dokchitser**
King's College London

*Keywords: Algebraic number theory, arithmetic geometry, computational number theory*

**Dr Danica Vukadinovic Greetham**
Knowledge Media Institute,
Open University

*Keywords: Network analysis, algorithmic graph theory, social network analysis, agent-based modelling, network optimisation, approximation algorithms, spectral graph theory*

**Professor Len Thomas**
University of St Andrews

*Keywords: Wildlife population assessment, Bayesian statistical inference, mark-recapture, spatial capture-recapture, distance sampling, wildlife population trend, population dynamics, bioacoustics, animal movement, anthropogenic disturbance, cumulative impacts, particle filter, sequential Monte Carlo methods*

**Professor Takashi Suzuki**
Osaka University

*Keywords: Mathematical Oncology, Nonlinear Partial*

**Professor Andreas Kyprianou**
University of Bath

*Keywords: Levy processes, diffusions, branching*

**Professor Alban Potherat**
Coventry University

*Keywords: Fluid mechanics, planetary interiors, wakes, transition to turbulence,* *Differential Equations, Dynamical Systems*

*processes, monte-carlo simulation, random particle systems, financial mathematics, population models, stochastic analysis*

*high Hartmann flows, alfven waves, spectral methods, quasi-two dimensional flows, anisotropy in turbulence, liquid metal flows*

**Dr Peter Stewart**
University of Glasgow

*Keywords: Mathematical biology and physiology, fluid-structure interaction, soft tissue mechanics, interfacial fluid mechanics, gas-liquid foams*

**Professor Tim Rogers**
University of Bath

*Keywords: Population dynamics, ecological and evolutionary models, individual based models, epidemic models, networks*

**Professor Rachel Bearon**
University of Liverpool

*Keywords: (Bio-)fluid dynamics, active matter, cell motility, cell signalling, gene regulatory networks, systems pharmacology, transport & diffusion models*

**Dr Feng Fu**
Dartmouth College

*Keywords: Network science, human behaviour, game theory, infectious diseases, cancer modelling, neuroscience, data sciences*

**Professor Adriano Barra**
Università del Salento

*Keywords: Statistical mechanics, complex systems, disordered systems, neural networks, machine learning, immune networks, collective properties, cell migration*

**Professor Dionne Aleman**
University of Toronto

*Keywords: Optimization, simulation, and machine learning applied to healthcare decision-making*

**Professor J. M. Sanz-Serna**
Universidad Carlos III de Madrid

*Keywords: Numerical solution of differential equations, Hamiltonian problems, Monte Carlo methods, optimization*

**Professor Enrique Zuazua**
Friedrich-Alexander-Universität Erlangen-Nürnberg

*Keywords: Partial differential equations, numerical analysis, control theory, machine learning*

**Dr Anastasios Matzavinos**
Pontifical Catholic University of Chile

*Keywords: Applied mathematics, computational biology, stochastic systems, Bayesian uncertainty quantification, data-driven modelling*

## Organismal and Evolutionary Biology

### Subject Editor

Professor Kevin Padian

---

**Dr Adam Reddon**
Liverpool John Moores University

*Keywords: Behaviour, brain, fish, cichlid, aggression, submission, communication, sociality, cooperation, cognition, nonapeptide*

**Professor Cinzia Chiandetti**
University of Trieste

*Keywords: Animal behaviour, learning, plasticity, lateralization, comparative cognition, evolution and development of cognition, behavioural neuroscience*

**Professor Sebastian Shimeld**
University of Oxford

*Keywords: Development, evolution, vertebrate, chordate, protostome, nervous system*

**Professor Marion Bamford**
University of the Witwatersrand

*Keywords: Palaeobotany, wood anatomy, palynology*

**Dr Agustina Gómez-Laich**
Instituto de Ecología, Genética y Evolución de Buenos Aires (IEGEBA) – Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET)

*Keywords: Seabirds, diving behaviour, accelerometer, GPS, animal borne video cameras, energy expenditure, big data*

**Dr Michael Doube**
City University of Hong Kong

*Keywords: Biomechanics, cell biology, image processing, medical imaging, bone microtomography, microscopy, biomimetics, bioimaging informatics*

**Dr Alecia Carter**
University College London

*Keywords: Animal behaviour, cultural evolution, social learning, social information,*

**Dr Polly Campbell**
University of California Riverside

*Keywords: Animal behaviour, sexual conflict, epigenetic inheritance,*

**Professor Kristina Sefc**
University of Graz

*Keywords: Mating systems, social systems, mate choice, parental care, parentage analysis, competition, sexual* *primatology, animal culture, phenotypic constraints, plasticity, animal personality, social network, information transmission, network based diffusion analysis, baboon*

*genomics, hybridization, parent-of-origin, reproduction, sex chromosome evolution, speciation, transcriptomics*

*selection, hybridisation, speciation, phylogeography, animal coloration*

**Dr Brandon E. Jackson**
Longwood University

*Keywords: Comparative biomechanics, locomotion, flight, avian evolution, allometry, kinematics, 3D videography*

**Dr Cynthia J Downs**
State University of New York College of Environmental Science and Forestry

*Keywords: Trade-offs, immunology, immunocompetence, pace-of-life hypothesis, basal metabolic rate, maximal metabolic rates, life history, artificial selection, allocation theory, constitutive immunity, immune defences, allometry, scaling, immune function*

**Professor Puni Jeyasingh**
Oklahoma State University

*Keywords: Evolutionary ecology, limnology, aquatic ecology, Daphnia, ecological physiology, nutritional ecology, ecological genetics, ecological stoichiometry*

**Professor Andrew M. Simons**
Carleton University

*Keywords: Life-history evolution, phenotypic plasticity, bet-hedging strategies, geometric-mean fitness, fluctuating natural selection, environmental variation, plant mating systems, phenology, experimental evolution, microsatellite markers*

**Dr. Dieter Lukas**
Max Planck Institute for Evolutionary Anthropology

*Keywords: Animal behaviour, ecology, evolution, phylogenetics, mating systems, population genetics, human evolution*

**Dr Bart A. Pannebakker**
Wageningen University & Research

*Keywords: Molecular ecology, evolutionary ecology, insects, endosymbionts, biological control, ecological genetics*

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*Keywords: Marine biology, health, disease and epidemiology, contaminants, tagging and tracking, reproduction, mortality and survival, pathogen surveillance, pregnancy, cumulative impacts on health and survival, marine mammals*

**Dr Ryan Y. Wong**
University of Nebraska at Omaha

*Keywords:Animal behaviour, behavioural genomics, behavioural neuroscience, stress response, transcriptomics, mate choice*

**Dr Emily Standen**
University of Ottawa

*Keywords: Biomechanics, evolution, comparative physiology, electromyography, particle imaging velocimetry, comparative morphology, kinematics, phenotypic plasticity, tissue imaging*

**Dr Claudia Wascher**
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**Dr Jonas Rubenson**
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*Keywords: Biomechanics, animal locomotion, muscle mechanics, locomotor energetics, plasticity, musculoskeletal modelling, neuromuscular, bio-machine interface, rehabilitation*

**Dr David Wilson**
Memorial University of Newfoundland

*Keywords: Animal behaviour, animal communication, evolution, ornithology, predator-prey interactions, sexual selection, social behaviour*

**Dr Jose Iriarte-Diaz**
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**Dr Ari S. Friedlaender**
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*Keywords: Foraging, behaviour, marine mammals, predators, diving, Antarctic*

**Professor Madhusudhan Venkadesan**
Yale University

*Keywords: Biomechanics, neuromechanics, motor control, muscle mechanics, human evolution, bio-inspired design*

*mammalian feeding,
muscle mechanics*

**Professor Brooke E. Flammang**
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*Keywords: Comparative biomechanics, functional morphology, fluid dynamics, bioinspired robotics*

**Professor Marcelo R. Sánchez-Villagra**
University of Zurich

*Keywords: Vertebrate Zoology, Palaeontology, Development, Domestication, Mammals, Chicken, Music, South America, Skeleton*

**Dr Olga Panagiotopoulou**
Monash University

*Keywords: Biomechanics, finite element analysis, musculoskeletal biology, locomotion, mastication, fracture mechanics and trauma, comparative functional anatomy, physical anthropology, oral and maxillofacial trauma and implant design*

**Dr Sean A Rands**
University of Bristol

*Keywords: Invertebrates, birds, group behaviour, collective behaviour, plant-pollinator interactions, pollination, predation, parental care*

**Dr Oliver Schülke**
University of Goettingen

*Keywords: Social behaviour, social relationships, social bonds, social networks, dominance hierarchies, coalitions, feeding competition, mate competition, reproductive skew, sociality and health, stress physiology, prenatal stress, primates*

**Professor André Ganswindt**
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*Keywords: Wildlife, endocrine monitoring, non-invasive hormone measurement, physiological stress response, faeces, androgens, progestagens, glucocorticoids*

**Professor Allison Daley**
University of Lausanne

*Keywords: Shale, Fezouata Biota, Predation, Cambrian, Ordovician, Palaeozoic, Radiodonta,*

**Dr Kimberley Mathot**
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*Keywords: Animal behaviour, phenotypic plasticity, developmental plasticity, animal personality,*

**Dr Jennifer Botha**
National Museum, Bloemfontein

*Keywords: Osteohistology, palaeohistology, End-Permian mass extinction*

*Phylogenetic Analyses, Cambrian Explosion, Burgess*

*trade-offs, multi-level variation, foraging ecology, energetics, parental care, parental investment theory*

**Professor Christian Rabeling**
University of Hohenheim

*Keywords: Ants, behavioural ecology, brood parasitism, eusociality, evolution, evolution of social behaviour, mutualisms, social insects, social parasitism, speciation*

**Dr Laura B. Porro**
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*Keywords: Evolutionary biomechanics, functional morphology, vertebrate anatomy, palaeontology, feeding, finite element analysis, early tetrapods, amphibians, reptiles, dinosaurs*

**Dr Etya Amsalem**
Pennsylvania State University

*Keywords: Bees, animal communication, social behaviour, social insects, pheromones/chemical ecology, insect physiology and genetics, the evolution of eusociality, diapause, CO2, bumble bee management and health*

## Physics and Biophysics

### Subject Editors

Professor Miles Padgett FRS and Professor Pietro Cicuta

---

**Dr Marco Palanca**
The University of Sheffield

*Keywords: Biomechanical engineering, biomedical engineering, bone, spine, vertebra, femur, digital image correlation, digital volume correlation, finite element model, stress analysis, strain analysis*

**Professor Jan Sładkowski**
University of Silesia in Katowice

*Keywords: Quantum information, fundamental interactions, astrophysics, econophysics*

**Professor Guy Genin**
Washington University in St. Louis

*Keywords: Interfaces and adhesions in nature, physiology and engineering, mechanobiology*

**Dr Daniel C. Thompson**
Swansea University

*Keywords: String theory, gauge theory, integrability, holography, supergravity*

**Professor Andrew Turberfield**
University of Oxford

*Keywords: DNA nanotechnology*

**Dr Jacopo Grilli**
The Abdus Salam International Centre for Theoretical Physics

*Keywords: Statistical mechanics, stochastic processes, population dynamics, microbial ecology, theoretical ecology, biological physics*

**Dr Peter Munro**
University College London

*Keywords: Biomedical imaging, X-ray phase imaging, optical imaging, optical coherence tomography, phase retrieval, confocal microscopy, numerical electromagnetism, imaging theory, diffraction theory, vectorial diffraction theory, finite different time domain, pseudo spectral methods, edge illumination x-ray phase imaging, coherent x-ray imaging*

**Professor Zhong-Ke Gao**
Tianjin University

*Keywords: Complex network and complex system, nonlinear dynamics and chaotic dynamics, complexity; Time series analysis, multiphase flow; Brain network, machine learning and deep learning, measurement science and technology*

**Professor Robert James Young**
Lancaster University

*Keywords: 2D materials, quantum dots, quantum optics, quantum information processing, epitaxial growth, nanostructures, random number generation, condensed matter, semiconductors, quantum physics*

**Dr Tommaso Tufarelli**
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*Keywords: Quantum Optics and Quantum Information*

**Dr Silvia Vignolini**
University of Cambridge

*Keywords: Nanophotonics, bio-inspired optics, soft matter*

**Dr Talha Erdem**
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*Keywords: Light-emitting diodes, fluorescent materials, self-assembly of nanoparticles, optoelectronic devices made of nanoparticles,* *nonradiative energy transfer between nanoparticles, photonics*

**Dr Chong Li**
University of Cambridge

*Keywords: Semiconductor devices, terahertz science and technology, imaging systems, nanotechnology, plasmonics, acoustics, communication systems*

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*Keywords: Gravitational physics, mathematical physics, loop quantum gravity, quantum cosmology, early universe cosmology*

**Professor Ruth Gregory**
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*Keywords: Gravity in string theory, black holes, gravitational instantons*

**Professor Bodo D. Wilts**
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*Keywords: Biophotonics, bio-inspired functional materials, soft matter, optical materials, optical imaging, 3D volumetric imaging*

**Professor Roland Bouffanais**
University of Ottawa

*Keywords: Swarm, flock, temporal networks, consensus dynamic*

**Professor David A. Meyer**
University of California, San Diego

*Keywords: Quantum algorithms, quantum walks, entanglement, causal sets, data science*

**Dr Diana Fusco**
University of Cambridge

*Keywords: Biological physics, population dynamics, microbial evolution and ecology, computational soft matter*

## Psychology and Cognitive Neuroscience

### Subject Editor

Professor Essi Viding

---

**Dr Anastasia Christakou**
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*Keywords: corticostriatal circuits; corticolimbic systems; functional anatomy; prefrontal cortex; basal ganglia; thalamus; midbrain; decision-making; adolescence; computational model; cognition/affect interaction; structural neuroimaging; functional magnetic resonance imaging; magnetic resonance spectroscopy*

**Dr Carina de Klerk**
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**Dr Teodora Gliga**
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*Keywords: Infancy, Learning, Autism, Conceptual, Language, Curiosity*

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*Keywords: Attitudes and persuasion, affective and cognitive processes, values, behaviour change, ambivalence, mindfulness*

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*Keywords: Music, Creativity, Complex cognition, Brain stimulation, Cognitive enhancement,Problem solving, Neural data analysis*

**Dr Daniela Sammler**
Max Planck Institute for Empirical Aesthetics

*Keywords: Music perception and production, music/language comparison, prosody, song and singing, neural networks*

**Dr Shinya Yamamoto**
Kyoto University

*Keywords: Comparative cognitive science, animal behaviour, primatology, social intelligence, empathy, cooperation, culture, tool-use*

**Dr Mark Walton**
University of Oxford

*Keywords: Psychopharmacology, decision making, reward, electrochemistry, prefontal, striatum, dopamine, rat, mouse, monkey, voltamnetry*

**Dr Gina Grimshaw**
Victoria University of Wellington

*Keywords: Attention, emotion, EEG, psychophysiology, virtual reality*

**Dr Oliver Robinson**
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*Keywords: Anxiety, fear, depression, computational modelling, computational psychiatry, neuroscience, mental health, cognition, decision making, serotonin, fMRI*

**Dr Andre M. Cravo**
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*Keywords: EEG, ERP, temporal perception, psychophysics, attention, timing, cognition*

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*Keywords: Values, personality traits, culture, biases, politics, similarities, working from home, well-being*

**Dr Isabelle Mareschal**
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*Keywords: Visual perception, psychophysics, gaze, eye tracking, visual crowding, adaptation, orientation, saliency*

**Dr Emma Hayiou-Thomas**
University of York

*Keywords: developmental language disorder, language development, language learning, literacy, individual differences, behavioural genetics*

**Professor Marcus Kaiser FRSB**
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**Dr Jennifer Cook**
University of Birmingham

**Dr Bruno Rossion**
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*Keywords: Computational neuroscience, neuroinformatics, connectomics, brain connectivity, computer simulations, in silico medicine, computational modelling, brain development, computational neurology*

*Keywords: Social learning, social cognition, cultural evolution, movement kinematics, autism, dopamine.*

*Keywords: Human face recognition, psychophysics, EEG, FMRI, human intracerebral recordings, prosopagnosia*

**Professor Zoltan Dienes**
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**Dr Dénes Szűcs**
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*Keywords: Mathematical cognition, numerical cognition, mathematical development, replication, meta-analysis, cognitive electro-physiology*

**Dr Alexa Morcom**
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**Dr Christina Demski**
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*Keywords: Risk perceptions and communication, attitudes and responses to emerging and/or complex socio-technical and environmental issues (e.g. energy technologies and systems, geoengineering, climate change), mixed-methods*

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*Keywords: Intelligence, evolution, cognitive abilities, animal cognition, canine cognition, behavioural genetics*

**Professor Martin Pickering**
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*Keywords: Production, comprehension, dialogue, joint action, and bilingualism*

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**Dr Rochelle Ackerley**
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University of Vienna

*Keywords: Social cognition and behavior, empathy, theory of mind, reward, autism, fMRI, neuropharmacology*

CNRS

*Keywords: Afferent, tactile, mechanoreceptor, thermoreceptor, nociceptor, peripheral nervous system, somatosensory cortex, microneurography, MRI, EEG, MEG, psychophysics, behaviour, nerve stimulation, affective touch, amputees*

*Keywords: Social psychology, individual differences, genetic essentialism, gender psychology, existential psychology, sexuality*

**Dr Kim-Pong Tam**
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*Keywords: Aggressive (human) behaviour, social information processing, hostility biases, forensic psychology, virtual reality, aggression assessment, aggression treatment*

## Science, Society and Policy

### Subject Editor

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Additional details regarding Science, Society and Policy are available at this link.

---

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**Prof Ambuj D. Sagar**

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**Prof Miranda Lowe**
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**Prof Chris J Budd**
University of Bath

*Keywords: Public Engagement and Maths Education*

# 2. Daftar Isi Volume 8, Issue 2

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## Table of Contents

New articles are published weekly in the latest journal issue, at the top of their section of the *Table of Contents*. The latest issue closes at the end of the month.

## Biochemistry, cellular and molecular biology

☐ Research articles

### Creation of a peptide database of corneous beta-proteins of marine turtles for the identification of tortoiseshell: archaeological combs as case study

Caroline Solazzo, Jean Soulat and Timothy Cleland

Published: **24 February 2021** | Article ID: **201857**

https://doi.org/10.1098/rsos.201857

Abstract | Full text | PDF | References

Preview Abstract

Back to top

Tortoiseshell is a proteinaceous material derived from the scutes of marine turtles, and was shaped into an abundance of objects, especially luxurious items, at its peak in the seventeenth and eighteenth century. It has continued to be used even after the ...

☐ Research articles

### Cooperation of partially transformed clones: an invisible force behind the early stages of carcinogenesis

Alessandro Esposito

Published: **10 February 2021** | Article ID: **201532**

https://doi.org/10.1098/rsos.201532

Abstract | Full text | PDF | References

Preview Abstract

Most tumours exhibit significant heterogeneity and are best described as communities of cellular populations competing for resources. Growing experimental evidence also suggests that cooperation between cancer clones is important as well for the ...

---

## Chemistry

Published in collaboration with the Royal Society of Chemistry

☐ Research articles

### Rapid synthesis and characterization of silver-loaded graphene oxide nanomaterials and their antibacterial applications

Jiang Zhu, Haitao Ni, Chunyan Hu, Yuxiang Zhu, Jinxia Cai, Song Liu, Jie Gao, Heshan Yang and Hongpan Liu

Published: **24 February 2021** | Article ID: **201744**

https://doi.org/10.1098/rsos.201744

Abstract | Full text | PDF | References

Preview Abstract

With the promising potential application of Ag/graphene-based nanomaterials in medicine and engineering materials, the large-scale production has attracted great interest of researchers on the basis of green synthesis. In this study, water-soluble silver/...

Back to top

☐ Research articles

## Synthesis and pharmacological characterization of glucopyranosyl-conjugated benzyl derivatives as novel selective cytotoxic agents against colon cancer

Boqiao Fu, Yingjie Li, Shaoyong Peng, Xiaolin Wang, Jingying Hu, Long Lv, Caifen Xia, Dai Lu and Caiqin Qin

Published: **24 February 2021** | Article ID: **201642**

https://doi.org/10.1098/rsos.201642

Abstract | Full text | PDF | References

Preview Abstract

Glucopyranosyl-conjugated benzyl derivatives containing a [1,2,3]-triazole linker were synthesized. Benzyl served as an important pharmacophore in anti-cancer compounds. Compound 8d inhibited the proliferation of colorectal cancer cells with the potency ...

---

☐ Research articles

## U(VI) adsorption in water by sodium alginate modified *Bacillus megaterium*

Dianxin Li, Yiqing Yang, Peng Zhang, Jiangang Liu, Tao Li and Junwei Yang

Published: **24 February 2021** | Article ID: **202098**

https://doi.org/10.1098/rsos.202098

Abstract | Full text | PDF | References

Preview Abstract

The surface of *Bacillus megaterium* was modified by coating sodium alginate. The modified *B. megaterium* before and after adsorption were characterized by SEM, FTIR and XPS. The effects of pH, reaction time, initial U(VI) concentration and adsorbent dosage ...

---

☐ Reply

## Factorial design-assisted reversed phase-high performance liquid chromatography method for simultaneous determination of fluconazole, itraconazole and terbinafine

Aya Roshdy, Heba Elmansi, Shereen Shalan and Amina El-Brashy

Published: **17 February 2021** | Article ID: **202130**

Back to top

https://doi.org/10.1098/rsos.202130

Abstract | Full text | PDF | References

Preview Abstract

A $2^3$ full factorial design model was used for the development of a new high performance liquid chromatography method with UV detection to estimate three antifungal drugs simultaneously. Fluconazole (FLU), itraconazole (ITR) and terbinafine (TRH) are co-...

---

☐ | Research articles

## An aptasensor using ceria electrodeposited-screen-printed carbon electrode for detection of epithelial sodium channel protein as a hypertension biomarker

Yeni Wahyuni Hartati, Dina Ratna Komala, Diana Hendrati, Shabarni Gaffar, Ari Hardianto, Yulia Sofiatin and Husein Hernandi Bahti

Published: **17 February 2021** | Article ID: **202040**

https://doi.org/10.1098/rsos.202040

Abstract | Full text | PDF | References

Preview Abstract

Epithelial sodium channel (ENaC) is a transmembrane protein that has an essential role in maintaining the levels of sodium in blood plasma. A person with a family history of hypertension has a high enough amount of ENaC protein in the kidneys or other ...

---

☐ | Research articles

## Structure validation of oxidized poly (2-hydroxyethyl acrylate) with multiple aldehyde groups and its application for collagen modification

Baohua Liu, Jian Wang, Lili Ji, Ting Bai, Yin Zhang and Dayu Liu

Published: **17 February 2021** | Article ID: **201892**

https://doi.org/10.1098/rsos.201892

Abstract | Full text | PDF | References

Preview Abstract

The structural characteristic of oxidized poly (2-hydroxyethyl acrylate) (OP) was confirmed by high-performance liquid chromatography, gel permeation chromatography and hydroxylamine hydrochloride titration. The results demonstrated that OP prepared ...

Back to top

☐ Research articles

### pH-sensitive thiamethoxam nanoparticles based on bimodal mesoporous silica for improving insecticidal efficiency

Wenjing Li, Qi Wang, Fang Zhang, Hui Shang, Shiyang Bai and Jihong Sun

Published: **17 February 2021** | Article ID: **201967**

https://doi.org/10.1098/rsos.201967

Abstract | Full text | PDF | References

Preview Abstract

In this study, we synthesized pH-sensitive thiamethoxam-3-(2-aminoethylamino) propyl-bimodal mesoporous silica (P/Thi-NN-BMMs) nanoparticles (NPs). We used this bimodal mesoporous silica (BMMs) mesoporous material as a carrier based on the principle of …

☐ Research articles

### The utilization of micro-mesoporous carbon-based filler in the P84 hollow fibre membrane for gas separation

Triyanda Gunawan, Nurul Widiastuti, Hamzah Fansuri, Wan Norharyati Wan Salleh, Ahmad Fauzi Ismail, Rijia Lin, Juliuz Motuzas and Simon Smart

Published: **10 February 2021** | Article ID: **201150**

https://doi.org/10.1098/rsos.201150

Abstract | Full text | PDF | References

Preview Abstract

This research involved carrying out a unique micro-mesoporous carbon particle incorporation into P84 co-polyimide membrane for improved gas separation performance. The carbon filler was prepared using a hard template method from zeolite and known as …

☐ Research articles

### Computational analysis the relationships of energy and mechanical properties with sensitivity for FOX-7 based PBXs via MD simulation

Jianbo Fu, Baoguo Wang, Yafang Chen, Yunchuan Li, Xing Tan, Biyuan Wang and Baoyun Ye

Published: **10 February 2021** | Article ID: **200345**

https://doi.org/10.1098/rsos.200345

Back to top

Abstract | Full text | PDF | References

Preview Abstract

Molecular dynamics (MD) simulations have been applied to investigate 1, 1-diamino-2, 2-dinitroethene (FOX-7) crystal and FOX-7 (011)-based polymer-bonded explosives (PBXs) with four typical polymers, polyethylene glycol (PEG), fluorine-polymer ($F_{2603}$), …

---

☐ Research articles

## The significance of long-range correction to the hydroperoxyl radical-scavenging reaction of trans-resveratrol and gnetin C

Vera Khoirunisa, Febdian Rusydi, Lusia S. P. Boli, Ira Puspitasari, Heni Rachmawati and Hermawan K. Dipojono

Published: **10 February 2021** | Article ID: **201127**

https://doi.org/10.1098/rsos.201127

Abstract | Full text | PDF | References

Preview Abstract

Density functional theory has been gaining popularity for studying the radical scavenging activity of antioxidants. However, only a few studies investigate the importance of calculation methods on the radical-scavenging reactions. In this study, we …

---

☐ Research articles

## Effect of B-site Co substitution on the structure and magnetic properties of nanocrystalline neodymium orthoferrite synthesized by auto-combustion

Edwin Akongnwi Nforna, Patrice Kenfack Tsobnang, Roussin Lontio Fomekong, Hypolite Mathias Kamta Tedjieukeng, John Ngolui Lambi and Julius Numbonui Ghogomu

Published: **03 February 2021** | Article ID: **201883**

https://doi.org/10.1098/rsos.201883

Abstract | Full text | PDF | References

Preview Abstract

Samples of cobalt-doped neodymium orthoferrite compounds, $NdCo_xFe_{1-x}O_3$ ($0.0 \leq x \leq 0.5$) were synthesized via glycine auto-combustion between 250 and 300°C and calcined at 500°C for 2 h. X-ray diffraction showed that all compounds had an orthorhombic …

Back to top

☐ Research articles

## The impact of trace metal cations and absorbed water on colour transition of turquoise

Xueding Wang and Ying Guo

Published: **03 February 2021** | Article ID: **201110**

https://doi.org/10.1098/rsos.201110

Abstract | Full text | PDF | References

Preview Abstract

Thirty-five gem-quality turquoise samples with various colours were investigated using energy-dispersive X-ray fluorescence spectroscopy, ultraviolet–visible spectroscopy, Fourier-transform infrared spectroscopy and scanning electron microscopy. Sample ...

☐ Research articles

## Simultaneous estimation of troxerutin and calcium dobesilate in presence of the carcinogenic hydroquinone using green spectrofluorimetric method

M. M. Tolba, M. M. Salim and M. El-Awady

Published: **03 February 2021** | Article ID: **201888**

https://doi.org/10.1098/rsos.201888

Abstract | Full text | PDF | References

Preview Abstract

In the present study, we conducted two facile and highly sensitive spectrofluorimetric approaches in order to quantify the vasoprotective agents; troxerutin (TROX) and calcium dobesilate (DOB) in the presence of hydroquinone (HQ) (as a highly toxic ...

# Computer science and artificial intelligence

☐ Research articles

## Understanding spatial patterns in rape reporting delays

Konstantin Klemmer, Daniel B. Neill and Stephen A. Jarvis

Published: **10 February 2021** | Article ID: **201795**

Back to top

https://doi.org/10.1098/rsos.201795

Abstract | Full text | PDF | References

⌄ Preview Abstract

Under-reporting and delayed reporting of rape crime are severe issues that can complicate the prosecution of perpetrators and prevent rape survivors from receiving needed support. Building on a massive database of publicly available criminal reports from …

---

☐ 🔓 | Research articles

### Stable leaders pave the way for cooperation under time-dependent exploration rates

Flávio L. Pinheiro, Jorge M. Pacheco and Francisco C. Santos

Published: **03 February 2021** | Article ID: **200910**

https://doi.org/10.1098/rsos.200910

Abstract | Full text | PDF | References

⌄ Preview Abstract

The exploration of different behaviours is part of the adaptation repertoire of individuals to new environments. Here, we explore how the evolution of cooperative behaviour is affected by the interplay between exploration dynamics and social learning, in …

---

## Earth and environmental science

☐ 🔓 | Research articles

### Organic agriculture and rural networks in the mountain environments of Região serrana fluminense, Rio de Janeiro, Brazil

Nádia Jarouche Aun and Renato Linhares de Assis

Published: **24 February 2021** | Article ID: **200498**

https://doi.org/10.1098/rsos.200498

Abstract | Full text | PDF | References

⌄ Preview Abstract

This paper presents a case study on organic agriculture at Região Serrana Fluminense, Rio de Janeiro State, Brazil. We sought to understand what was the role of organic farming, and if it can be cons

Back to top

an aggregating element between different kinds …

---

☐ Research articles

## Climate change affected the spatio-temporal occurrence of disasters in China over the past five centuries

Chuan Yan, Huidong Tian, Xinru Wan, Jinxing He, Guoyu Ren, Ulf Büntgen, Nils Chr. Stenseth and Zhibin Zhang

Published: **17 February 2021** | Article ID: **200731**

https://doi.org/10.1098/rsos.200731

Abstract | Full text | PDF | References

Preview Abstract

Climate change may contribute to the spatio-temporal occurrence of disasters. Long-term studies of either homogeneous or heterogeneous responses of historical disasters to climate change are, however, limited by the quality and quantity of the available …

---

☐ Research articles

## Carrier and dilution effects of $CO_2$ on thoron emissions from a zeolitized tuff exposed to subvolcanic temperatures

Silvio Mollo, Piergiorgio Moschini, Gianfranco Galli, Paola Tuccimei, Carlo Lucchetti, Gianluca Iezzi and Piergiorgio Scarlato

Published: **10 February 2021** | Article ID: **201539**

https://doi.org/10.1098/rsos.201539

Abstract | Full text | PDF | References

Preview Abstract

Radon ($^{222}$Rn) and thoron ($^{220}$Rn) are two isotopes belonging to the noble gas radon (*sensu lato*) that is frequently employed for the geochemical surveillance of active volcanoes. Temperature gradients operating at subvolcanic conditions may induce chemical …

---

# Ecology, acoustics, and physiology

☐ Research articles

Back to top

### The everyday acoustic environment and its association with human heart rate: evidence from real-world data logging with hearing aids and wearables

Jeppe H. Christensen, Gabrielle H. Saunders, Michael Porsbo and Niels H. Pontoppidan

Published: **17 February 2021** | Article ID: **201345**

https://doi.org/10.1098/rsos.201345

Abstract | Full text | PDF | References

⌄ Preview Abstract

We investigate the short-term association between multidimensional acoustic characteristics of everyday ambient sound and continuous mean heart rate. We used in-market data from hearing aid users who logged ambient acoustics via smartphone-connected …

---

## Ecology, conservation, and global change biology

☐ | **Research articles**

### Individual-based acoustic variation of the alarm calls in the long-tailed ground squirrel

Denis Goncharov, Richard Policht, Lucie Hambálková, Viktor Salovarov and Vlastimil Hart

Published: **24 February 2021** | Article ID: **200147**

https://doi.org/10.1098/rsos.200147

Abstract | Full text | PDF | References

⌄ Preview Abstract

Based on their phylogenetic position, Nearctic ground squirrels are closest relatives to the long-tailed ground squirrel *Urocitellus undulates* even though it has Palaearctic distribution. We aimed to investigate the variability of alarm calls of the long-…

☐ | **Research articles**

### Temperature surpasses the effects of velocity and turbulence on swimming performance of two invasive non-native fish species

V. Muhawenimana, J. R. Thomas, C. A. M. E. Wilson, J. Nefjodova, A. C. Chapman, F. C. Williams, D. G. Davies, S. W. Griffiths and J. Cable

Published: **24 February 2021** | Article ID: **201516**

^
Back to top

https://doi.org/10.1098/rsos.201516

Abstract | Full text | PDF | References

Preview Abstract

Global climate change continues to impact fish habitat quality and biodiversity, especially in regard to the dynamics of invasive non-native species. Using individual aquaria and an open channel flume, this study evaluated the effects of water temperature,...

---

☐ 🔓 | Research articles

### The search for a sustainable alternative to slash-and-burn agriculture in the World's rain forests: the Guama Model and its implementation

Michael Hands

Published: **17 February 2021** | Article ID: **201204**

https://doi.org/10.1098/rsos.201204

Abstract | Full text | PDF | References

Preview Abstract

This account describes the context, history and outcomes of a series of studies into the ecology of slash-and-burn (S-B) agriculture in the world's humid tropics. These studies, which began in the mid-1980s, identified promising lines of research and ...

---

☐ 🔓 | Research articles

### Kin relationships in cultural species of the marine realm: case study of a matrilineal social group of sperm whales off Mauritius island, Indian Ocean

Francois Sarano, Justine Girardet, Véronique Sarano, Hugues Vitry, Axel Preud'homme, René Heuzey, Ana M. Garcia-Cegarra, Bénédicte Madon, Fabienne Delfour, ... **See all authors**

Published: **10 February 2021** | Article ID: **201794**

https://doi.org/10.1098/rsos.201794

Abstract | Full text | PDF | References

Preview Abstract

Understanding the organization and dynamics of social groups of marine mammals through the study of kin relationships is particularly challenging. Here, we studied a stable social group of sperm whales off Mauritius, using underwater observations, ...

Back to top

☐ | Research articles

### Comparison of the temporal efficacy of Aquatain surface films for the control of *Anopheles arabiensis* and *Ochlerotatus caspius* larvae from Sudan

Alaa Mahmoud Ali Almalik, R. Guy Reeves and Rasha Siddig Azrag

Published: **10 February 2021** | Article ID: **200980**

https://doi.org/10.1098/rsos.200980

Abstract | Full text | PDF | References

Preview Abstract

Aquatain mosquito formulation (AMF) is a surfactant that spreads across the surface of water bodies to produce a monomolecular film. This study experimentally evaluates the temporal efficacy of AMF against aquatic stages of *Anopheles arabiensis* and ...

---

☐ | Research articles

### New insights into large tropical tree mass and structure from direct harvest and terrestrial lidar

Andrew Burt, Matheus Boni Vicari, Antonio C. L. da Costa, Ingrid Coughlin, Patrick Meir, Lucy Rowland and Mathias Disney

Published: **10 February 2021** | Article ID: **201458**

https://doi.org/10.1098/rsos.201458

Abstract | Full text | PDF | References

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All Journals

Sections

---

☐ | Research articles

### A novel metabarcoding primer pair for environmental DNA analysis of Cephalopoda (Mollusca) targeting the nuclear 18S rRNA region

Daniëlle S. W. de Jonge, Véronique Merten, Till Bayer, Oscar Puebla, Thorsten B. H. Reusch and Henk-Jan T. Hoving

Published: **10 February 2021** | Article ID: **201388**

Back to top

https://doi.org/10.1098/rsos.201388

Abstract | Full text | PDF | References

Preview Abstract

Cephalopods are pivotal components of marine food webs, but biodiversity studies are hampered by challenges to sample these agile marine molluscs. Metabarcoding of environmental DNA (eDNA) is a potentially powerful technique to study oceanic cephalopod …

---

☐ Research articles

## Dental microwear texture analysis along reptile tooth rows: complex variation with non-dietary variables

Jordan Bestwick, David M. Unwin, Donald M. Henderson and Mark A. Purnell

Published: **03 February 2021** | Article ID: **201754**

https://doi.org/10.1098/rsos.201754

Abstract | Full text | PDF | References

Preview Abstract

Dental microwear texture analysis (DMTA) is a powerful technique for reconstructing the diets of extant and extinct taxa. Few studies have investigated intraspecific microwear differences along with tooth rows and the influence of endogenous non-dietary …

---

☐ Research articles

## Population-specific sex and size variation in long-term foraging ecology of belugas and narwhals

Marie Louis, Mikkel Skovrind, Eva Garde, Mads Peter Heide-Jørgensen, Paul Szpak and Eline D. Lorenzen

Published: **03 February 2021** | Article ID: **202226**

https://doi.org/10.1098/rsos.202226

Abstract | Full text | PDF | References

Preview Abstract

Intraspecific variation in resource use by individuals of different age, sex or size may reflect differing energetic requirements and physiological constraints. Males and females often show differences in diet owing to sexual size dimorphism, different …

Back to top

# Engineering

☐ Research articles

## An experimental investigation to model wheezing in lungs

A. L. Gregory, A. Agarwal and J. Lasenby

Published: **24 February 2021** | Article ID: **201951**

https://doi.org/10.1098/rsos.201951

Abstract | Full text | PDF | References

Preview Abstract

A quarter of the world's population experience wheezing. These sounds have been used for diagnosis since the time of the Ebers Papyrus (*ca* 1500 BC). We know that wheezing is a result of the oscillations of the airways that make up the lung. However, the …

☐ Review articles

## A survey of human judgement and quantitative forecasting methods

Maximilian Zellner, Ali E. Abbas, David V. Budescu and Aram Galstyan

Published: **24 February 2021** | Article ID: **201187**

https://doi.org/10.1098/rsos.201187

Abstract | Full text | PDF | References

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This paper's top-level goal is to provide an overview of research conducted in the many academic domains concerned with forecasting. By providing a summary encompassing these domains, this survey connects them, establishing a common ground for future …

☐ Research articles

## The validation of new phase-dependent gait stability measures: a modelling approach

Jian Jin, Dinant Kistemaker, Jaap H. van Dieën, Andreas Daffertshofer and Sjoerd M. Bruijn

Published: **10 February 2021** | Article ID: **201122**

https://doi.org/10.1098/rsos.201122

Back to top

Abstract | Full text | PDF | References

Preview Abstract

Identification of individuals at risk of falling is important when designing fall prevention methods. Current measures that estimate gait stability and robustness appear limited in predicting falls in older adults. Inspired by recent findings on changes …

---

# Mathematics

☐ Research articles

## Cost and social distancing dynamics in a mathematical model of COVID-19 with application to Ontario, Canada

I. R. Moyles, J. M. Heffernan and J. D. Kong

Published: **24 February 2021** | Article ID: **201770**

https://doi.org/10.1098/rsos.201770

Abstract | Full text | PDF | References

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A mathematical model of COVID-19 is presented where the decision to increase or decrease social distancing is modelled dynamically as a function of the measured active and total cases as well as the perceived cost of isolating. Along with the cost of …

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☐ Research articles

## Network geometry and market instability

Areejit Samal, Hirdesh K. Pharasi, Sarath Jyotsna Ramaia, Harish Kannan, Emil Saucan, Jürgen Jost and Anirban Chakraborti

Published: **24 February 2021** | Article ID: **201734**

https://doi.org/10.1098/rsos.201734

Abstract | Full text | PDF | References

Preview Abstract

The complexity of financial markets arise from the strategic interactions among agents trading stocks, which manifest in the form of vibrant correlation patterns among stock prices. Over the past few decades, complex financial markets have often been …

Back to top

☐ Research articles

### A minimalist model for coevolving supply and drainage networks

Shashank Kumar Anand, Milad Hooshyar, Jan Martin Nordbotten and Amilcare Porporato

Published: **17 February 2021** | Article ID: **201407**

https://doi.org/10.1098/rsos.201407

Abstract | Full text | PDF | References

Preview Abstract

Numerous complex systems, both natural and artificial, are characterized by the presence of intertwined supply and/or drainage networks. Here, we present a minimalist model of such coevolving networks in a spatially continuous domain, where the obtained ...

---

☐ Research articles

### Effectiveness and feasibility of convalescent blood transfusion to reduce COVID-19 fatality ratio

Xi Huo, Xiaodan Sun, Nicola Bragazzi and Jianhong Wu

Published: **10 February 2021** | Article ID: **202248**

https://doi.org/10.1098/rsos.202248

Abstract | Full text | PDF | References

Preview Abstract

*Background:* As of December 2020, COVID-19 has spread all over the world with more than 81 million cases and more than 1.8 million deaths. The rapidly increasing number of patients mandates the consideration of potential treatments for patients under ...

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☐ Research articles

### An improved algorithm for the maximal information coefficient and its application

Dan Cao, Yuan Chen, Jin Chen, Hongyan Zhang and Zheming Yuan

Published: **10 February 2021** | Article ID: **201424**

https://doi.org/10.1098/rsos.201424

Abstract | Full text | PDF | References

Back to top

Preview Abstract

The maximal information coefficient (MIC) captures both linear and nonlinear correlations between variable pairs. In this paper, we proposed the BackMIC algorithm for MIC estimation. The BackMIC algorithm adds a searching back process on the ...

## Organismal and evolutionary biology

☐ Research articles

### Earliest Palaeocene purgatoriids and the initial radiation of stem primates

Gregory P. Wilson Mantilla, Stephen G. B. Chester, William A. Clemens, Jason R. Moore, Courtney J. Sprain, Brody T. Hovatter, William S. Mitchell, Wade W. Mans, ... **See all authors**

Published: **24 February 2021** | Article ID: **210050**

https://doi.org/10.1098/rsos.210050

Abstract | Full text | PDF | References

Preview Abstract

Plesiadapiform mammals, as stem primates, are key to understanding the evolutionary and ecological origins of Pan-Primates and Euarchonta. The Purgatoriidae, as the geologically oldest and most primitive known plesiadapiforms and one of the oldest known ...

☐ Research articles

### A new species of *Proegernia* from the Namba Formation in South Australia and the early evolution and environment of Australian egerniine skinks

K. M. Thorn, M. N. Hutchinson, M. S. Y. Lee, N. J. Brown, A. B. Camens and T. H. Worthy

Published: **17 February 2021** | Article ID: **201686**

https://doi.org/10.1098/rsos.201686

Abstract | Full text | PDF | References

Preview Abstract

The diverse living Australian lizard fauna contrasts greatly with their limited Oligo-Miocene fossil record. New Oligo-Miocene fossil vertebrates from the Namba Formation (south of Lake Frome, South Australia) were uncovered from multiple expeditions from ...

Back to top

☐ Research articles

### Revisiting the classification of squamate adhesive setae: historical, morphological and functional perspectives

Austin M. Garner and Anthony P. Russell

Published: **17 February 2021** | Article ID: **202039**

https://doi.org/10.1098/rsos.202039

Abstract | Full text | PDF | References

Preview Abstract

Research on gecko-based adhesion has become a truly interdisciplinary endeavour, encompassing many disciplines within the natural and physical sciences. Gecko adhesion occurs by the induction of van der Waals intermolecular (and possibly other) forces ...

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☐ Research articles

### Group housing and social dominance hierarchy affect circadian activity patterns in mice

Yuri Robbers, Mayke M. H. Tersteeg, Johanna H. Meijer and Claudia P. Coomans

Published: **17 February 2021** | Article ID: **201985**

https://doi.org/10.1098/rsos.201985

Abstract | Full text | PDF | References

Preview Abstract

In this study, we investigated the effect of social environment on circadian patterns in activity by group housing either six male or six female mice together in a cage, under regular light–dark cycles. Based on the interactions among the animals, the ...

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☐ Research articles

### Are publications on zoological taxonomy under attack?

Ângelo Parise Pinto, Gabriel Mejdalani, Ross Mounce, Luís Fábio Silveira, Luciane Marinoni and José Albertino Rafael

Published: **10 February 2021** | Article ID: **201617**

https://doi.org/10.1098/rsos.201617

Abstract | Full text | PDF | References

Back to top

Preview Abstract

Taxonomy is essential to biological sciences and the priority field in face of the biodiversity crisis. The industry of scientific publications has made extensive promotion and display of bibliometric indexes, resulting in side effects such as the Journal …

---

☐ Research articles

### Slaying the last unicorn: discovery of histones in the microalga *Nanochlorum eucaryotum*

Valerie W. C. Soo and Tobias Warnecke

Published: **10 February 2021** | Article ID: **202023**

https://doi.org/10.1098/rsos.202023

Abstract | Full text | PDF | References

Preview Abstract

Histones are the principal constituents of eukaryotic chromatin. The four core histones (H2A, H2B, H3 and H4) are conserved across sequenced eukaryotic genomes and therefore thought to be universal to eukaryotes. In the early 1980s, however, a series of …

---

☐ Research articles

### Using strontium isotopes to determine philopatry and dispersal in primates: a case study from Kibale National Park

Marian I. Hamilton, Diego P. Fernandez and Sherry V. Nelson

Published: **10 February 2021** | Article ID: **200760**

https://doi.org/10.1098/rsos.200760

Abstract | Full text | PDF | References

Preview Abstract

Strontium isotope ratios ($^{87}$Sr/$^{86}$Sr) allow researchers to track changes in mobility throughout an animal's life and could theoretically be used to reconstruct sex-biases in philopatry and dispersal patterns in primates. Dispersal patterns are a life-…

---

☐ Research articles

### Non-kin adoption in the common vampire bat

Imran Razik, Bridget K. G. Brown, Rachel A. Page and Gerald G. Carter

Back to top

Published: **10 February 2021** | Article ID: **201927**

https://doi.org/10.1098/rsos.201927

Abstract | Full text | PDF | References

Preview Abstract

Individual animals across many different species occasionally ‘adopt’ unrelated, orphaned offspring. Although adoption may be best explained as a by-product of adaptive traits that enhance parental care or promote the development of parental skills, one …

---

☐ 🔓 | **Research articles**

### Contributions of spatial and temporal control of step length symmetry in the transfer of locomotor adaptation from a motorized to a non-motorized split-belt treadmill

Daniel L. Gregory, Frank C. Sup and Julia T. Choi

Published: **10 February 2021** | Article ID: **202084**

https://doi.org/10.1098/rsos.202084

Abstract | Full text | PDF | References

Preview Abstract

Walking requires control of where and when to step for stable interlimb coordination. Motorized split-belt treadmills which constrain each leg to move at different speeds lead to adaptive changes to limb coordination that result in after-effects (e.g. …

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☐ 🔓 | **Registered report**

### Evaluating the influence of action- and subject-specific factors on chimpanzee action copying

Alba Motes-Rodrigo, Roger Mundry, Josep Call and Claudio Tennie

Published: **10 February 2021** | Article ID: **200228**

https://doi.org/10.1098/rsos.200228

Abstract | Full text | PDF | References

Preview Abstract

The ability to imitate has been deemed crucial for the emergence of human culture. Although non-human animals also possess culture, the acquisition mechanisms underlying behavioural variation between populations in other species is still under debate. It …

Back to top

☐ | Research articles

### Juvenile hormone III skipped bisepoxide is widespread in true bugs (Hemiptera: Heteroptera)

Keiji Matsumoto, Toyomi Kotaki, Hideharu Numata, Tetsuro Shinada and Shin G. Goto

Published: **03 February 2021** | Article ID: **202242**

https://doi.org/10.1098/rsos.202242

Abstract | Full text | PDF | References

Preview Abstract

Juvenile hormone (JH) plays important roles in almost every aspect of insect development and reproduction. JHs are a group of acyclic sesquiterpenoids, and their farnesol backbone has been chemically modified to generate a homologous series of hormones in …

---

☐ | Research articles

### Genomic variation, population history and within-archipelago adaptation between island bird populations

Claudia A. Martin, Claire Armstrong, Juan Carlos Illera, Brent C. Emerson, David S. Richardson and Lewis G. Spurgin

Published: **03 February 2021** | Article ID: **201146**

https://doi.org/10.1098/rsos.201146

Abstract | Full text | PDF | References

Preview Abstract

Oceanic island archipelagos provide excellent models to understand evolutionary processes. Colonization events and gene flow can interact with selection to shape genetic variation at different spatial scales. Landscape-scale variation in biotic and …

---

☐ | Research articles

### Consensus of travel direction is achieved by simple copying, not voting, in free-ranging goats

D. W. E. Sankey, L. R. O'Bryan, S. Garnier, G. Cowlishaw, P. Hopkins, M. Holton, I. Fürtbauer and A. J. King

Published: **03 February 2021** | Article ID: **201128**

Back to top

https://doi.org/10.1098/rsos.201128

Abstract | Full text | PDF | References

Preview Abstract

For group-living animals to remain cohesive they must agree on where to travel. Theoretical models predict shared group decisions should be favoured, and a number of empirical examples support this. However, the behavioural mechanisms that underpin shared ...

☐ Research articles

### Effects of social experience, aggressiveness and comb size on contest success in male domestic fowl

Anna Favati, Hanne Løvlie and Olof Leimar

Published: **03 February 2021** | Article ID: **201213**

https://doi.org/10.1098/rsos.201213

Abstract | Full text | PDF | References

Preview Abstract

The ability to dominate conspecifics and thereby gain access to resources depends on a number of traits and skills. Experience of dominance relationships during development is a potential source of learning such skills. We here study the importance of ...

## Psychology and cognitive neuroscience

☐ Research articles

### Video game play is positively correlated with well-being

Niklas Johannes, Matti Vuorre and Andrew K. Przybylski

Published: **17 February 2021** | Article ID: **202049**

https://doi.org/10.1098/rsos.202049

Abstract | Full text | PDF | References

Preview Abstract

People have never played more video games, and many stakeholders are worried that this activity might be bad for players. So far, research has not had adequate data to test whether these worries are justified and if policymakers should act to regulate ...

Back to top

☐ 🔓 Registered report

### Stress and worry in the 2020 coronavirus pandemic: relationships to trust and compliance with preventive measures across 48 countries in the COVIDiSTRESS global survey

Andreas Lieberoth, Shiang-Yi Lin, Sabrina Stöckli, Hyemin Han, Marta Kowal, Rebekah Gelpi, Stavroula Chrona, Thao Phuong Tran, Alma Jeftić, Jesper Rasmussen, **... See all authors**

Published: **10 February 2021** | Article ID: **200589**

https://doi.org/10.1098/rsos.200589

Abstract | Full text | PDF | References

Preview Abstract

The COVIDiSTRESS global survey collects data on early human responses to the 2020 COVID-19 pandemic from 173 429 respondents in 48 countries. The open science study was co-designed by an international consortium of researchers to investigate how ...

---

☐ 🔓 Research articles

### An updated investigation of the multidimensional structure of language lateralization in left- and right-handed adults: a test–retest functional transcranial Doppler sonography study with six language tasks

Z. V. J. Woodhead, P. A. Thompson, E. M. Karlsson and D. V. M. Bishop

Published: **03 February 2021** | Article ID: **200696**

https://doi.org/10.1098/rsos.200696

Abstract | Full text | PDF | References

Preview Abstract

A previous study we reported in this journal suggested that left and right-handers may differ in their patterns of lateralization for different language tasks (Woodhead *et al.* 2019 *R. Soc. Open Sci.* 6, 181801. (doi:10.1098/rsos.181801)). However, it had ...

---

## Corrections

☐ 🔓 Corrections

Back to top

## Correction to ‘Sensorimotor control dynamics and cultural biases: learning to move in the right (or left) direction’

Amanda Waterman, Oscar Giles, Jelena Havelka, Sumaya Ali, Peter Culmer, Richard Wilkie and Mark Mon-Williams

Published: **24 February 2021** | Article ID: **210231**

https://doi.org/10.1098/rsos.210231

This article corrects the following

Research article

**Sensorimotor control dynamics and cultural biases: learning to move in the right (or left) direction**

https://doi.org/10.1098/rsos.160806

**... See all authors**

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☐ Corrections

## Correction to ‘Augmenting disease maps: a Bayesian meta-analysis approach’

Farzana Jahan, Earl W. Duncan, Susanna M. Cramb, Peter D. Baade and Kerrie L. Mengersen

Published: **10 February 2021** | Article ID: **210085**

https://doi.org/10.1098/rsos.210085

This article corrects the following

Research articles

**Augmenting disease maps: a Bayesian meta-analysis approach**

https://doi.org/10.1098/rsos.192151

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VOLUME 7, ISSUE 8, ROYAL SOCIETY OPEN SCIENCE 5 AUGUST 2020

Full text | PDF

Back to top

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Volume 8, Issue 2

Editor-In-Chief

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- evolution (8606)
- ecology (8353)
- behaviour (6721)
- environmental science (2330)
- cognition (2145)
- neuroscience (2069)
- computational biology (1836)
- biophysics (1798)
- biomechanics (1756)
- applied mathematics (1680)
- health and disease and epidemiology (1661)
- molecular biology (1336)
- materials science (1332)
- genetics (1312)
- cellular biology (1228)
- biochemistry (1227)
- palaeontology (1183)
- developmental biology (1154)
- biomathematics (1142)
- systems biology (1022)
- mechanical engineering (983)
- physiology (970)

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Back to top

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Back to top

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| **Title** | The significance of long-range correction to the hydroperoxyl radical-scavenging reaction of trans-resveratrol and gnetin C |
| **Authors** | Khoirunisa, Vera<br>Rusydi, Febdian<br>Boli, Lusia<br>Puspitasari, Ira<br>Rachmawati, Heni<br>Dipojono, Hermawan |
| **Date Submitted** | 25-Jun-2020 |

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# The significance of long-range correction to the hydroperoxyl radical-scavenging reaction of trans-resveratrol and gnetin C

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| Subject: | Computational chemistry < CHEMISTRY |
| Keywords: | radical-scavenging reaction, long-range correction, dispersion correction, density functional theory, hydrogen atom transfer |
| Subject Category: | Chemistry |
| | |

## Author-supplied statements

Relevant information will appear here if provided.

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The supporting data of this article has been uploaded as part of the supplementary material.

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I/We declare we have no competing interests

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CUST_STATE_CONFLICT :No data available.

### *Authors' contributions*

This paper has multiple authors and our individual contributions were as below

*Statement (if applicable):*
VK carried out the simulations, designed the methodology, participated in data analysis and drafted the manuscript. FR conceived of the study, designed the methodology, and critically revised the manuscript. LSPB carried out the simulations. IP and HR participated in data analysis. HKD critically revised the manuscript. All authors have read and agreed to the published version of the manuscript.

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Research

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# The significance of long-range correction to the hydroperoxyl radical-scavenging reaction of trans-resveratrol and gnetin C

Vera Khoirunisa[3,2,4], Febdian Rusydi[1,2], Lusia S.P. Boli[2,4], Ira Puspitasari[5,2], Heni Rachmawati[6,7] and Hermawan K. Dipojono[4,7]

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[2]Research Center for Quantum Engineering Design, Faculty of Science and Technology, Universitas Airlangga, Jl. Mulyorejo, Surabaya 60115, Indonesia
[3]Engineering Physics Study Program, Institut Teknologi Sumatera, Jl. Terusan Ryacudu, Lampung Selatan 35365, Indonesia
[4]Advanced Functional Material Research Group, Institut Teknologi Bandung, Jl. Ganesha 10,Bandung 40132, Indonesia
[5]Information System Study Program, Faculty of Science and Technology, Universitas Airlangga, Jl. Mulyorejo, Surabaya 60115, Indonesia
[6]School of Pharmacy, Institut Teknologi Bandung, Jl. Ganesha 10, Bandung 40132, Indonesia
[7]Research Center for Nanoscience and Nanotechnology, Institut Teknologi Bandung, Jl. Ganesha no. 10, Bandung 40132, Indonesia

Density functional calculation is a promising tool to study the scavenging activity of antioxidants, but there are only a few studies that investigate the importance of calculation methods on the radical-scavenging reactions. In this study, we examine the significance of long-range correction to the hydroperoxyl radical-scavenging reaction of trans-resveratrol and gnetin C. We employed B3LYP, CAM-B3LYP (long-range correction), M06-2X exchange-correlation functionals, and B3LYP with D3 version of Grimme's dispersion in the calculations. The results showed that long-range correction had a significant effect on the increase of reaction and activation energies. The increase was in line with the change of hydroperoxyl radical's orientation in the transition state structure. Meanwhile, the dispersion correction only had a minor effect on the transition state structure, reaction energy, and activation energy. Overall, long-range correction had a significant impact on the radical-scavenging reaction.

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## 1. Introduction

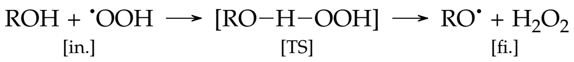
Density functional theory (DFT) has been gaining popularity for studying the radical-scavenging activity of antioxidants. [1–15] DFT offers many advantages in exploring the chemical properties of antioxidant molecules based on their quantum electronic structures. [16] Early application of DFT in the study of radical-scavenging reactions successfully explained antioxidant activities through their thermodynamic quantities. [15,17–19] With the recent development in the DFT algorithm, it is possible to probe the possible activated complex of the reactions; hence to study the reaction kinetics that leads to the antioxidant activity mechanism. [1,2,5,11,12,20] As such, DFT becomes a favorable tool for studying scavenging activities in order to find a better antioxidant.

Despite its vast application in DFT, B3LYP exchange-correlation functional has limitations in non-covalent interactions and barrier height calculations. [21–23] These limitations can be overcome by adding corrections. Long-range correction is one example, as it improves the calculations by enhancing the proportion of the Hartree-Fock (HF) exchange term for long-range interactions. [24,25] However, long-range correction cannot describe the correct asymptotic $R^{-6}$ potential for large intermolecular distances. The correction that can describe this potential correctly is dispersion correction. [26–28] Another way to overcome the limitations is by applying the exchange-correlation functionals from Minnesota density functionals. M06-2X functional, one of Minnesota density functionals, has been tested in many cases–it improved the accuracy for thermodynamic, kinetics, and non-covalent parametric quantities of various simple chemical reactions. [29–31]

Non-covalent interactions have a major influence on the activity of phenolic antioxidants. [32] However, the importance of calculation methods in studying radical-scavenging activity is less known. In this study, we examine the effect of long-range correction on the transition state and activation energy calculations of two radical-scavenging reactions. The two reactions, which we use to study the antioxidant activity of melinjo resveratrol, are the scavenging reaction of hydroperoxyl radical by trans-resveratrol and gnetin C. We use B3LYP as the referenced functional since it has provided a good prediction in our previous studies. [33–35] For long-range correction, we use a version of B3LYP that has been corrected using the Coulomb-attenuating method in CAM-B3LYP exchange-correlation functionals. [24] For comparison, we use B3LYP with the D3 version of Grimme's dispersion [26] and M06-2X [31] functional.

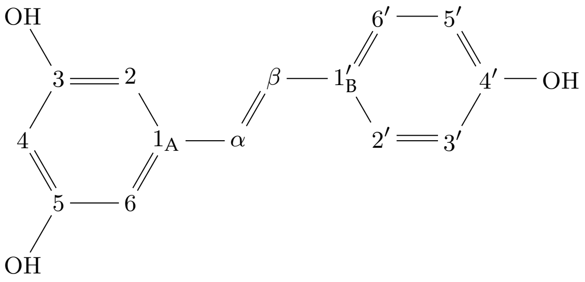
## 2. Model and Computational Details

**Reaction model** We modeled the radical-scavenging reaction based on the hydrogen atom transfer (HAT) mechanism, as shown in scheme 1. In the initial and final states (abbreviated to [in.] and [fi.] respectively), molecules were in the ground state. The reactants were ROH (an antioxidant agent) and $^\bullet$OOH (hydroperoxyl, a free radical). We used two antioxidant agents–trans-resveratrol (tR) and gnetin C (gC)–as shown in figure 1a and figure 1b respectively. We only considered one active site of ROH for the hydrogen donation, which was 4$'$ −OH site, as shown in figure 1c. It was the lowest bond dissociation energy amongst other sites. [36,37] Between [in.] and [fi.], we considered one transition state [TS], where we assumed the activated complexes, [RO−H−OOH], were formed.

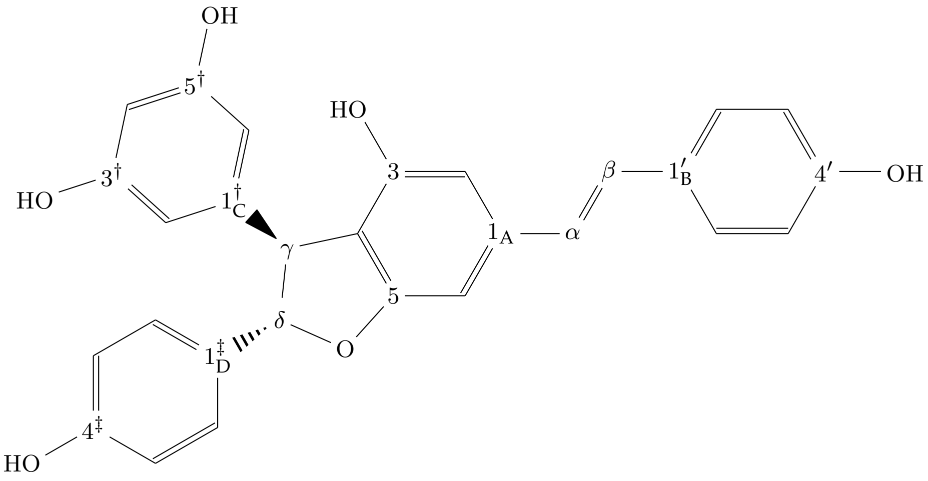


$$\underset{[\text{in.}]}{\mathrm{ROH} + {}^\bullet\mathrm{OOH}} \longrightarrow \underset{[\text{TS}]}{[\mathrm{RO{-}H{-}OOH}]} \longrightarrow \underset{[\text{fi.}]}{\mathrm{RO}^\bullet + \mathrm{H_2O_2}}$$

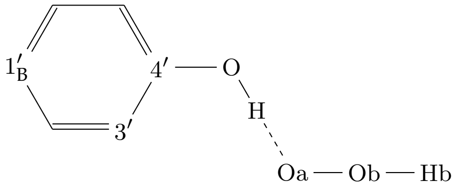
Scheme 1: The radical-scavenging reaction model, with [in.], [TS], and [fi.] were initial, transition, and final states.



(a) Trans-resveratrol (tR) in the ground state



(b) Gnetin C (gC) in the ground state



(c) Ring B and hydroperoxyl in the [TS]

Figure 1: Molecular model for ROH in this study with the nomenclature used throughout the manuscript. The numbering of oxygen and hydrogen followed the numbering of its attaching carbon. The A, B, C, and D indexes at the first carbon atom in each ring referred to phenyl ring's labels. The prime, dagger, and double dagger symbols were for numbering ring B, C, and D respectively.

**Activation and reaction energy calculations** We constructed the reaction progress in an energy level diagram for scheme 1. It allowed us to calculate the reaction energy ($\Delta G^\circ$) and the activation energy ($\Delta^\ddagger G^\circ$) directly in terms of the standard Gibbs free energy at 298.15 K. $\Delta G^\circ$ was the energy difference between [fi.] and [in.]; while $\Delta^\ddagger G^\circ$ was the energy difference between [TS] and [in.].

**DFT calculation setup** We utilized DFT calculations for obtaining the geometry in the ground and the transition states. In addition to the DFT calculations, we coupled it with frequency

Table 1: Method's order according to the XC.

| | | |
|---|---|---|
| M1 | B3LYP | The reference throughout the analysis |
| M2 | B3LYP with GD3 | dispersion correction term |
| M3 | CAM-B3LYP | long-range correction term |
| M4 | M06-2X | Parameterization and evaluation for non-covalent interactions |

calculations at 298.15 K to determine the Gibbs free energy correction. Furthermore, we used NBO calculations for the charge population analysis.

While we only used one basis set, which was 6-31++G(d,p), we performed all calculations using three different exchange-correlational functionals (XCs), namely B3LYP, CAM-B3LYP, and M06-2X. We also performed the calculations using B3LYP with D3 version of Grimme's dispersion (GD3). Therefore, we were able to study the long-range and dispersion correction effect in the transition state.

The routine calculations were as follows. First, we performed the geometry optimization to obtain the most stable spin-state. We considered singlet, triplet, and quintet spin state for molecules with an even number of electrons. As for molecules with an odd number of electrons, the doublet and quartet spin state were considered. Second, we used the most stable spin-state for further calculations to obtain the optimized geometry and energy of molecules in the ground and transition state. We began the geometry optimization by employing B3LYP. The optimized structures were re-optimized with B3LYP + GD3, CAM-B3LYP, and M06-2X (See table 1 for the calculation's orders). The relevant activated complex structures were the ones with the vibration of H atom between the $4'-$OH site and $^{\bullet}$OOH having the imaginary frequency. All calculations were done in the gas phase using Gaussian 09 software. [38]

# 3. Results and Discussions

## 3.1. The ground state structures

The optimization geometry calculations for trans-resveratrol and gnetin C using three XCs obtained spin-singlet state was the lowest in energy level. The energy difference between the singlet and triplet states was about 2.0 eV (trans-resveratrol) and 6.5 eV (gnetin C); while between the singlet and quintet states was about 6.2 eV (trans-resveratrol) and 10.4 eV (gnetin C). The differences are significant, which indicates that the spin-singlet state is very stable. The result agrees with the most organic compounds that are stable in the spin-singlet state, with carbenes as the exception. [39,40] Therefore, we only considered the spin-singlet state for further calculations. As for hydroperoxyl, the spin-doublet was the ground state and the next spin state was a quintet with energy difference 2.8 eV on average.

Overall, the obtained ground state geometries of trans-resveratrol and hydroperoxyl were in good agreement with the experimental result, as shown in table 2(a.i) – (a.xii) and (b.xv) – (b.xvii). The discrepancies were less than 0.017 Å and 1.4 degrees, which were considered accurate for DFT calculations. [41] The higher discrepancies were for $\mathrm{C4'} - \mathrm{O}$ bond length and $\mathrm{Oa} - \mathrm{Ob} - \mathrm{Hb}$ bond angle by M3 and M4. However, when we considered the experimental error, these values were still in the range. Therefore, all methods were capable to determine an accurate geometric structure for trans-resveratrol and hydroperoxyl. It implies we can use all methods for further calculations.

In detail, there was a significant difference in the dihedral angles of trans-resveratrol [table 2(a.xiii)]. The calculations obtained phenyl ring A and B were twisted, while experimental showed they were preferably planar. The NBO calculations determined that all hydrogens were positively charged (see Table S1, electronic supplementary material); hence the coulombic repulsions of $\mathrm{H2} - \mathrm{H}\alpha$ and $\mathrm{H6'} - \mathrm{H}\beta$ were responsible for $D\,(\mathrm{A, B})$. However, the coulombic

Table 2: The selected geometric parameters of (a) trans-resveratrol and (b) hydroperoxyl in the ground state, the bond length ($R$, in Å), the bond angle ($A$, in degree), and the dihedral angle ($D$, in degree). Parameter (i) – (xii) and (xv) – (xvii) are the discrepancy from the experimental values. Parameter (xiii) is the difference between ring A and ring B calculated with the same method. Parameter (xiv) is the absolute value (without any reference).

| | Parameter | Expr. | M1 | M2 | M3 | M4 |
|---|---|---|---|---|---|---|
| (a) | Trans-resveratrol | | | | | |
| (i) | $R(3, 2)$ | 1.387 | +0.006 | +0.006 | +0.001 | +0.004 |
| (ii) | $R(2, 1)$ | 1.404 | +0.002 | +0.002 | −0.006 | −0.005 |
| (iii) | $R(1, \alpha)$ | 1.471 | −0.003 | −0.003 | −0.001 | 0.000 |
| (iv) | $R(\alpha, \beta)$ | 1.338 | +0.012 | +0.012 | +0.002 | +0.004 |
| (v) | $R(\beta, 1')$ | 1.462 | +0.003 | +0.003 | +0.006 | +0.007 |
| (vi) | $R(1', 2')$ | 1.400 | +0.009 | +0.009 | +0.000 | +0.001 |
| (vii) | $R(2', 3')$ | 1.385 | +0.007 | +0.007 | +0.003 | +0.005 |
| (viii) | $R(5, \mathrm{O})$ | 1.378 | −0.008 | −0.008 | −0.014 | −0.016 |
| (ix) | $R(4', \mathrm{O})$ | 1.381 | −0.011 | −0.011 | −0.017 | −0.019 |
| (x) | $A(4, 5, 6)$ | 121.1 | 0.0 | 0.0 | 0.0 | +0.1 |
| (xi) | $A(1, \alpha, \beta)$ | 126.0 | +0.8 | +0.6 | +0.2 | −0.7 |
| (xii) | $A(3', 4', 5')$ | 120.3 | −0.6 | −0.6 | −0.5 | −0.3 |
| (xiii) | $D(\mathrm{A, B})$ | 8.7 | 17.4 | 21.2 | 30.5 | 39.6 |
| (xiv) | $D(3', 4', \mathrm{O}, \mathrm{H})$ | 32.0 | 0.0 | 0.0 | 0.1 | 0.7 |
| (b) | Hydroperoxyl | | | | | |
| (xv) | $R$ (Oa, Ob) | 1.335 | −0.001 | −0.001 | −0.014 | −0.023 |
| (xvi) | $R$ (Ob, Hb) | 0.977 | +0.004 | +0.004 | +0.001 | −0.001 |
| (xvii) | $A$ (Oa, Ob, Hb) | 104.1 | +1.4 | +1.4 | +1.7 | +1.7 |

Note: Experimental values: trans-resveratrol from [42]; hydroperoxyl from [43].

repulsions were unlikely to play a dominant role in the experiment. As Zarychta et al. [42] reported, trans-resveratrol was prepared in crystal form, where one trans-resveratrol was surrounded by six others. Each trans-resveratrol formed hydrogen bonds with its six neighbor molecules through OH−O. The hydrogen bonds were predominant over the coulombic repulsions; hence the measured dihedral angle showed the rings were preferably planar.

We also showed the planarity of H4′ in term of the dihedral angle $D(3', 4', \mathrm{O}, \mathrm{H})$ [table 2(a.xiv)]. This particular H atom would be interacting with $^{\bullet}$OOH in the transition state. The experimental value showed that it was not planar. It was due to the aforementioned experimental condition. However, all methods obtained planar H4′ with respect to Ring B. We shall recall this quantity later in the activation energy discussion.

We remarked that the dihedral angle calculation was sensitive to the calculation method. The comparison results among four calculation methods showed that dispersion (M2) and long-range correction (M3) increased the twisting $D$(A, B). Both simultaneously corrections (M4) increased $D$(A, B) even further. This trend was consistent for the case of gnetin C (See Table S2, electronic supplementary material). The results suggest the long-range correction plays a dominant role in the twisting compared to the dispersion correction.

## 3.2. The transition state structures

Figure 2 shows the optimized structures in the [TS] of scheme 1 obtained from all calculation methods for both trans-resveratrol and gnetin C. All structures possessed a single imaginary frequency, which was the O4′ −H−OOH vibration. The magnitudes of imaginary frequency were more than 1300/cm for trans-resveratrol and 1200/cm for gnetin C. These magnitudes were

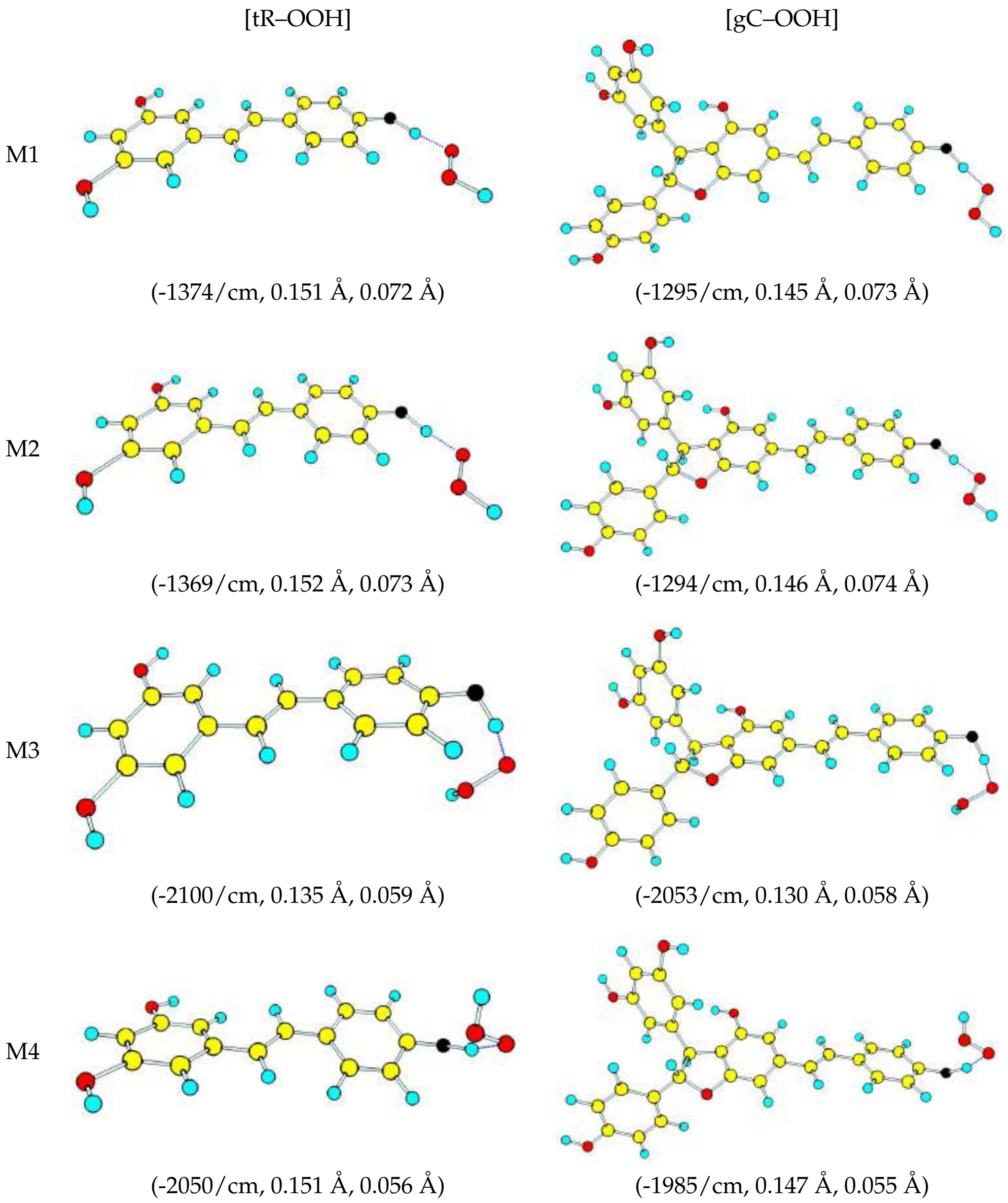


Figure 2: Optimized activated complex structures for trans-resveratrol and gnetin C with $^{\bullet}$OOH. The black atom is O at the active site 4′, written as O4′ in the texts. The numbers in parentheses represent the required imaginary vibrational frequency for a transition state, the elongation of O4′ −H and Oa − Ob bonds with respect to its ground state bond length.

strong, which indicated that the O4′ −H−OOH vibration encouraged the displacement of H4′. The displacement of H4′ can also be seen from the elongation of O4′ −H bond length, which was about 0.140 Å (or, 15% longer than in its ground state). Meanwhile, the Oa − Ob bond of $^{\bullet}$OOH was not significantly elongated (only about 5%). It means $^{\bullet}$OOH is attracting H4′. Therefore, the obtained structures are the activation complex of the radical-scavenging reaction in scheme 1.

The optimized [TS] structures revealed the different orientation of $^{\bullet}$OOH with respect to the ring B in the activated complexes. The presence of ring C and D did not contribute to the

Table 3: The difference of selected parameters of [RO−H−OOH] complex [1c] from M1. (a) is the torsion angle (degree), (b) - (f) are the interatomic distance (Å), (g) is the bond angle (degree). For (h), the relative electronic energy (eV), M1 is set to be the reference.

| Parameter | ROH | M1 | M2 | M3 | M4 |
|---|---|---|---|---|---|
| (a) $\phi\,(3', 4', \mathrm{O}, \mathrm{H})$ | tR | 0.0 | +1.0 | +43.4 | −52.8 |
|  | gC | 0.5 | +0.3 | +43.1 | −55.5 |
| (b) $R\,(\mathrm{H4}', \mathrm{Oa})$ | tR | 1.296 | −0.001 | −0.008 | −0.030 |
|  | gC | 1.307 | −0.002 | −0.010 | −0.034 |
| (c) $R\,(\mathrm{H3}', \mathrm{Hb})$ | tR | 3.234 | −0.041 | +0.274 | +0.384 |
|  | gC | 3.231 | −0.040 | +0.278 | +0.338 |
| (d) $R\,(\mathrm{H3}', \mathrm{Ob})$ | tR | 2.317 | −0.039 | +0.313 | +0.437 |
|  | gC | 2.314 | −0.038 | +0.319 | +0.460 |
| (e) $R\,(\mathrm{Oa}, \mathrm{Ob})$ | tR | 1.406 | 0.001 | −0.026 | −0.037 |
|  | gC | 1.406 | 0.001 | −0.027 | −0.039 |
| (f) $R\,(\mathrm{Ob}, \mathrm{Hb})$ | tR | 0.972 | 0.000 | +0.001 | 0.000 |
|  | gC | 0.971 | 0.000 | +0.001 | 0.000 |
| (g) $A\,(\mathrm{Oa}, \mathrm{Ob}, \mathrm{Hb})$ | tR | 101.9 | 0.0 | +1.4 | +2.0 |
|  | gC | 101.9 | 0.0 | +1.5 | +2.1 |
| (h) $E_r$ | tR | 0 | −0.69 | +12.21 | +11.11 |
|  | gC | 0 | −1.65 | +22.30 | +19.15 |

Note: Negative value of $\phi$ means that O4′–H bond rotates in a clockwise direction.

orientation, as the orientation was alike between [tR-OOH] and [gC-OOH]. However, the change in calculation methods altered the orientation. The significant alteration was obtained by M3 and M4, which implies that long-range correction plays a significant role in the orientation.

The orientation of $^{\bullet}$OOH in the activated complexes can be measured as a torsion angle of $3' - 4' - \mathrm{O} - \mathrm{H}$, or $\phi$ (in degree). Table 3(a) shows the value of phi for all computational methods. Both M1 and M2 obtained phi was about zero, or $^{\bullet}$OOH was planar with respect to the ring B. However, $^{\bullet}$OOH was twisted up to 50 degrees according to M3 and M4 results. It implies that long-range correction was the reason for the twist. Therefore, the long-range correction plays a significant role both in the ground and the transition states of trans-resveratrol and gnetin C.

The origin of $^{\bullet}$OOH orientation is likely the same with the aforementioned ring A and B twisting origin in the ground state. The twisting presented after the long-range correction was introduced. Here, NBO calculations also determined that all the hydrogen atoms were positively charged, but both oxygen atoms in $^{\bullet}$OOH were negatively charged. Therefore, coulombic interactions between the closest atoms in ring B and $^{\bullet}$OOH are the reason for the twisting. While Oa was attracted to H4′ , Hb was repelled by H3′ . The effect of repulsion and attractions can be seen from the interatomic distance between these atoms. 3(b) dan (c) show that $\mathrm{H4}' - \mathrm{Oa}$ distances decreased while $\mathrm{H3}' - \mathrm{Oa}$ distances increased after the long-range correction was introduced.

While the long-range correction determined the orientation of $^{\bullet}$OOH, the dispersion correction affected the interatomic distance [table 3(c) and (d)]. The latter contracted the interatomic distance of H−H and H−O by about 1.3% and 1.7%, respectively. The correction did not affect the covalent bond parameters [table 3(b), (e), (f), and (g)], which is reasonable since the dispersion only works in the non-covalent region. These results complemented the report by Grimme et al. [26]. They reported that the effect began to arise at about 2.0 Å for C−C interatomic distance. Meanwhile, the contraction of $\mathrm{H} - \mathrm{H}$ and $\mathrm{H} - \mathrm{O}$ showed a critical difference between M1 and M2. Both

Table 4: The difference of reaction ($\Delta G^{\circ}$) and activation ($\Delta^{\ddagger} G^{\circ}$) energy from M1 (in kcal/mol).

| Parameter | ROH | M1 | M2 | M3 | M4 |
|---|---|---|---|---|---|
| (a) $\Delta G^{\circ}$ | tR | $-6.00$ | $+0.25$ | $+2.58$ | $+3.55$ |
| | gC | $-6.10$ | $-0.35$ | $+3.67$ | $+5.68$ |
| (b) $\Delta^{\ddagger} G^{\circ}$ | tR | 6.42 | $-1.85$ | $+8.26$ | $+8.97$ |
| | gC | 6.51 | $-1.31$ | $+8.07$ | $+8.91$ |

methods resulted in a planar $^{\bullet}$OOH's orientation, but the dispersion correction stabilize the activated complex, as shown in their electronic energy [table 3(h)]. The stability of the activated complex naturally affected the energy barrier so it may affect the kinetic study or even the reaction pathways.

## 3.3. The radical-scavenging reaction

Table 4(a) shows the reaction energy of scheme 1 with the transition state described in the previous section. All methods predicted that the reaction was exergonic. The experiment demonstrated that this reaction was indeed exergonic by showing its observable antioxidant activity. [44] Even though the reaction occurred in the solution experimentally, other studies using DFT with M05-2X functional in aqueous solution also obtained exergonic. [12,45] Therefore, our results can be accountable for further analysis.

Even though all methods obtained an exergonic reaction for scheme 1, the dispersion (M2) and long-range (M3) correction led to a different result. Since the activated complex determined the product, the exergonic difference level was aligned with the orientation of $^{\bullet}$OOH: the more twisting, the less exergonic. Since the twisting was due to the long-range correction as we discussed previously [table 3(a)-(d)], it implies that long-range correction also affects a reaction's exergonic level.

Dispersion and long-range correction also result in a different activation energy $\Delta^{\ddagger} G^{\circ}$, as shown in table 4(a). The former decreased $\Delta^{\ddagger} G^{\circ}$ by more than 20%, while the latter increased $\Delta^{\ddagger} G^{\circ}$ by more than 120%. The trend of the activation energy is similar to that of the activation complex stability [table 3(h)]. It implies that the activated complex structure indeed determine the activation energy.

The increasing $\Delta^{\ddagger} G^{\circ}$ by the long-range correction was remarkable. Regarding the planarity difference of H4$'$ with respect to Ring B between in the ground and the transition state, the former was plane [table 2(a.xiv)] and the later was twisted [table 3(a)]. The results suggest that the increasing $\Delta^{\ddagger} G^{\circ}$ is due to the required energy to twist H4$'$ with respect to Ring B.

Overall, the similarity in the higher $\Delta G^{\circ}$ and $\Delta^{\ddagger} G^{\circ}$ calculations by M3 and M4 is a noteworthy results. It appears that the similarity originates from the Hatree-Fock exchange functional contribution to the selected calculation methods. B3LYP functional (M1) contained 20% of the Hartree-Fock exchange functional [46], CAM-B3LYP (M3) contained 19% for short-range and 65% for long-range exchange [24], and M06-2X (M4) contained 54% [31]. Therefore, the exact exchange such as Hartree-Fock functional plays a significant role in this study. It supported the study by Zhao and Truhlar [31] that recommends the use of M06-2X for studying the thermodynamic, kinetics, and non-covalent interactions of the main-group element. Specifically, this study validates the study by Chai and Head-Gordon[47] that showed the importance of long-range corrected hybrid functional in thermochemistry, kinetics, and non-covalent interactions calculations.

## 4. Conclusion

We have reported the effect of long-range and dispersion correction on the hydroperoxyl radical-scavenging reaction of trans-resveratrol and gnetin C. We found that long-range correction, which was included in CAM-B3LYP, showed significant effects on the reaction. The effects predicted by CAM-B3LYP were similar to that of M06-2X. Both CAM-B3LYP and M06-2X predicted higher reaction and activation energy (in terms of Gibbs free energy) than B3LYP. The increase was 2.6-3.6 kcal/mol (trans-resveratrol) and 3.7-5.7 kcal/mol (gnetin C) for the reaction energy, while for activation energy, the increase was up to 8 kcal/mol. We argued that the higher values of reaction and activation energy were due to the twisted orientation of hydroperoxyl radical in the transition state. Hydroperoxyl radical was twisted up to 50 degrees with respect to the phenyl ring attached to it. This twisted orientation of hydroperoxyl radical showed another similarity between CAM-B3LYP and M06-2X.

On the other hand, we noted that dispersion correction did not have a significant effect. B3LYP, without or with the Grimme's dispersion correction, obtained similar geometry and energy in the transition state. These results support other theoretical studies that reported the importance of long-range correction for the thermochemistry, kinetics, and non-covalent interactions calculations. Therefore, our study verifies the significance of long-range correction in the hydroperoxyl radical-scavenging reaction of trans-resveratrol and gnetin C.

Data Accessibility. The supporting data of this article has been uploaded as part of the supplementary material.

Authors' Contributions. VK carried out the simulations, designed the methodology, participated in data analysis, and drafted the manuscript. FR conceived of the study, designed the methodology, and critically revised the manuscript. LSPB carried out the simulations. IP and HR participated in data analysis. HKD critically revised the manuscript. All authors have read and agreed to the published version of the manuscript.

Competing Interests. The author declares no competing interests.

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# The significance of long-range correction to the hydroperoxyl radical-scavenging reaction of trans-resveratrol and gnetin C

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# The significance of long-range correction to the hydroperoxyl radical-scavenging reaction of trans-resveratrol and gnetin C

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Density functional theory has been gaining popularity for studying the radical scavenging activity of antioxidants. However, only a few studies investigate the importance of calculation methods on the radical-scavenging reactions. In this study, we examined the significance of (1) the long-range correction on the coulombic interaction and (2) the London dispersion correction to the hydroperoxyl radical-scavenging reaction of trans-resveratrol and gnetin C. We employed B3LYP, CAM-B3LYP, M06-2X exchange-correlation functionals, and B3LYP with the D3 version of Grimme's dispersion in the calculations. The results showed that long-range correction on the coulombic interaction had a significant effect on the increase of reaction and activation energies. The increase was in line with the change of hydroperoxyl radical's orientation in the transition state structure. Meanwhile, the London dispersion correction only had a minor effect on the transition state structure, reaction energy, and activation energy. Overall, long-range correction on the coulombic interaction had a significant impact on the radical-scavenging reaction.

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# 1. Introduction

Radical scavenging is an important property of antioxidants. It is the act of antioxidant to deactivate or remove free radicals to prevent oxidative damage in the biological system. A common radical scavenging example is the inhibition process of lipid peroxidation. In the inhibition process, an antioxidant scavenges the peroxyl radical to stop the chain reaction, which leads to lipid peroxidation. A phenolic antioxidant, such as resveratrol, is known to scavenge the peroxyl radical by donating its hydrogen atom [1]. The hydrogen donation can be affected by non-covalent interactions such as hydrogen bonding and steric repulsion in the system. Therefore, it is expected that non-covalent interactions significantly influence the activity of phenolic antioxidant [2].

The radical scavenging activity of antioxidants is widely studied theoretically using density functional theory (DFT). [1,3–16] DFT has been successfully predicted the antioxidant activity through thermodynamic quantities. [1,17–19] However, the limitation of exchange-correlation functionals in DFT for non-covalent interaction and barrier height calculations [20–22] are the challenges for studying the radicals scavenging reaction that leads to reaction kinetics and mechanism. Therefore, corrections to exchange-correlation functionals are needed to overcome the limitations.

One to handle the limitation of exchange-correlation functionals in DFT is the long-range correction. It improves calculations by partitioning exchange interaction into two regions, Hartree-Fock exchange at long-range interaction and pure DFT at short-range interaction. [23,24] However, long-range correction cannot describe the correct asymptotic $R^{-6}$ potential for large intermolecular distances. The potential can be described by dispersion correction, which adds an empirical term to account for dispersion. [25–27] Another way to overcome the limitations is by applying the exchange-correlation functionals from Minnesota density functionals. M06-2X functional, one of Minnesota density functionals, has been tested in many cases–it improved the accuracy for thermodynamic, kinetics, and non-covalent parametric quantities of various simple chemical reactions. [28,29]

In this study, we use four calculation methods for studying the hydroperoxyl radical-scavenging reaction of trans-resveratrol and gnetin C. We aim to examine the effect of long-range and dispersion correction on the transition state and activation energy of the two radical-scavenging reactions. We use B3LYP as a referenced functional since it is the most popular density functionals in chemistry [30] and has provided a good prediction in our previous studies. [31–33]. We use a version of B3LYP that has been corrected using the Coulomb-attenuating method in CAM-B3LYP exchange-correlation functionals [23] and B3LYP with the D3 version of Grimme's dispersion [25] for performing long-range correction on the coulombic interaction and London dispersion correction, respectively. As a comparison, we also use M06-2X functional [29]. The two radical-scavenging reactions are the representative model for the inhibition process of lipid peroxidation by melinjo resveratrol.

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## 2. Model and Computational Details

**Reaction model** We modeled the radical-scavenging reaction based on the hydrogen atom transfer (HAT) mechanism, as shown in scheme 1. In the initial and final states (abbreviated to [in.] and [fi.] respectively), molecules were in the ground state. The reactants were ROH (an antioxidant agent) and $^{\bullet}$OOH (hydroperoxyl, a model of peroxyl radicals in general). We used two antioxidant agents from melinjo–trans-resveratrol (tR) and gnetin C (gC)–as shown in figure 1a and figure 1b respectively. We only considered one active site of ROH for the hydrogen donation, which was 4′ −OH site, as shown in figure 1c. It was the lowest bond dissociation energy amongst other sites. [34,35] Between [in.] and [fi.], we considered one transition state [TS], where we assumed the activated complexes, [RO−H−OOH], were formed.

$$\underset{\text{[in.]}}{\mathrm{ROH} + {}^{\bullet}\mathrm{OOH}} \longrightarrow \underset{\text{[TS]}}{[\mathrm{RO{-}H{-}OOH}]} \longrightarrow \underset{\text{[fi.]}}{\mathrm{RO}^{\bullet} + \mathrm{H_2O_2}}$$

Scheme 1: The radical-scavenging reaction model, with [in.], [TS], and [fi.] were initial, transition, and final states.

**Activation and reaction energy calculations** We constructed the reaction progress in an energy level diagram for scheme 1. It allowed us to calculate the reaction energy ($\Delta G^{\circ}$) and the activation energy ($\Delta^{\ddagger}G^{\circ}$) directly in terms of the standard Gibbs free energy at 298.15 K. $\Delta G^{\circ}$ was the energy difference between [fi.] and [in.]:

$$\Delta G^{\circ} = (G^{\circ}_{\mathrm{RO}^{\bullet}} + G^{\circ}_{\mathrm{H_2O_2}}) - (G^{\circ}_{\mathrm{ROH}} + G^{\circ}_{^{\bullet}\mathrm{OOH}}), \tag{2.1}$$

while $\Delta^{\ddagger}G^{\circ}$ was the energy difference between [TS] and [in.]:

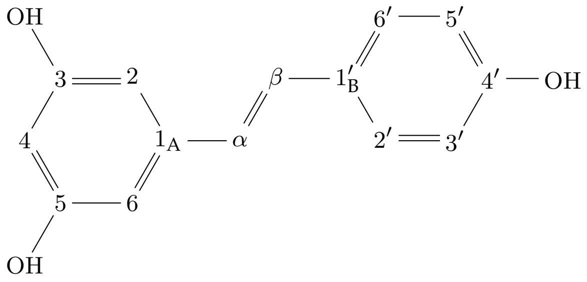
$$\Delta^{\ddagger}G^{\circ} = G^{\circ}_{\mathrm{TS}} - (G^{\circ}_{\mathrm{ROH}} + G^{\circ}_{^{\bullet}\mathrm{OOH}}). \tag{2.2}$$

$G^{\circ}$ is the total electronic energy with a correction from Gibbs free energy.

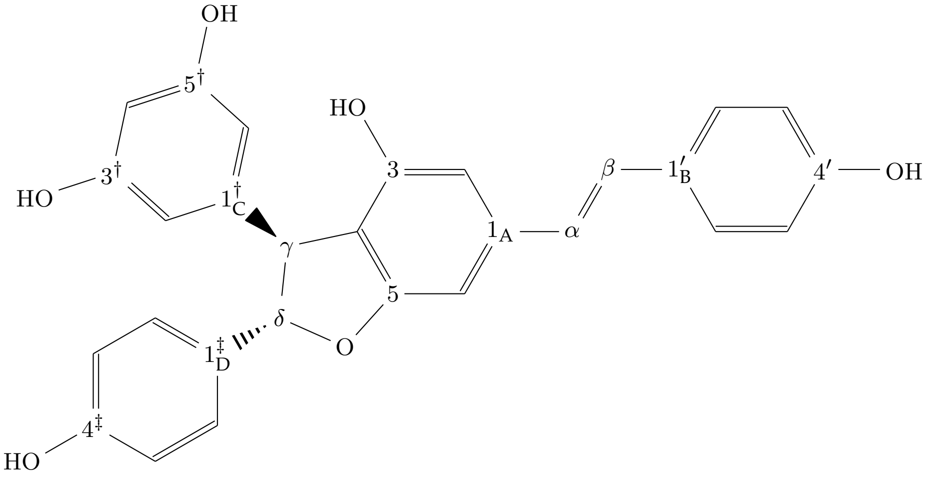
**DFT calculation setup** We utilized DFT calculations for obtaining the geometry in the ground and the transition states. In addition to the DFT calculations, we coupled it with frequency calculations at 298.15 K to determine the Gibbs free energy correction. Furthermore, we used NBO calculations for the charge population analysis.

While we only used one basis set, which was 6-31++G(d,p), we performed all calculations using three different exchange-correlational functionals (XCs), namely B3LYP, CAM-B3LYP, and M06-2X. We also performed the calculations using B3LYP with D3 version of Grimme's dispersion (GD3). Therefore, we were able to study the effect of long-range correction on the coulombic interaction and London dispersion correction in the transition state. List of methods and their notation is shown in table 1.

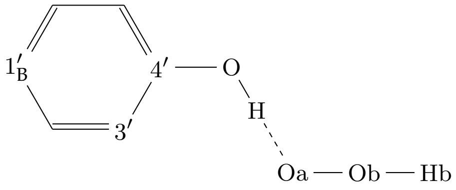
The routine calculations were as follows. First, we performed the geometry optimization to obtain the most stable spin-state. We considered singlet, triplet, and quintet spin state for molecules with an even number of electrons. As for molecules with an odd number of electrons, the doublet and quartet spin state were considered. Second, we used the most stable spin-state for further calculations to obtain the optimized geometry and energy of molecules in the ground and transition state. We obtained the transition state by tracking a particular vibrational mode that decreased along the designed pathway, as demonstrated in our previous study [36]. We began the geometry optimization by employing B3LYP. The optimized structures were re-optimized with B3LYP + GD3, CAM-B3LYP, and M06-2X. The relevant activated complex structures were the ones with the vibration of H atom between the 4′ −OH site and $^{\bullet}$OOH having the imaginary frequency. All calculations were done in the gas phase using Gaussian 09 software. [37]



(a) Trans-resveratrol (tR) in the ground state



(b) Gnetin C (gC) in the ground state



(c) Ring B and hydroperoxyl in the [TS]

Figure 1: Molecular model for ROH in this study with the nomenclature used throughout the manuscript. The numbering of oxygen and hydrogen followed the numbering of its attaching carbon. The A, B, C, and D indexes at the first carbon atom in each ring referred to phenyl ring's labels. The prime, dagger, and double dagger symbols were for numbering ring B, C, and D respectively.

## 3. Results and Discussions

### 3.1. The ground state structures

The optimization geometry calculations for trans-resveratrol and gnetin C using three XCs obtained spin-singlet state was the lowest in energy level. The energy difference between the singlet and triplet states was about 2.0 eV (trans-resveratrol) and 6.5 eV (gnetin C); while between the singlet and quintet states was about 6.2 eV (trans-resveratrol) and 10.4 eV (gnetin C). The differences are significant, which indicates that the spin-singlet state is very stable. The result

Table 1: List of methods and their notation.

| | | |
|---|---|---|
| M1 | B3LYP | The reference throughout the analysis |
| M2 | B3LYP with GD3 | London dispersion correction |
| M3 | CAM-B3LYP | Long-range correction on the coulombic interaction |
| M4 | M06-2X | Parameterization and evaluation for non-covalent interactions |

Table 2: The selected geometric parameters of (a) trans-resveratrol and (b) hydroperoxyl in the ground state, the bond length ($R$, in Å), the bond angle ($A$, in degree), and the dihedral angle ($D$, in degree). Parameter (i) – (xii) and (xv) – (xvii) are the discrepancy from the experimental values. Parameter (xiii) is the difference between ring A and ring B calculated with the same method. Parameter (xiv) is the absolute value (without any reference).

| | Parameter | Expr. | M1 | M2 | M3 | M4 |
|---|---|---|---|---|---|---|
| (a) | Trans-resveratrol | | | | | |
| (i) | $R(3,2)$ | 1.387 | +0.006 | +0.006 | +0.001 | +0.004 |
| (ii) | $R(2,1)$ | 1.404 | +0.002 | +0.002 | −0.006 | −0.005 |
| (iii) | $R(1,\alpha)$ | 1.471 | −0.003 | −0.003 | −0.001 | 0.000 |
| (iv) | $R(\alpha,\beta)$ | 1.338 | +0.012 | +0.012 | +0.002 | +0.004 |
| (v) | $R(\beta,1')$ | 1.462 | +0.003 | +0.003 | +0.006 | +0.007 |
| (vi) | $R(1',2')$ | 1.400 | +0.009 | +0.009 | +0.000 | +0.001 |
| (vii) | $R(2',3')$ | 1.385 | +0.007 | +0.007 | +0.003 | +0.005 |
| (viii) | $R(5,\mathrm{O})$ | 1.378 | −0.008 | −0.008 | −0.014 | −0.016 |
| (ix) | $R(4',\mathrm{O})$ | 1.381 | −0.011 | −0.011 | −0.017 | −0.019 |
| (x) | $A(4,5,6)$ | 121.1 | 0.0 | 0.0 | 0.0 | +0.1 |
| (xi) | $A(1,\alpha,\beta)$ | 126.0 | +0.8 | +0.6 | +0.2 | −0.7 |
| (xii) | $A(3',4',5')$ | 120.3 | −0.6 | −0.6 | −0.5 | −0.3 |
| (xiii) | $D(\mathrm{A},\mathrm{B})$ | 8.7 | 17.4 | 21.2 | 30.5 | 39.6 |
| (xiv) | $D(3',4',\mathrm{O},\mathrm{H})$ | 32.0 | 0.0 | 0.0 | 0.1 | 0.7 |
| (b) | Hydroperoxyl | | | | | |
| (xv) | $R\,(\mathrm{Oa},\mathrm{Ob})$ | 1.335 | −0.001 | −0.001 | −0.014 | −0.023 |
| (xvi) | $R\,(\mathrm{Ob},\mathrm{Hb})$ | 0.977 | +0.004 | +0.004 | +0.001 | −0.001 |
| (xvii) | $A\,(\mathrm{Oa},\mathrm{Ob},\mathrm{Hb})$ | 104.1 | +1.4 | +1.4 | +1.7 | +1.7 |

Note: Experimental values: trans-resveratrol from [40]; hydroperoxyl from [41].

agrees with the most organic compounds that are stable in the spin-singlet state, with carbenes as the exception. [38,39] Therefore, we only considered the spin-singlet state for further calculations. As for hydroperoxyl, the spin-doublet was the ground state and the next spin state was a quintet with energy difference 2.8 eV on average.

Overall, the obtained ground state geometries of trans-resveratrol and hydroperoxyl were in good agreement with the experimental result, as shown in table 2(a.i) – (a.xii) and (b.xv) – (b.xvii). The discrepancies were less than 0.017 Å and 1.4 degrees, which were considered accurate for DFT calculations. [30] The higher discrepancies were for C4′ − O bond length and Oa − Ob − Hb bond angle by M3 and M4. However, when we considered the experimental error, these values were still in the range. Therefore, all methods were capable to determine an accurate geometric structure for trans-resveratrol and hydroperoxyl. It implies we can use all methods for further calculations.

In detail, there was a significant difference in the dihedral angles of trans-resveratrol [table 2(a.xiii)]. The calculations obtained phenyl ring A and B were twisted, while experimental showed they were preferably planar. The NBO calculations determined that all hydrogens were positively charged (see table S1, electronic supplementary material); hence the coulombic repulsions of H2 − H$\alpha$ and H6$'$ − H$\beta$ were responsible for $D$ (A, B). However, the coulombic repulsions were unlikely to play a dominant role in the experiment. As Zarychta et al. [40] reported, trans-resveratrol was prepared in crystal form, where one trans-resveratrol was surrounded by six others. Each trans-resveratrol formed hydrogen bonds with its six neighbor molecules through OH−O. The hydrogen bonds were predominant over the coulombic repulsions; hence the measured dihedral angle showed the rings were preferably planar.

We also showed the planarity of H4$'$ in term of the dihedral angle $D(3', 4', \mathrm{O}, \mathrm{H})$ [table 2(a.xiv)]. This particular H atom would be interacting with •OOH in the transition state. The experimental value showed that it was not planar. It was due to the aforementioned experimental condition. However, all methods obtained planar H4$'$ with respect to Ring B. We shall recall this quantity later in the activation energy discussion.

We remarked that the dihedral angle calculation was sensitive to the calculation method. The comparison results among four calculation methods showed that dispersion (M2) and long-range correction (M3) increased the twisting $D$(A, B). Both simultaneously corrections (M4) increased $D$(A, B) even further. This trend was consistent for the case of gnetin C (See table S2, electronic supplementary material). The results suggest the long-range correction plays a dominant role in the twisting compared to the dispersion correction.

## 3.2. The transition state structures

Figure 2 shows the optimized structures in the [TS] of scheme 1 obtained from all calculation methods for both trans-resveratrol and gnetin C. All structures possessed a single imaginary frequency, which was the O4$'$ −H−OOH vibration. The magnitudes of imaginary frequency were more than 1300/cm for trans-resveratrol and 1200/cm for gnetin C. These magnitudes were strong, which indicated that the O4$'$ −H−OOH vibration encouraged the displacement of H4$'$. The displacement of H4$'$ can also be seen from the elongation of O4$'$ −H bond length, which was about 0.140 Å (or, 15% longer than in its ground state). Meanwhile, the Oa − Ob bond of •OOH was not significantly elongated (only about 5%). It means •OOH is attracting H4$'$. Therefore, the obtained structures are the activation complex of the radical-scavenging reaction in scheme 1.

The optimized [TS] structures revealed the different orientation of •OOH with respect to the ring B in the activated complexes. The presence of ring C and D did not contribute to the orientation, as the orientation was alike between [tR-OOH] and [gC-OOH]. However, the change in calculation methods altered the orientation. The significant alteration was obtained by M3 and M4, which implies that long-range correction plays a significant role in the orientation.

The orientation of •OOH in the activated complexes can be measured as a torsion angle of 3$'$ − 4$'$ − O − H, or $\phi$ (in degree). Table 3(a) shows the value of phi for all computational methods. Both M1 and M2 obtained phi was about zero, or •OOH was planar with respect to the ring B. However, •OOH was twisted up to 50 degrees according to M3 and M4 results. It implies that long-range correction was the reason for the twist. Therefore, the long-range correction plays a significant role both in the ground and the transition states of trans-resveratrol and gnetin C.

The origin of •OOH orientation is likely the same with the aforementioned ring A and B twisting origin in the ground state. The twisting presented after the long-range correction was introduced. Here, NBO calculations also determined that all the hydrogen atoms were positively charged, but both oxygen atoms in •OOH were negatively charged. Therefore, coulombic interactions between the closest atoms in ring B and •OOH are the reason for the twisting. While Oa was attracted to H4$'$, Hb was repelled by H3$'$. The effect of repulsion and attractions can be seen from the interatomic distance between these atoms. 3(b) dan (c) show that H4$'$ − Oa distances decreased while H3$'$ − Oa distances increased after the long-range correction was introduced.

While the long-range correction determined the orientation of •OOH, the dispersion correction affected the interatomic distance [table 3(c) and (d)]. The latter contracted the interatomic distance of H−H and H−O by about 1.3% and 1.7%, respectively. The correction did not affect the covalent

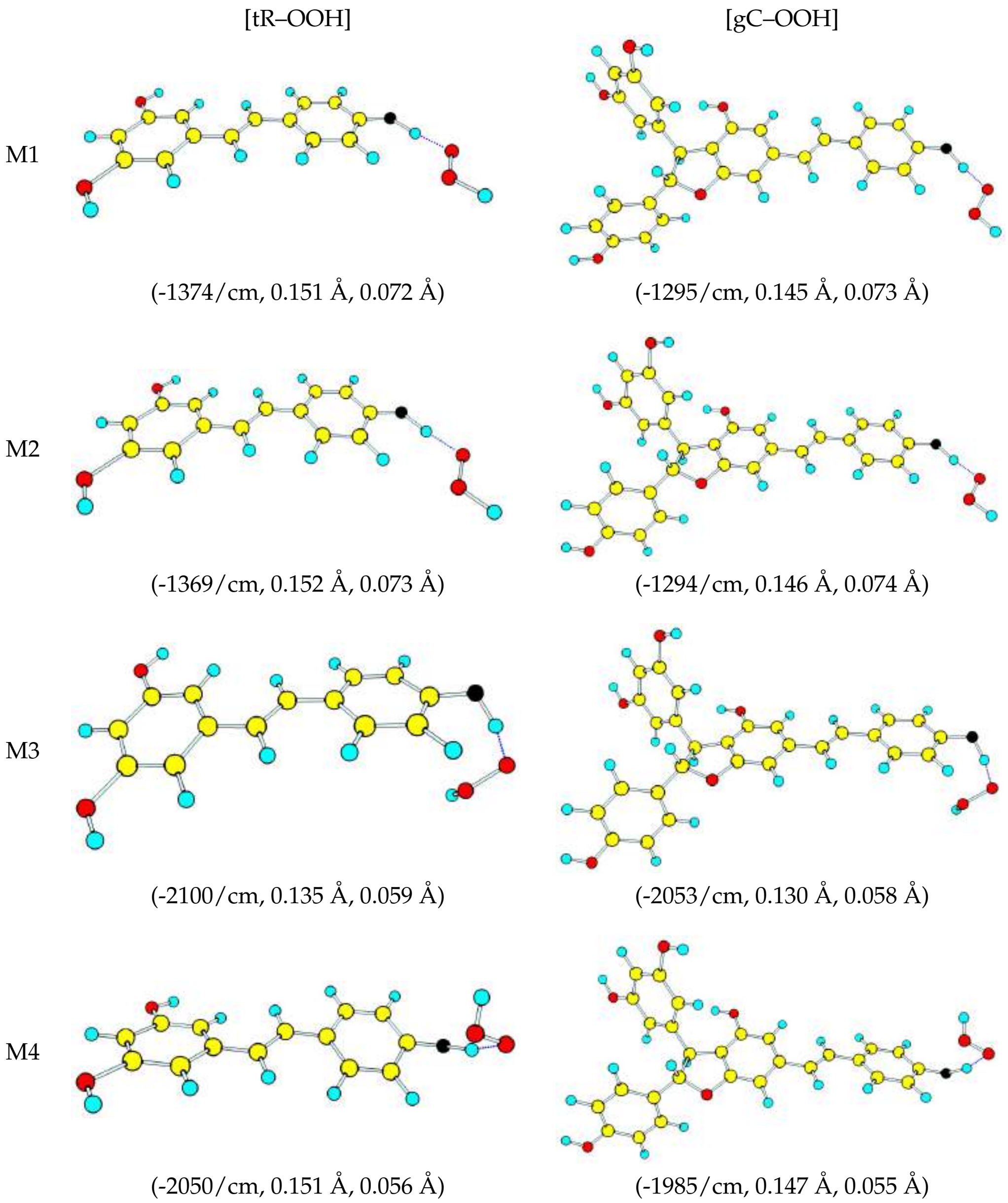


Figure 2: Optimized activated complex structures for trans-resveratrol and gnetin C with $^{\bullet}$OOH. Blue, red, yellow atoms represented H, O and C atoms. The black atom is O at the active site 4′, written as O4′ in the texts. The numbers in parentheses represent the required imaginary vibrational frequency for a transition state, the elongation of O4′ −H and Oa − Ob bonds with respect to its ground state bond length.

bond parameters [table 3(b), (e), (f), and (g)], which is reasonable since the dispersion only works in the non-covalent region. These results complemented the report by Grimme et al. [25]. They reported that the effect began to arise at about 2.0 Å for C−C interatomic distance. Meanwhile, the contraction of H − H and H − O showed a critical difference between M1 and M2. Both methods resulted in a planar $^{\bullet}$OOH's orientation, but the dispersion correction stabilize the activated complex, as shown in their electronic energy [table 3(h)]. The stability of the activated

Table 3: The difference of selected parameters of [RO−H−OOH] complex [1c] from M1. (a) is the torsion angle (degree), (b) - (f) are the interatomic distance (Å), (g) is the bond angle (degree). For (h), the relative electronic energy (eV), M1 is set to be the reference.

| Parameter | ROH | M1 | M2 | M3 | M4 |
|---|---|---|---|---|---|
| (a) $\phi\,(3', 4', \mathrm{O}, \mathrm{H})$ | tR | 0.0 | $+1.0$ | $+43.4$ | $-52.8$ |
| | gC | 0.5 | $+0.3$ | $+43.1$ | $-55.5$ |
| (b) $R\,(\mathrm{H4}', \mathrm{Oa})$ | tR | 1.296 | $-0.001$ | $-0.008$ | $-0.030$ |
| | gC | 1.307 | $-0.002$ | $-0.010$ | $-0.034$ |
| (c) $R\,(\mathrm{H3}', \mathrm{Hb})$ | tR | 3.234 | $-0.041$ | $+0.274$ | $+0.384$ |
| | gC | 3.231 | $-0.040$ | $+0.278$ | $+0.338$ |
| (d) $R\,(\mathrm{H3}', \mathrm{Ob})$ | tR | 2.317 | $-0.039$ | $+0.313$ | $+0.437$ |
| | gC | 2.314 | $-0.038$ | $+0.319$ | $+0.460$ |
| (e) $R\,(\mathrm{Oa}, \mathrm{Ob})$ | tR | 1.406 | 0.001 | $-0.026$ | $-0.037$ |
| | gC | 1.406 | 0.001 | $-0.027$ | $-0.039$ |
| (f) $R\,(\mathrm{Ob}, \mathrm{Hb})$ | tR | 0.972 | 0.000 | $+0.001$ | 0.000 |
| | gC | 0.971 | 0.000 | $+0.001$ | 0.000 |
| (g) $A\,(\mathrm{Oa}, \mathrm{Ob}, \mathrm{Hb})$ | tR | 101.9 | 0.0 | $+1.4$ | $+2.0$ |
| | gC | 101.9 | 0.0 | $+1.5$ | $+2.1$ |
| (h) $E_{rel}$ | tR | 0 | $-0.69$ | $+12.21$ | $+11.11$ |
| | gC | 0 | $-1.65$ | $+22.30$ | $+19.15$ |

Note: Negative value of $\phi$ means that O4′–H bond rotates in a clockwise direction.

complex naturally affected the energy barrier so it may affect the kinetic study or even the reaction pathways.

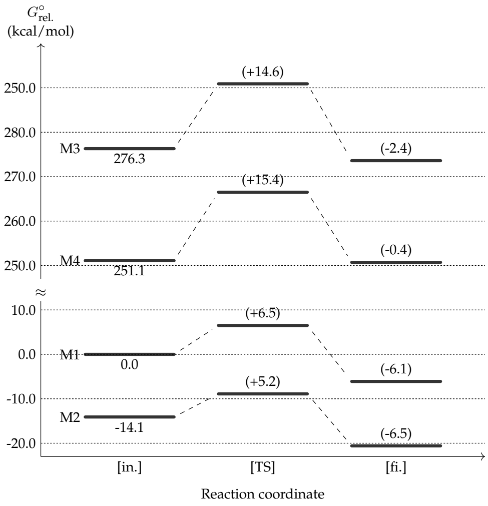
## 3.3. The radical-scavenging reaction

Figure 3 shows the reaction progress of Scheme 1 with the transition state described in the previous section. All methods predicted that the reaction was exergonic. The experiment demonstrated that this reaction was indeed exergonic by showing its observable antioxidant activity. [42] Even though the reaction occurred in the solution experimentally, other studies using DFT with M05-2X functional in aqueous solution also obtained exergonic. [14,43] Therefore, our results can be accountable for further analysis.

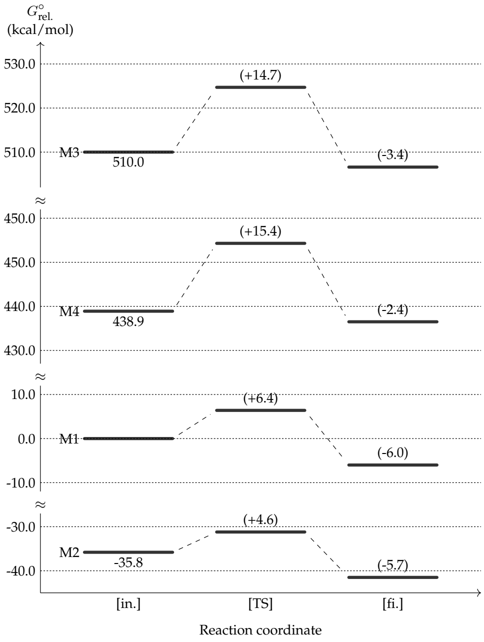
Even though all methods obtained an exergonic reaction for Scheme 1, the dispersion (M2) and long-range (M3) correction led to a different result. Since the activated complex determined the product, the exergonic difference level was aligned with the orientation of $^{\bullet}$OOH: the more twisting, the less exergonic. Since the twisting was due to the long-range correction as we discussed previously [table 3(a)-(d)], it implies that long-range correction also affects a reaction's exergonic level.

Dispersion (M2) and long-range correction (M3) also result in a different activation energy ($\Delta^{\ddagger}G^{\circ}$). As compared to M1, the former decreased $\Delta^{\ddagger}G^{\circ}$ by more than 20%, while the latter increased $\Delta^{\ddagger}G^{\circ}$ by more than 120%. The trend of the activation energy is similar to that of the activation complex stability [Table 3(h)]. It implies that the activated complex structure indeed determine the activation energy.

The increasing $\Delta^{\ddagger}G^{\circ}$ by the long-range correction was remarkable. Regarding the planarity difference of H4′ with respect to Ring B between in the ground and the transition state, the former was plane [table 2(a.xiv)] and the later was twisted [table 3(a)]. The results suggest that the increasing $\Delta^{\ddagger}G^{\circ}$ is due to the required energy to twist H4′ with respect to Ring B.



(a) For trans-reveratrol scavenging



(b) For gnetin C scavenging

Figure 3: The reaction in Scheme 1 in an energy level diagram. The y-axis is the relative free Gibbs energy at room temperature ($G^\circ_{\text{rel.}}$) with the total energy of reactant calculated by M1 as the reference. For clarity, only $G^\circ$ of reactants are written and the parenthesized numbers are the $\Delta G^\circ$ with respect to the reactant's total energy.

Overall, the similarity in the higher $\Delta G^\circ$ and $\Delta^\ddagger G^\circ$ calculations by M3 and M4 is a noteworthy results. It appears that the similarity originates from the Hatree-Fock exchange functional contribution to the selected calculation methods. B3LYP functional (M1) contained 20% of the Hartree-Fock exchange functional [44], CAM-B3LYP (M3) contained 19% for short-range and

65% for long-range exchange [23], and M06-2X (M4) contained 54% [29]. Therefore, the exact exchange such as Hartree-Fock functional plays a significant role in this study. It supported the study by Zhao and Truhlar [29] that recommends the use of M06-2X for studying the thermodynamic, kinetics, and non-covalent interactions of the main-group element. Specifically, this study validates the study by Chai and Head-Gordon[45] that showed the importance of long-range corrected hybrid functional in thermochemistry, kinetics, and non-covalent interactions calculations.

## 4. Conclusion

We have reported the effect of long-range and dispersion correction on the hydroperoxyl radical-scavenging reaction of trans-resveratrol and gnetin C. We found that long-range correction on the coulombic interaction, which was included in CAM-B3LYP, showed significant effects on the reaction. The effects predicted by CAM-B3LYP were similar to that of M06-2X. Both CAM-B3LYP and M06-2X predicted higher reaction and activation energy (in terms of Gibbs free energy) than B3LYP. The increase was 2.6-3.6 kcal/mol (trans-resveratrol) and 3.7-5.7 kcal/mol (gnetin C) for the reaction energy, while for activation energy, the increase was up to 8 kcal/mol. We argued that the higher values of reaction and activation energy were due to hydroperoxyl radicals' twisted orientation in the transition state. Hydroperoxyl radical was twisted up to 50 degrees with respect to the phenyl ring attached to it. This twisted orientation of hydroperoxyl radical showed another similarity between CAM-B3LYP and M06-2X.

On the other hand, we noted that dispersion correction did not have a significant effect. B3LYP, without or with the Grimme's dispersion correction (GD3), obtained similar geometry and energy in the transition state. These results support other theoretical studies that reported the importance of long-range correction for the thermochemistry, kinetics, and non-covalent interactions calculations. Therefore, our study verifies the significance of long-range correction in the hydroperoxyl radical-scavenging reaction of trans-resveratrol and gnetin C.

Data Accessibility. The supporting data of this article has been uploaded as part of the supplementary material.

Authors' Contributions. VK carried out all simulations, participated in the design of the study, participated in data analysis, and drafted the manuscript. FR conceived of the study, designed the methodology, and critically revised the manuscript. LSPB and IP participated in data analysis. HR and HKD critically revised the manuscript. All authors have read and agreed to the published version of the manuscript.

Competing Interests. The author declares no competing interests.

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**To: Reviewer 1**
**Subject: response and revision to the comments and questions**

We are grateful for the reviewer's constructive comments on our manuscript. Here we respond to the reviewer's questions point by point. We mark the new sentences with the red font.

Sincerely,

on the behalf of the authors
Vera Khoirunisa

BEGIN

**Question 1**

Discuss in the introduction the reason for choosing the molecules (hydroperoxyl, trans-resveratrol, gnetin C) in this study. What are their applications or what is/are the significance of these molecules?

We choose trans-resveratrol and gnetin C because we are motivated to study the antioxidant activity of resveratrol in general and resveratrol from melinjo seed (melinjo resveratrol) in particular. To study the activity, we construct the radical-scavenging reaction model in the case of lipid peroxidation. In this reaction, we use $^{\bullet}$OOH as a general molecule model for a peroxyl radical, the radical that has to be terminated to stop lipid peroxidation.

In alignment with other reviewer's requests, we revise the introduction majorly. We add a new paragraph as the first paragraph of "1.Introduction" section to introduce the radical scavenging reaction. The new paragraph is as follows.

`In the manuscript`

Radical scavenging is an important property of antioxidants. It is the act of antioxidant to deactivate or remove free radicals to prevent oxidative damage in the biological system. A common radical scavenging example is the inhibition process of lipid peroxidation. In the inhibition process, an antioxidant scavenges the peroxyl radical to stop the chain reaction, which leads to lipid peroxidation. A phenolic antioxidant, such as resveratrol, is known to scavenge the peroxyl radical by donating its hydrogen atom [1]. The hydrogen donation can be affected by non-covalent interactions such as hydrogen bonding and steric repulsion in the system. Therefore, it is expected that non-covalent interactions significantly influence the activity of phenolic antioxidant [2].

We also revise the last paragraph of "1.Introduction" section to state the reaction's application involving trans-resveratrol, gnetin C, and hydroperoxyl radical and the reason of choosing the methods. The paragraph is as follows. The revised sentences which relevant to the application are marked in bold.

`In the manuscript`

**In this study, we use four calculation methods for studying the $^{\bullet}$OOH radical-scavenging reaction of trans-resveratrol and gnetin C.** We aim to examine the effect of long-range and dispersion correction on the transition state and activation energy of the two radical-scavenging reactions. We use B3LYP as a referenced functional since it is the most popular density functionals in chemistry [30] and has provided a good prediction in our previous studies. [31-33] We use a version of B3LYP that has been corrected using the Coulomb-attenuating method in CAM-B3LYP exchange-correlation functionals [23] and B3LYP with the D3 version of Grimme's dispersion [25] for performing long-range correction on the coulombic interaction and London dispersion correction, respectively. As a comparison, we also use M06-2X functional [29]. **The two radical-scavenging reactions are the representative model for the inhibition process of lipid peroxidation by melinjo resveratrol.**

**Question 2**

Elaborate or provide the equation/s used in getting the energies in terms of the standard Gibbs free energy at 298 K.

The equation for the standard Gibbs free energy is provided as follows.

`In the manuscript`

It allowed us to calculate the reaction energy ($\Delta G^\circ$) and the activation energy ($\Delta^{\ddagger} G^\circ$) directly in terms of the standard Gibbs free energy at 298.15 K. $\Delta G^\circ$ was the energy difference between [fi.] and [in.]:

$$\Delta G^\circ = (G^\circ_{\mathrm{RO}^\bullet} + G^\circ_{\mathrm{H_2O_2}}) - (G^\circ_{\mathrm{ROH}} + G^\circ_{{}^\bullet\mathrm{OOH}}), \tag{1}$$

while $\Delta^{\ddagger} G^\circ$ was the energy difference between [TS] and [in.],

$$\Delta^{\ddagger} G^\circ = G^\circ_{\mathrm{TS}} - (G^\circ_{\mathrm{ROH}} + G^\circ_{{}^\bullet\mathrm{OOH}}). \tag{2}$$

$G^\circ$ is the total electronic energy with a correction from Gibbs free energy.

**Question 3**

Define clearly the meaning of positive and negative energies in Table 4. This will help the audience to understand the energy reaction profile. For instance, what is the physical meaning of the negative energy difference in Table 4b?

We have defined the physical meaning of positive and negative energies in Table 4 in our manuscript.

The energies in Table 4a is the reaction energy ($\Delta G^\circ$). It is the energy difference between the total energy of product and of reactant in term of Gibbs free energy.

Positive reaction energy means the reaction is not spontaneous (endergonic). Negative reaction energy means the reaction is spontaneous (exergonic).

The energies in Table 4b is the activation energy ($\Delta^{\ddagger} G^\circ$). It is the energy difference between activated complex and reactant energy in term of Gibbs free energy.

Positive activation energy means the reaction has a potential barrier. Negative reaction energy means the reaction is barrierless.

To clearly present the data to the readers, we decide to replace Table 4 with Figure 3. Figure 3 is the energy level of reactant, activated complex and product for all calculation methods. The y-axis is the relative energy, where we set the total energy of reactant calculated by M1 to be zero. The Figure 3 is as follows.

Question 4

Are the differences in the energy values presented in Table 4 (especially for the activation energy) really that significant using the different functionals and/or corrections? Why? It will help if the authors show the energy vs the reaction path graph.

Yes, the differences are significant in the activation energy when we use CAM-B3LYP (long-range correction) and M06-2X functional.

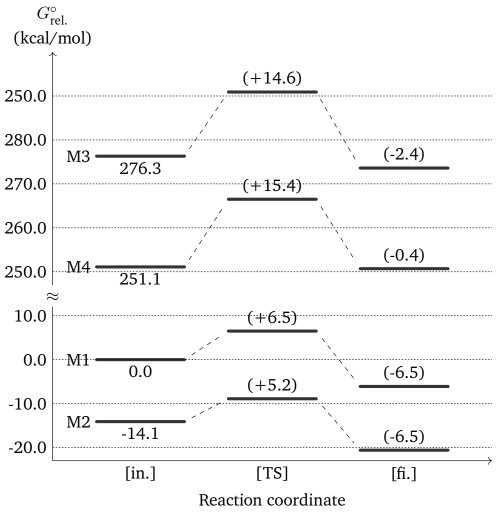
The difference in activation energy is about 8 kcal/mol. This amount of energy is significant to give a change on the vibrational mode of $^{\bullet}$OOH. It requires 5.8 kcal/mol of energy to change the vibrational mode of $^{\bullet}$OOH from linear stretching mode ($\nu_1$) to bending mode ($\nu_2$). [1]

As it is suggested by the reviewer, we change Table 4 into energy level diagrams in Figure 3. We have shown Figure 3 earlier to answer Question 3.

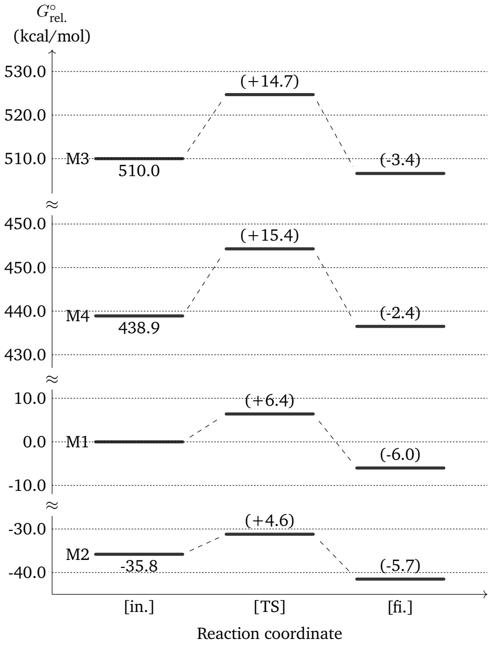
Question 5

Given the obtained results, how to decide on which functional and/or correction should be used? If possible, cite experimental studies that will support the findings of this work.

Our study found the long-range coulombic interaction plays an important role in the radical scavenging reaction of resveratrol. The effect can be seen at the ground state structure, where the long-range coulombic interaction causes the twisting, as well as at the transition state structure (see Figure 2 in the manuscript) that directly impacts the energy barrier. Therefore, one needs to consider the exchange-correlation



(a) For trans-reveratrol scavenging



(b) For gnetin C scavenging

**Figure 3**: The reaction in Scheme 1 in an energy level diagram. The y-axis is the relative free Gibbs energy at room temperature ($G^{\circ}_{\text{rel.}}$) with the total energy of reactant calculated by M1 is the reference. For clarity, only $G^{\circ}$ of reactants are written and the parenthesized numbers are the $\Delta G^{\circ}$ with respective to the reactant's total energy.

functionals with long-range columbic interaction formulae better than B3LYP has. CAM-B3LYP and M06-2X fit into this purpose.

In addition, our study extends the previous study reported by Iuga and Cordova-Gomez [2, 3] , where they used M02-5X to study the antioxidant activity of trans-resveratrol. However, they only used one exchange-correlation functional hence they did not explain what interaction plays the important role in the radical scavenging activity of trans-resveratrol with $^{\bullet}$OOH.

Question 6

Additional Comments:
1. The authors should identify the atoms in Figure 2.
2. The statement "See table 1 for calculation's orders" in page 5 may be confusing. Revise if necessary.

1. We take reviewer's suggestion. We add a sentence in the caption of the Figure 2 to identify the atoms. The caption of Figure 2 is as follows.

`In the manuscript`

> **Figure 2**. Optimized activated complex structures for trans-resveratrol and gnetin C with $^{\bullet}$OOH. Blue, red, yellow atoms represented H, O and C atoms. The black atom is O at the active site 4′, written as O4′ in the texts. The numbers in parentheses represent the required imaginary vibrational frequency for a transition state, the elongation of O4′ −H and Oa − Ob bonds with respect to its ground state bond length.

2. We apologize for the confusion. We revise the sentence and move the sentence to the fifth paragraph of section "2. Model and Computational Details". The revised sentence is as follows.

`In the manuscript`

While we only used one basis set, which was 6-31++G(d,p), we performed all calculations using three different exchange-correlational functionals (XCs), namely B3LYP, CAM-B3LYP, and M06-2X. We also performed the calculations using B3LYP with D3 version of Grimme's dispersion (GD3). Therefore, we were able to study the long-range and dispersion correction effect in the transition state. List of methods and their notation is shown in table 1.

# References

[1] W. M. Haynes 2014 CRC Handbook of Chemistry and Physics, 95th ed., CRC Press, Boca Rotan,Chp.9.

[2] Iuga C, Alvarez-Idaboy JR, Russo N. 2012 Antioxidant Activity of trans-Resveratrol toward Hydroxyl and Hydroperoxyl Radicals: A Quantum Chemical and Computational Kinetics Study. The Journal of Organic Chemistry 77, 3868–3877.

[3] Cordova-Gomez M, Galano A, Alvarez-Idaboy JR. 2013 Piceatannol, a better peroxyl radical scavenger than resveratrol. RSC Advances 3, 20209–20218.

**To: Reviewer 2**
**Subject: response and revision to the comments and questions**

We are grateful for the question and comments on our manuscript. We have revised the introduction majorly to address the reviewer's questions. We mark the new sentences with the red font.

Here we respond to the reviewer's questions point by point. We hope that our revised manuscript meets the reviewer's expectations.

Sincerely,

on the behalf of the authors
Vera Khoirunisa

`BEGIN`

Question 1

Abstract: There is some confusion here in the authors' use of the terms "long-range" and "dispersion". I would consider "dispersion" a long-range force; I would re-word the abstract, and this part in particular, in order to avoid confusion to the reader.

We can understand the confusion regarding the term long-range and dispersion. To differentiate the terms, we re-word and specify the terms in our revised manuscript. The changes are as follows.

`In the manuscript`

Density functional theory has been gaining popularity for studying the radical scavenging activity of antioxidants. However, only a few studies investigate the importance of calculation methods on the radical-scavenging reactions. In this study, we examined the significance of (1) the long-range correction on the coulombic interaction and (2) the London dispersion correction to the hydroperoxyl radical-scavenging reaction of trans-resveratrol and gnetin C. We employed B3LYP, CAM-B3LYP, M06-2X exchange-correlation functionals, and B3LYP with the D3 version of Grimme's dispersion in the calculations. The results showed that long-range correction on the coulombic interaction had a significant effect on the increase of reaction and activation energies. The increase was in line with the change of hydroperoxyl radical's orientation in the transition state structure. Meanwhile, the London dispersion correction only had a minor effect on the transition state structure, reaction energy, and activation energy. Overall, long-range correction on the coulombic interaction had a significant impact on the radical-scavenging reaction.

Question 2

Introduction: It would be useful for the reader to introduce what a radical-scavenging is.

We are glad the reviewer pointed out this issue. We agree that the introduction of radical-scavenging is useful for the reader. We add a new paragraph as the first paragraph in "1. Introduction" section to address this issue. The paragraph is as follows.

`In the manuscript`

Radical scavenging is an important property of antioxidants. It is the act of antioxidant to deactivate or remove free radicals to prevent oxidative damage in the biological system. A common radical scavenging example is the inhibition process of lipid peroxidation. In the inhibition process, an antioxidant scavenges the peroxyl radical to stop the chain reaction, which leads to lipid peroxidation. A phenolic antioxidant, such as resveratrol, is known to scavenge the peroxyl radical by donating its hydrogen atom [1]. The hydrogen donation can be affected by non-covalent interactions such as hydrogen bonding and steric repulsion in the system. Therefore, it is expected that non-covalent interactions significantly influence the activity of phenolic antioxidant [2].

Question 3

Introduction: I don't like the first introductory paragraph. The sentence: "DFT offers many advantages in exploring the chemical properties of antioxidants molecules based on their quantum electronic structure" does not make sense because the same could be said by any material.

We revise majorly the introduction to address all the reviewer's questions. Therefore, we no longer have this sentence in our revised manuscript.

Question 4

The introduction should be revised and extended considerably. In particular:

1. Why is it critical to have a DFT method that includes long-range and dispersion corrections? The author mentions that B3LYP gave predictions (refs. 33-35)
2. Why the two reactions used as benchmark?
3. Why the choice of these functionals? Four DFT methods have been chosen out of the hundreds available. In particular, I can understand the choice of CAM-B3LYP and B3LYP+D3. However, what is the connection with the M06-2X method?

We are aware that these questions arise since we do not clearly state our motivation and consideration of choosing the corrections, reactions, and methods. Therefore, we majorly revise our introduction to give a clear explanation.

Here is our answer to each question.

1. The interactions are classified into two: orbital (that leads to covalent bond) and dispersion interaction. Orbital interactions have short and long-range terms, while dispersion interactions only have long-range terms.

The mathematical formulation of interactions is defined by the exchange-correlation functional in DFT. B3LYP functional, for example, does not have a good description of the long range term of coulombic interaction as well as the dispersion interaction. While B3LYP is proven powerful for study ground state molecules, it gives some problems when we use it to study complex molecules, particularly in the transition state (reaction kinetic). That is why some new exchange-correlation functionals come to improve the results.

We revise the second paragraph of "1. Introduction" section to address this question. The paragraph is as follows.

`In the manuscript`

> The radical scavenging activity of antioxidants is widely studied theoretically using density functional theory (DFT). [1,3-16] DFT has been successfully predicted the antioxidant activity through thermodynamic quantities. [1,17–19] However, the limitation of exchange-correlation functional in DFT for non-covalent interaction and barrier height calculations [20–22] can be challenges for studying the radicals scavenging reaction that leads to reaction kinetics and mechanism. Therefore, corrections to exchange-correlation functional are needed to overcome the limitations.

2. We use the two reactions as a benchmark because the two reactions are the reaction model for the inhibition process of lipid peroxidation by melinjo resveratrol.

We address this question in the last paragraph of "1. Introduction" section. The paragraph is as follows. The relevant sentences are marked in bold.

`In the manuscript`

**In this study, we use four calculation methods for studying the $^{\bullet}$OOH radical-scavenging reaction of trans-resveratrol and gnetin C.** We aim to examine the effect of long-range and dispersion correction on the transition state and activation energy of the two radical-scavenging reactions. We use B3LYP as a referenced functional since it is the most popular density functionals in chemistry [30] and has provided a good prediction in our previous studies. [31-33] We use a version of B3LYP that has been corrected using the Coulomb-attenuating method in CAM-B3LYP exchange-correlation functionals [23] and B3LYP with the D3 version of Grimme's dispersion [25] for performing long-range and dispersion correction, respectively. As a comparison, we also use M06-2X functional [29]. **The two radical-scavenging reactions are the representative model for the inhibition process of lipid peroxidation by melinjo resveratrol.**

3. M06-2X is a hybrid functional designed for the main group thermochemistry, barrier heights, and non-covalent interactions. [2, 3] Unlike CAM-B3LYP (long-range correction) and B3LYP+GD3 (dispersion correction), M06-2X accounts for non-covalent interactions implicitly by parameterization and has an improved accuracy to describe such a system. Therefore, we use M06-2X in our work.

The connection of choosing M06-2X with other functionals is explained in the third paragraph of the “1. Introduction” section. The paragraph is as follows. The explanation about M06-2X is marked in blue font.

`In the manuscript`

One to handle the limitations is long-range correction. It improves calculations by partitioning exchange interaction into two regions, Hartree-Fock exchange at long-range interaction and pure DFT at short-range interaction. [23,24] However, long-range correction cannot describe the correct asymptotic $R^{-6}$ potential for large intermolecular distances. The potential can be described by dispersion correction, which adds an empirical term to account dispersion. [25–27] Another way to overcome the limitations is by applying the exchange-correlation functionals from Minnesota density functionals. M06-2X functional, one of Minnesota density functionals, has been tested in many cases–it improved the accuracy for thermodynamic, kinetics, and non-covalent parametric quantities of various simple chemical reactions. [28,29]

Question 5

Methods: The authors should explain in more detail what is the difference between the long-range and dispersion correction.

We understand the reviewer's concern. To maintain the story flow of the manuscript, we explain the difference between the long-range and dispersion correction in the third paragraph of “1. Introduction”. The paragraph is as follows.

`In the manuscript`

One way to handle DFT limitations is long-range correction. It improves calculations by partitioning exchange interaction into two regions, Hartree-Fock exchange at long-range interaction and pure DFT at short-range interaction. [23,24] However, long-range correction cannot describe the correct asymptotic $R^{-6}$ potential for large intermolecular distances. The potential can be describe by dispersion correction, which adds an empirical term to account dispersion. [25–27] Another way to overcome the limitations is by applying the exchange-correlation functionals from Minnesota density functionals. M06-2X functional, one of Minnesota density functionals, has been tested in many cases–it improved the accuracy for thermodynamic, kinetics, and non-covalent parametric quantities of various simple chemical reactions. [28,29]

Question 6

Results, Table 3, reaction energies. What are the values obtained with the B3LYP method?

There is no value of reaction energy obtained with the B3LYP method in Table 3. The only energy parameter in Table 3 is the relative electronic energy of [RO−H−OOH] complex, $E_{\mathrm{r}}$. The [RO−H−OOH] complex energy obtained by M1 is used as a reference. Therefore, the energy is set to be zero.

To avoid misleading the reader, we decide to change $E_r$ into $E_{\mathrm{rel.}}$ in Table 3.

Question 7

Results, section 3.3. From this analysis, it is difficult to understand what method is right or wrong, especially for the reaction energies. The authors should find a real reference value such as higher-level calculations. This is an important aspect of the paper that the authors should consider otherwise the manuscript is simply the comparison of the results obtained with four different DFT methods.

We appreciate the reviewer's opinion. However, in this case, we have a different point of view.

To the best of our knowledge, there is no real reference value for the reaction and activation energy of the radical scavenging reaction of trans-resveratrol and OOH, both from experimental results and from higher-level calculation results.

Furthermore, this study is part of a continuous kinetic study. For the current stage, we focus on studying the interaction that can not be ignored in the radical scavenging activity of resveratrol, instead of obtaining accuracy in the activation and reaction energy. This study is only possible when we do a comparative study with four different DFT methods. We will continue our study to obtain accuracy in the kinetics of the radical scavenging reaction for future stage.

As a choice of functionals, we recommend exchange-correlation that incorporates the correction for the coulombic interaction in the long range region. CAM-B3LYP and M06-2X fits into this category.

`END`

## References

[1] Foresman JB, Frisch A. 2015 Exploring Chemistry with Electronic Structure Methods, 3rd ed., Gaussian, Inc.: Wallingford, CT.

[2] La Rocca V, Malvina R, Ringeissen S, Gomar J, Frantz MC, Ngom S, Adamo C. 2016 Benchmarking the DFT methodology for assessing antioxidant-related properties: quercetin and edaravone as case studies. Journal of Molecular Modeling 22.

[3] Zhao Y, Truhlar DG. 2008 The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: two new functionals and systematic testing of four M06-class functionals and 12 other functionals. Theoretical Chemistry Accounts 120, 215–241

## Table 1

List of methods and their notation.

## Table 2

The selected geometric parameters of (a) trans-resveratrol and (b) hydroperoxyl in the ground state, the bond length (*R*, in Å), the bond angle (*A*, in degree), and the dihedral angle (*D*, in degree). Parameter (i) -- (xii) and (xv) -- (xvii) are the discrepancy from the experimental values. Parameter (xiii) is the difference between ring A and ring B calculated with the same method. Parameter (xiv) is the absolute value (without any reference).

## Table 3

The difference of selected parameters of [RO-H-OOH] complex [1c] from M1. (a) is the torsion angle (degree), (b) - (f) are the interatomic distance (Å), (g) is the bond angle (degree). For (h), the relative electronic energy (eV), M1 is set to be the reference.

## Figure 1

Molecular model for ROH in this study with the nomenclature used throughout the manuscript. The numbering of oxygen and hydrogen followed the numbering of its attaching carbon. The A, B, C, and D indexes at the first carbon atom in each ring referred to phenyl ring's labels. The prime, dagger, and double dagger symbols were for numbering ring B, C, and D respectively.

## Figure 2

Optimized activated complex structures for trans-resveratrol and gnetin C with •OOH. Blue, red, yellow atoms represented H, O and C atoms. The black atom is O at the active site 4', written as O4' in the texts. The numbers in parentheses represent the required imaginary vibrational frequency for a transition state, the elongation of O4' -H and Oa - Ob bonds with respect to its ground state bond length.

## Figure 3

The reaction in Scheme 1 in an energy level diagram. The y-axis is the relative free Gibbs energy at room temperature ($G°_{rel}$) with the total energy of reactant calculated by M1 as the reference. For clarity, only ($G°$) of reactants are written and the parenthesized numbers are the ($\Delta G°$) with respect to the reactant's total energy.

Table 1

| | | |
|---|---|---|
| M1 | B3LYP | The reference throughout the analysis |
| M2 | B3LYP with GD3 | London dispersion correction |
| M3 | CAM-B3LYP | long-range correction on the coulombic interaction |
| M4 | M06-2X | Parameterization and evaluation for non-covalent interactions |

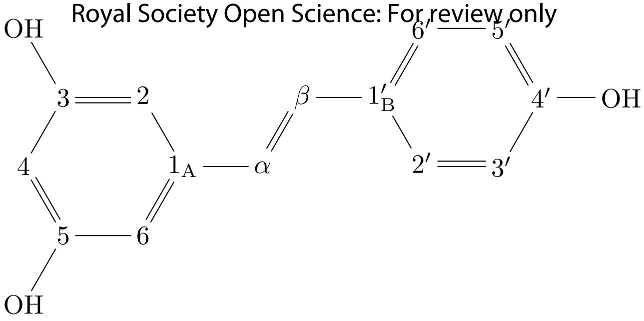
Tabel 2

| | Parameter | Expr. | M1 | M2 | M3 | M4 |
|---|---|---|---|---|---|---|
| (a) | Trans-resveratrol | | | | | |
| (i) | *R* (3, 2) | 1.387 | +0.006 | +0.006 | +0.001 | +0.004 |
| (ii) | *R* (2,1) | 1.404 | +0.002 | +0.002 | -0.006 | -0.005 |
| (iii) | *R* (1, α) | 1.471 | -0.003 | -0.003 | -0.001 | 0.000 |
| (iv) | *R* (α, β) | 1.338 | +0.012 | +0.012 | +0.002 | +0.004 |
| (v) | *R* (β, 1′) | 1.462 | +0.003 | +0.003 | +0.006 | +0.007 |
| (vi) | *R* (1′, 2′) | 1.400 | +0.009 | +0.009 | +0.000 | +0.001 |
| (vii) | *R* (2′, 3′) | 1.385 | +0.007 | +0.007 | +0.003 | +0.005 |
| (viii) | *R* (5, O) | 1.378 | -0.008 | -0.008 | -0.014 | -0.016 |
| (ix) | *R* (4′, O) | 1.381 | -0.011 | -0.011 | -0.017 | -0.019 |
| (x) | *A* (4, 5, 6) | 121.1 | 0.0 | 0.0 | +0.0 | +0.1 |
| (xi) | *A* (1, α, β) | 126.0 | +0.8 | +0.6 | +0.2 | -0.7 |
| (xii) | *A* (3′, 4′, 5′) | 120.3 | -0.6 | -0.6 | -0.5 | -0.3 |
| (xiii) | *D* (A, B) | 8.7 | 17.4 | 21.2 | 30.5 | 39.6 |
| (xiv) | *D* (3′, 4′, O, H) | 32.0 | 0.0 | 0.0 | 0.1 | 0.7 |
| (b) | Hydroperoxyl | | | | | |
| (xv) | *R* (Oa, Ob) | 1.335 | -0.001 | -0.001 | -0.014 | -0.023 |
| (xvi) | *R* (Ob, Hb) | 0.977 | +0.004 | +0.004 | +0.001 | -0.001 |
| (xvii) | *A* (Oa, Ob, Hb) | 104.1 | +1.4 | +1.4 | +1.7 | +1.7 |

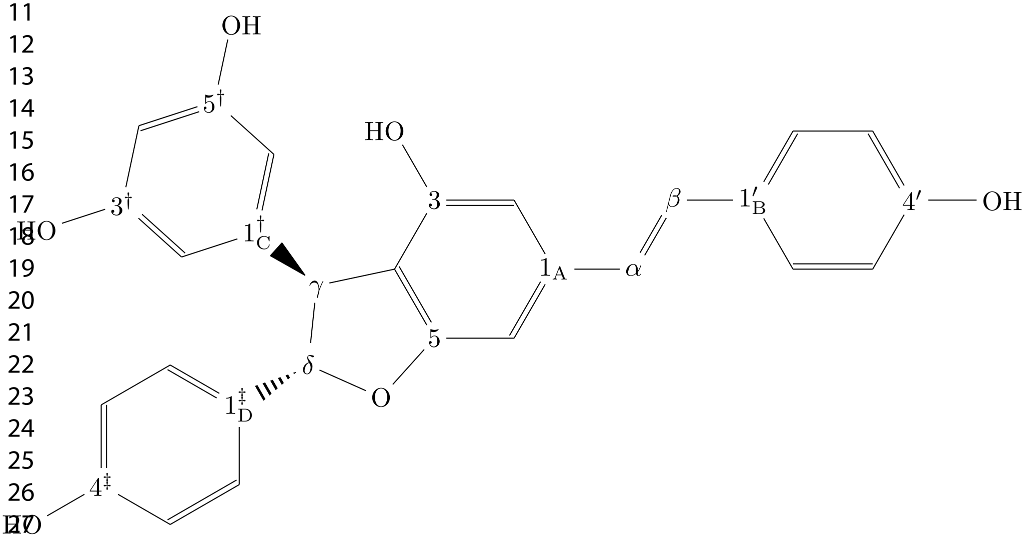
Note: Experimental values: trans-resveratrol from [40]; hydroperoxyl from [41].

Tabel 3

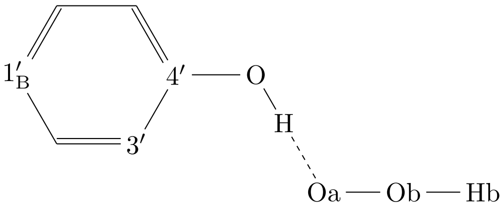
| Parameter | ROH | M1 | M2 | M3 | M4 |
|---|---|---|---|---|---|
| (a) $\phi$ (3′, 4′, O, H) | tR | 0.0 | +1.0 | +43.4 | -52.8 |
| | gC | 0.5 | +0.3 | +43.1 | -55.5 |
| (b) $R$ (H4′, Oa) | tR | 1.296 | -0.001 | -0.008 | -0.030 |
| | gC | 1.307 | -0.002 | -0.010 | -0.034 |
| (c) $R$ (H3′, Hb) | tR | 3.234 | -0.041 | +0.274 | +0.384 |
| | gC | 3.231 | -0.040 | +0.278 | +0.338 |
| (d) $R$ (H3′, Ob) | tR | 2.317 | -0.039 | +0.313 | +0.437 |
| | gC | 2.314 | -0.038 | +0.319 | +0.460 |
| (e) $R$ (Oa, Ob) | tR | 1.406 | 0.001 | -0.026 | -0.037 |
| | gC | 1.406 | 0.001 | -0.027 | -0.039 |
| (f) $R$ (Ob, Hb) | tR | 0.972 | 0.000 | +0.001 | 0.000 |
| | gC | 0.971 | 0.000 | +0.001 | 0.000 |
| (g) $A$ (Oa, Ob, Hb) | tR | 101.9 | 0.0 | +1.4 | +2.0 |
| | gC | 101.9 | 0.0 | +1.5 | +2.1 |
| (h) $E_{rel}$ | tR | 0 | -0.69 | +12.21 | +11.11 |
| | gC | 0 | -1.65 | +22.30 | +19.15 |



(a) Trans-resveratrol (tR) in the ground state



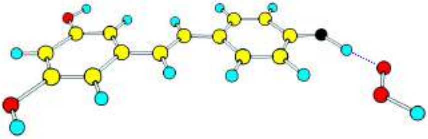
(b) Gnetin C (gC) in the ground state



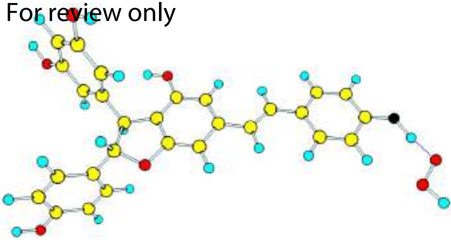
(c) Ring B and hydroperoxyl in the [TS]

[tR–OOH] [gC–OOH]

M1

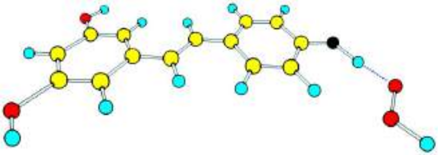


(-1374/cm, 0.151 Å, 0.072 Å)

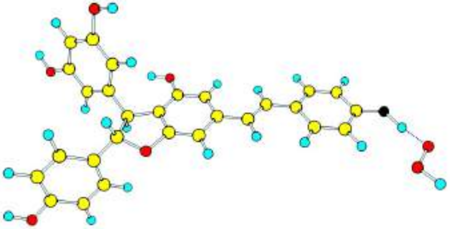


(-1295/cm, 0.145 Å, 0.073 Å)

M2

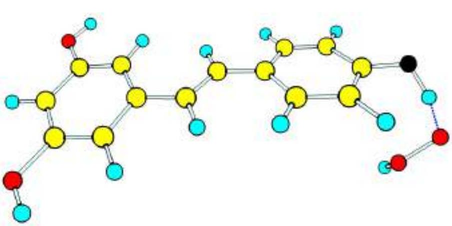


(-1369/cm, 0.152 Å, 0.073 Å)

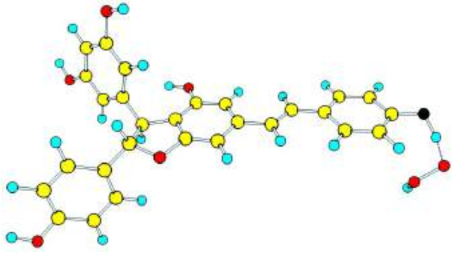


(-1294/cm, 0.146 Å, 0.074 Å)

M3

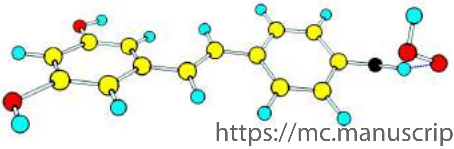


(-2100/cm, 0.135 Å, 0.059 Å)

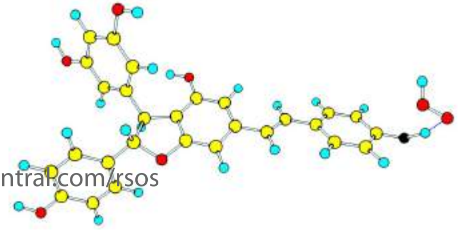


(-2053/cm, 0.130 Å, 0.058 Å)

M4



(-2050/cm, 0.151 Å, 0.056 Å)



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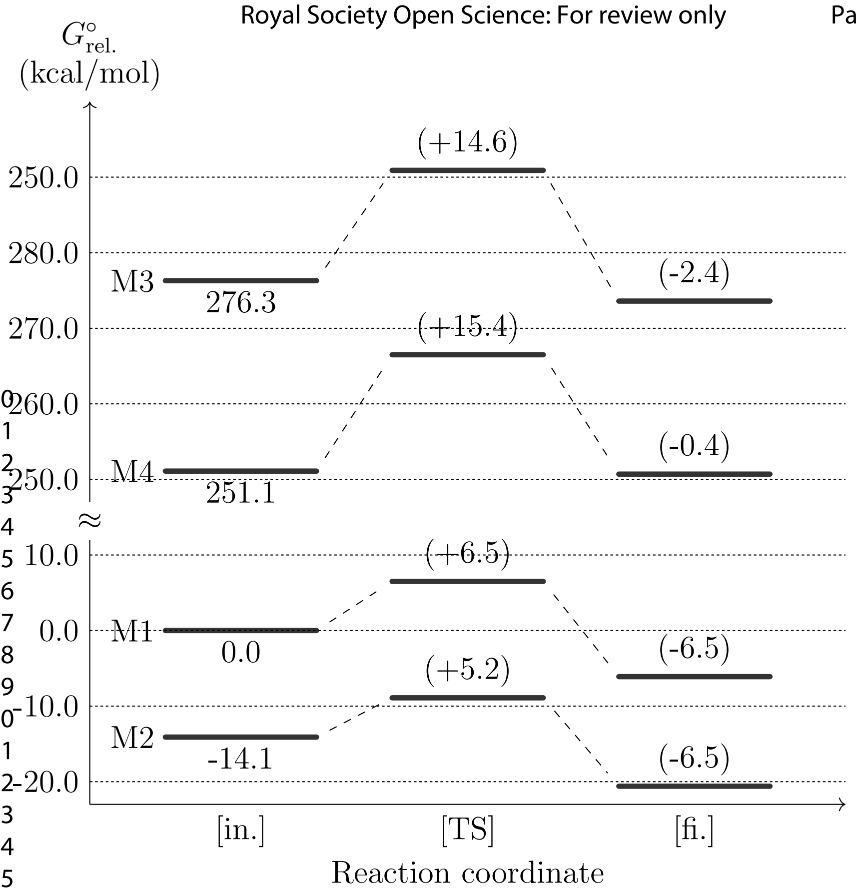
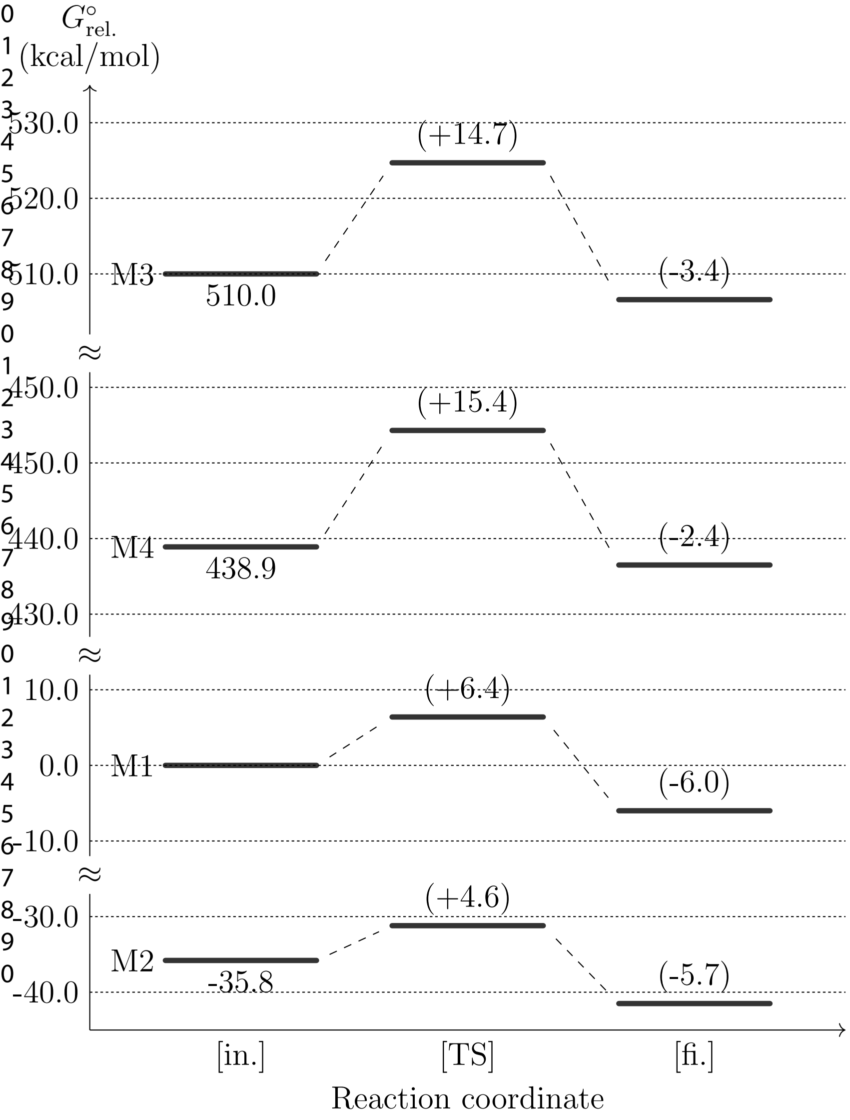


(a) For trans-reveratrol scavenging



(b) For gnetin C scavenging

# 5. Manuskrip Diterima

**Vera Khoirunisa <vera.khoirunisa@tf.itera.ac.id>**

# Royal Society Open Science - Decision on Manuscript ID RSOS-201127.R1

3 messages

**Royal Society Open Science** <onbehalfof@manuscriptcentral.com>  Wed, Dec 23, 2020 at 4:10 PM

Reply-To: chemistryopenscience@rsc.org
To: vera.khoirunisa@tf.itera.ac.id
Cc: vera.khoirunisa@tf.itera.ac.id, rusydi@fst.unair.ac.id, lusia_silfia@yahoo.co.id, ira-p@fst.unair.ac.id, h_rachmawati@fa.itb.ac.id, dipojono@gmail.com, journal-submit@datadryad.org, openscience@royalsociety.org

This year has been very difficult for everyone, and we want to take the opportunity to thank you for your continued support in 2020.

The Royal Society Open Science editorial office will be closed from the evening of Friday 18 December 2020 until Monday 4 January 2021. We will not be responding during this time. If you have received a deadline within this time period, please contact us as soon as possible to allow us to extend the deadline. If you receive any automated messages during this time asking you to meet a deadline, we offer apologies and invite you to respond after the festive period or during normal working hours.

With our best for a peaceful festive period and New Year, and we look forward to working with you in 2021.

Dear Ms Khoirunisa:

Title: The significance of long-range correction to the hydroperoxyl radical-scavenging reaction of trans-resveratrol and gnetin C
Manuscript ID: RSOS-201127.R1

It is a pleasure to accept your manuscript in its current form for publication in Royal Society Open Science. The chemistry content of Royal Society Open Science is published in collaboration with the Royal Society of Chemistry.

The comments of the reviewer(s) who reviewed your manuscript are included at the end of this email.

Thank you for your fine contribution. On behalf of the Editors of Royal Society Open Science and the Royal Society of Chemistry, I look forward to your continued contributions to the Journal.

Yours sincerely,
Dr Laura Smith
Publishing Editor, Journals

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Royal Society Open Science - Chemistry Editorial Office

On behalf of the Subject Editor Professor Anthony Stace and the Associate Editor Professor Kim Jelfs.

********

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Comments to the Author:
(There are no comments.)

RSC Subject Editor:
Comments to the Author:
(There are no comments.)

*********

Reviewer(s)' Comments to Author:
Reviewer: 1

Comments to the Author(s)
The authors made the necessary revisions and addressed the comments and questions. The manuscript is recommended for publication.

***************************

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Abstract: Density functional theory has been gaining popularity for studying the radical scavenging activity of antioxidants. However, only a few studies investigate the importance of calculation methods on the radical-scavenging reactions. In this study, we examined the significance of (1) the long-range correction on the coulombic interaction and (2) the London dispersion correction to the hydroperoxyl radical-scavenging reaction of trans-resveratrol and gnetin C. We employed B3LYP, CAM-B3LYP, M06-2X exchange-correlation functionals, and B3LYP with the D3 version of Grimme's dispersion in the calculations. The results showed that long-range correction on the coulombic interaction had a significant effect on the increase of reaction and activation energies. The increase was in line with the change of hydroperoxyl radical's orientation in the transition state structure. Meanwhile, the London dispersion correction only had a minor effect on the transition state structure, reaction energy, and activation energy. Overall, long-range correction on the coulombic interaction had a significant impact on the radical-scavenging reaction.
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Thank you very much for your assistance.

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# The significance of long-range correction to the hydroperoxyl radical-scavenging reaction of trans-resveratrol and gnetin C

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Density functional theory has been gaining popularity for studying the radical scavenging activity of antioxidants. However, only a few studies investigate the importance of calculation methods on the radical-scavenging reactions. In this study, we examined the significance of (i) the long-range correction on the coulombic interaction and (ii) the London dispersion correction to the hydroperoxyl radical-scavenging reaction of trans-resveratrol and gnetin C. We employed B3LYP, CAM-B3LYP, M06-2X exchange-correlation functionals and B3LYP with the D3 version of Grimme's dispersion in the calculations. The results showed that long-range correction on the coulombic interaction had a significant effect on the increase of reaction and activation energies. The increase was in line with the change of hydroperoxyl radical's orientation in the transition state structure. Meanwhile, the London dispersion correction only had a minor effect on the transition state structure, reaction energy and activation energy. Overall, long-range correction on the coulombic interaction had a significant impact on the radical-scavenging reaction.

# 1. Introduction

Radical scavenging is an important property of antioxidants. It is the act of antioxidant to deactivate or remove free radicals to prevent oxidative damage in the biological system. A common radical scavenging example is the inhibition process of lipid peroxidation. In the inhibition process, an antioxidant scavenges the peroxyl radical to stop the chain reaction, which leads to lipid peroxidation. A phenolic antioxidant, such as resveratrol, is known to scavenge the peroxyl radical by donating its hydrogen atom [1]. The hydrogen donation can be affected by non-covalent interactions such as hydrogen bonding and steric repulsion in the system. Therefore, it is expected that non-covalent interactions significantly influence the activity of phenolic antioxidant [2].

The radical scavenging activity of antioxidants is widely studied theoretically using density functional theory (DFT) [1,3–16]. DFT has been successfully predicted the antioxidant activity through thermodynamic quantities [1,17–19]. However, the limitation of exchange-correlation functionals in DFT for non-covalent interaction and barrier height calculations [20–22] are the challenges for studying the radicals scavenging reaction that leads to reaction kinetics and mechanism. Therefore, corrections to exchange-correlation functionals are needed to overcome the limitations.

One to handle the limitation of exchange-correlation functionals in DFT is the long-range correction. It improves calculations by partitioning exchange interaction into two regions, Hartree–Fock exchange at long-range interaction and pure DFT at short-range interaction [23,24]. However, long-range correction cannot describe the correct asymptotic $R^{-6}$ potential for large intermolecular distances. The potential can be described by dispersion correction, which adds an empirical term to account for dispersion [25–27]. Another way to overcome the limitations is by applying the exchange-correlation functionals from Minnesota density functionals. M06-2X functional, one of Minnesota density functionals, has been tested in many cases—it improved the accuracy for thermodynamic, kinetics and non-covalent parametric quantities of various simple chemical reactions [28,29].

In this study, we use four calculation methods for studying the hydroperoxyl radical-scavenging reaction of trans-resveratrol and gnetin C. We aim to examine the effect of long-range and dispersion correction on the transition state and activation energy of the two radical-scavenging reactions. We use B3LYP as a referenced functional since it is the most popular density functionals in chemistry [30] and has provided a good prediction in our previous studies [31–33]. We use a version of B3LYP that has been corrected using the Coulomb-attenuating method in CAM-B3LYP exchange-correlation functionals [23] and B3LYP with the D3 version of Grimme's dispersion [25] for performing long-range correction on the coulombic interaction and London dispersion correction, respectively. As a comparison, we also use M06-2X functional [29]. The two radical-scavenging reactions are the representative model for the inhibition process of lipid peroxidation by melinjo resveratrol.

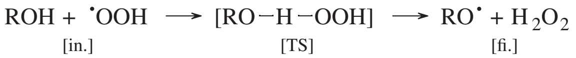
# 2. Model and computational details

## 2.1. Reaction model

We modelled the radical-scavenging reaction based on the hydrogen atom transfer (HAT) mechanism, as shown in scheme 1. In the initial and final states (abbreviated to [in.] and [fi.], respectively), molecules were in the ground state. The reactants were ROH (an antioxidant agent) and $^{\bullet}$OOH (hydroperoxyl, a model of peroxyl radicals in general). We used two antioxidant agents from melinjo–trans-resveratrol (tR) and gnetin C (gC)–as shown in figure 1*a*,*b* respectively. We only considered one active site of ROH for the hydrogen donation, which was 4′OH site, as shown in figure 1*c*. It was the lowest bond dissociation energy among other sites [34,35]. Between [in.] and [fi.], we considered one transition state [TS], where we assumed the activated complexes, [RO—H—OOH], were formed.

## 2.2. Activation and reaction energy calculations

We constructed the reaction progress in an energy level diagram for scheme 1. It allowed us to calculate the reaction energy ($\Delta G^{\circ}$) and the activation energy ($\Delta^{\ddagger}G^{\circ}$) directly in terms of the standard Gibbs free



$$\underset{[\text{in.}]}{\mathrm{ROH} + {}^{\bullet}\mathrm{OOH}} \longrightarrow \underset{[\text{TS}]}{[\mathrm{RO{-}H{-}OOH}]} \longrightarrow \underset{[\text{fi.}]}{\mathrm{RO}^{\bullet} + \mathrm{H_2O_2}}$$

**Scheme 1.** The radical-scavenging reaction model, with [in.], [TS] and [fi.] were initial, transition and final states.

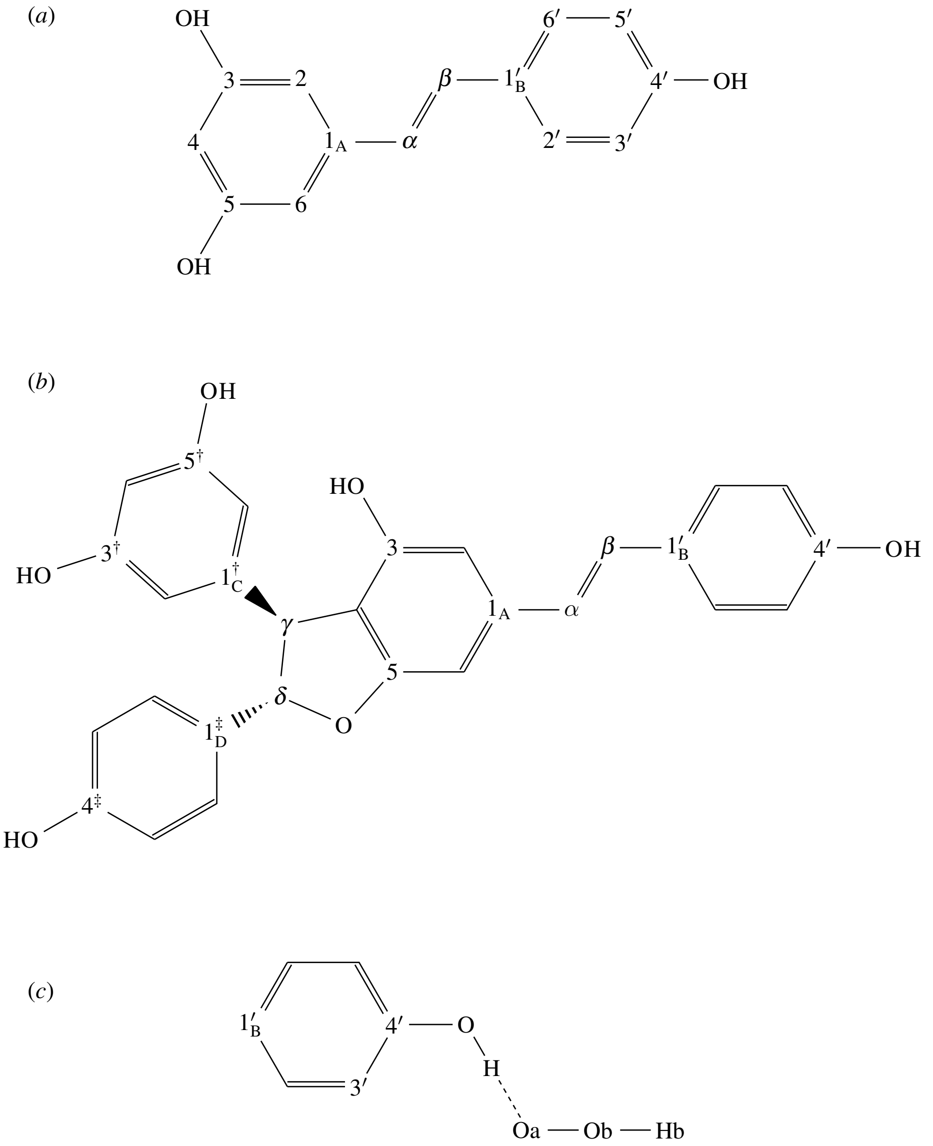


**Figure 1.** Molecular model for ROH in this study with the nomenclature used throughout the manuscript. The numbering of oxygen and hydrogen followed the numbering of its attaching carbon. The A, B, C and D indexes at the first carbon atom in each ring referred to phenyl ring's labels. The prime, dagger and double dagger symbols were for numbering ring B, C and D, respectively. (*a*) Trans-resveratrol (tR) in the ground state. (*b*) Gnetin C (gC) in the ground state. (*c*) Ring B and hydroperoxyl in the [TS].

energy at 298.15 K. $\Delta G^{\circ}$ was the energy difference between [fi.] and [in.]:

$$\Delta G^{\circ} = (G^{\circ}_{\mathrm{RO}^{\bullet}} + G^{\circ}_{\mathrm{H_2O_2}}) - (G^{\circ}_{\mathrm{ROH}} + G^{\circ}_{{}^{\bullet}\mathrm{OOH}}), \tag{2.1}$$

while $\Delta^{\ddagger}G^{\circ}$ was the energy difference between [TS] and [in.]

$$\Delta^{\ddagger}G^{\circ} = G^{\circ}_{\mathrm{TS}} - (G^{\circ}_{\mathrm{ROH}} + G^{\circ}_{{}^{\bullet}\mathrm{OOH}}). \tag{2.2}$$

$G^{\circ}$ is the total electronic energy with a correction from Gibbs free energy.

**Table 1.** List of methods and their notation.

| | | |
|---|---|---|
| M1 | B3LYP | the reference throughout the analysis |
| M2 | B3LYP with GD3 | London dispersion correction |
| M3 | CAM-B3LYP | long-range correction on the coulombic interaction |
| M4 | M06-2X | parameterization and evaluation for non-covalent interactions |

### 2.3. DFT calculation set-up

We used DFT calculations for obtaining the geometry in the ground and the transition states. In addition to the DFT calculations, we coupled it with frequency calculations at 298.15 K to determine the Gibbs free energy correction. Furthermore, we used NBO calculations for the charge population analysis.

While we only used one basis set, which was 6-31++G(d,p), we performed all calculations using three different exchange-correlational functionals (XCs), namely B3LYP, CAM-B3LYP and M06-2X. We also performed the calculations using B3LYP with D3 version of Grimme's dispersion (GD3). Therefore, we were able to study the effect of long-range correction on the coulombic interaction and London dispersion correction in the transition state. List of methods and their notation is shown in table 1.

The routine calculations were as follows. First, we performed the geometry optimization to obtain the most stable spin-state. We considered singlet, triplet and quintet spin state for molecules with an even number of electrons. As for molecules with an odd number of electrons, the doublet and quartet spin state were considered. Second, we used the most stable spin-state for further calculations to obtain the optimized geometry and energy of molecules in the ground and transition state. We obtained the transition state by tracking a particular vibrational mode that decreased along the designed pathway, as demonstrated in our previous study [36]. We began the geometry optimization by employing B3LYP. The optimized structures were re-optimized with B3LYP + GD3, CAM-B3LYP and M06-2X. The relevant activated complex structures were the ones with the vibration of H atom between the 4′—OH site and $^{\bullet}$OOH having the imaginary frequency. All calculations were done in the gas phase using Gaussian 09 software [37].

## 3. Results and discussions

### 3.1. The ground state structures

The optimization geometry calculations for trans-resveratrol and gnetin C using three XCs obtained spin-singlet state was the lowest in energy level. The energy difference between the singlet and triplet states was about 2.0 eV (trans-resveratrol) and 6.5 eV (gnetin C); while between the singlet and quintet states was about 6.2 eV (trans-resveratrol) and 10.4 eV (gnetin C). The differences are significant, which indicates that the spin-singlet state is very stable. The result agrees with the most organic compounds that are stable in the spin-singlet state, with carbenes as the exception [38,39]. Therefore, we only considered the spin-singlet state for further calculations. As for hydroperoxyl, the spin-doublet was the ground state and the next spin state was a quintet with energy difference 2.8 eV on average. Overall, the obtained ground state geometries of trans-resveratrol and hydroperoxyl were in good agreement with the experimental result, as shown in table 2(a.i)—(a.xii) and (b.xv)—(b.xvii).

The discrepancies were less than 0.017 Å and 1.4 °, which were considered accurate for DFT calculations. [30] The higher discrepancies were for C4′—O bond length and Oa—Ob—Hb bond angle by M3 and M4. However, when we considered the experimental error, these values were still in the range. Therefore, all methods were capable to determine an accurate geometric structure for trans-resveratrol and hydroperoxyl. It implies we can use all methods for further calculations.

In detail, there was a significant difference in the dihedral angles of trans-resveratrol [table 2(a.xiii)]. The calculations obtained phenyl ring A and B were twisted, while experimental showed they were preferably planar. The NBO calculations determined that all hydrogens were positively charged (see electronic supplementary material, table S1); hence the coulombic repulsions of H2′—H$\alpha$ and H2—H$\beta$ were responsible for *Dcolon*(A, B). However, the coulombic repulsions were unlikely to play a dominant role in the experiment. As Zarychta *et al.* [40] reported, trans-resveratrol was prepared in crystal form, where one trans-resveratrol was surrounded by six others. Each trans-resveratrol formed hydrogen bonds with its six neighbour molecules through OH—O. The hydrogen bonds were

**Table 2.** The selected geometric parameters of (a) trans-resveratrol and (b) hydroperoxyl in the ground state, the bond length (*R*, in Å), the bond angle (*A*, in degree) and the dihedral angle (*D*, in degree). Parameter (i)—(xii) and (xv)—(xvii) are the discrepancy from the experimental values. Parameter (xiii) is the difference between ring A and ring B calculated with the same method. Parameter (xiv) is the absolute value (without any reference).

| | parameter | Expr. | M1 | M2 | M3 | M4 |
|---|---|---|---|---|---|---|
| (a) | trans-resveratrol | | | | | |
| (i) | $R(3, 2)$ | 1.387 | +0.006 | +0.006 | +0.001 | +0.004 |
| (ii) | $R(2, 1)$ | 1.404 | +0.002 | +0.002 | −0.006 | −0.005 |
| (iii) | $R(1, \alpha)$ | 1.471 | −0.003 | −0.003 | −0.001 | 0.000 |
| (iv) | $R(\alpha, \beta)$ | 1.338 | +0.012 | +0.012 | +0.002 | +0.004 |
| (v) | $R(\beta, 1')$ | 1.462 | +0.003 | +0.003 | +0.006 | +0.007 |
| (vi) | $R(1', 2')$ | 1.400 | +0.009 | +0.009 | +0.000 | +0.001 |
| (vii) | $R(2', 3')$ | 1.385 | +0.007 | +0.007 | +0.003 | +0.005 |
| (viii) | $R(5, 0)$ | 1.378 | -0.008 | −0.008 | −0.014 | −0.016 |
| (ix) | $R(4', 0)$ | 1.381 | −0.011 | −0.011 | −0.017 | −0.019 |
| (x) | $A(4, 5, 6)$ | 121.1 | 0.0 | 0.0 | 0.0 | +0.1 |
| (xi) | $A(1, \alpha, \beta)$ | 126.0 | +0.8 | +0.6 | +0.2 | −0.7 |
| (xii) | $A(3', 4', 5')$ | 120.3 | −0.6 | −0.6 | −0.5 | −0.3 |
| (xiii) | $D(\mathrm{A}, \mathrm{B})$ | 8.7 | 17.4 | 21.2 | 30.5 | 39.6 |
| (xiv) | $D(3', 4', 0, \mathrm{H})$ | 32.0 | 0.0 | 0.0 | 0.1 | 0.7 |
| (b) | hydroperoxyl | | | | | |
| (xv) | $R$ (Oa, Ob) | 1.335 | −0.001 | −0.001 | −0.014 | −0.023 |
| (xvi) | $R$ (Ob, Hb) | 0.977 | +0.004 | +0.004 | +0.001 | −0.001 |
| (xvii) | $A$ (Oa, Ob, Hb) | 104.1 | +1.4 | +1.4 | +1.7 | +1.7 |

Note: Experimental values: trans-resveratrol from [40]; hydroperoxyl from [41].

predominant over the coulombic repulsions; hence the measured dihedral angle showed the rings were preferably planar.

We also showed the planarity of H4′ in term of the dihedral angle $D(3', 4', \mathrm{O}, \mathrm{H})$ [table 2(a.xiv)]. This particular H atom would be interacting with $^{\bullet}$OOH in the transition state. The experimental value showed that it was not planar. It was due to the aforementioned experimental condition. However, all methods obtained planar H4′ with respect to Ring B. We shall recall this quantity later in the activation energy discussion.

We remarked that the dihedral angle calculation was sensitive to the calculation method. The comparison results among four calculation methods showed that dispersion (M2) and long-range correction (M3) increased the twisting $D(\mathrm{A}, \mathrm{B})$. Both simultaneously corrections (M4) increased $D(\mathrm{A}, \mathrm{B})$ even further. This trend was consistent for the case of gnetin C (see electronic supplementary material, table S2). The results suggest the long-range correction plays a dominant role in the twisting compared to the dispersion correction.

## 3.2. The transition state structures

Figure 2shows the optimized structures in the [TS] of scheme 1 obtained from all calculation methods for both trans-resveratrol and gnetin C. All structures possessed a single imaginary frequency, which was the O4″—H—OOH vibration. The magnitudes of imaginary frequency were more than 1300 cm$^{-1}$ for trans-resveratrol and 1200/cm for gnetin C. These magnitudes were strong, which indicated that the O4′—H—OOH vibration encouraged the displacement of H4′. The displacement of H4′ can also be seen from the elongation of O4′—H bond length, which was about 0.140 Å (or, 15% longer than in its ground state). Meanwhile, the Oa—Ob bond of $^{\bullet}$OOH was not significantly elongated (only about 5%).

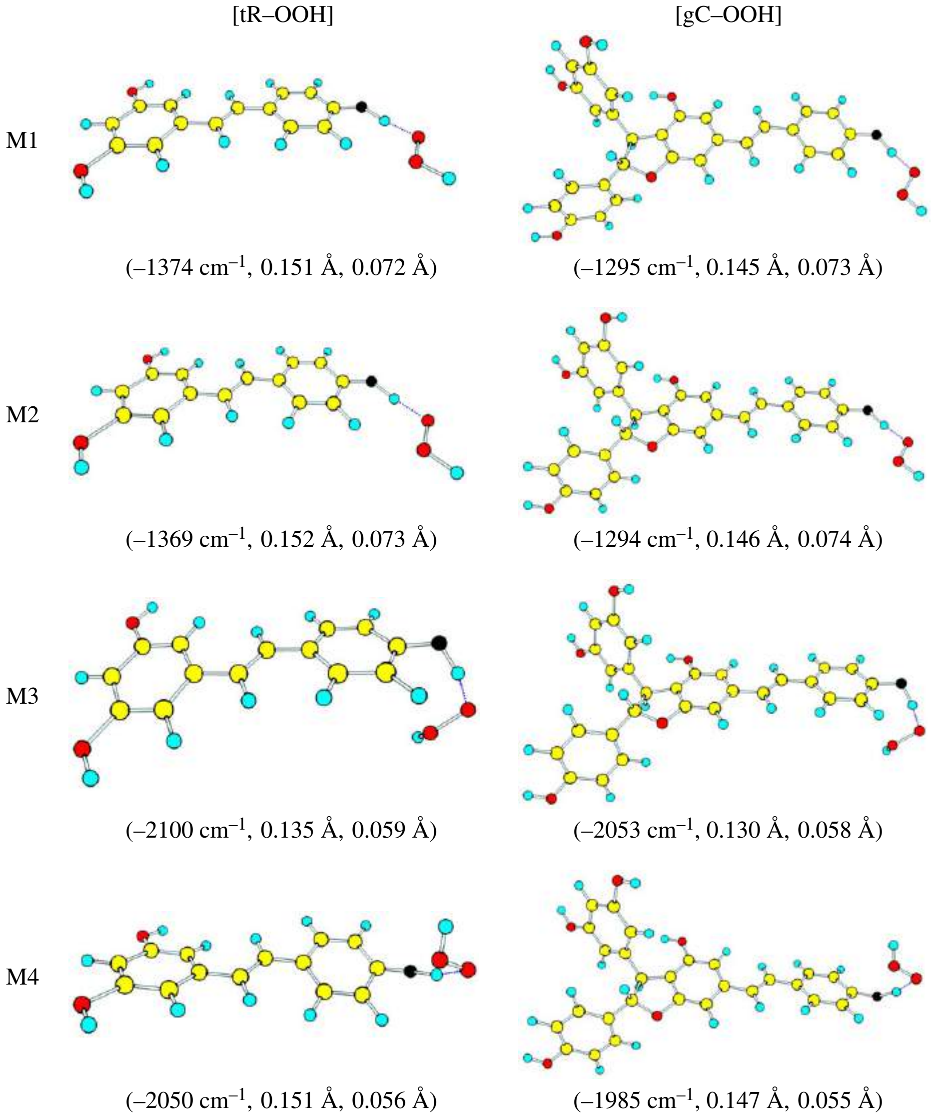


**Figure 2.** Optimized activated complex structures for trans-resveratrol and gnetin C with $^{\bullet}$OOH. Blue, red, yellow atoms represented H, O and C atoms. The black atom is O at the active site 4′, written as O4′ in the texts. The numbers in parentheses represent the required imaginary vibrational frequency for a transition state, the elongation of O4′—H and Oa—Ob bonds with respect to its ground state bond length.

It means $^{\bullet}$OOH is attracting H4′. Therefore, the obtained structures are the activation complex of the radical-scavenging reaction in scheme 1.

The optimized [TS] structures revealed the different orientation of $^{\bullet}$OOH with respect to the ring B in the activated complexes. The presence of ring C and D did not contribute to the orientation, as the orientation was alike between [tR-OOH] and [gC-OOH]. However, the change in calculation methods altered the orientation. The significant alteration was obtained by M3 and M4, which implies that long-range correction plays a significant role in the orientation.

The orientation of $^{\bullet}$OOH in the activated complexes can be measured as a torsion angle of 3′— 4′—O—H, or $\phi$ (in degree). Table 3(a) shows the value of phi for all computational methods. Both M1 and M2 obtained phi was about zero, or $^{\bullet}$OOH was planar with respect to the ring B. However, $^{\bullet}$OOH was twisted up to 50 degrees according to M3 and M4 results. It implies that long-range correction was the reason for the twist. Therefore, the long-range correction plays a significant role both in the ground and the transition states of trans-resveratrol and gnetin C.

The origin of $^{\bullet}$OOH orientation is likely the same with the aforementioned ring A and B twisting origin in the ground state. The twisting presented after the long-range correction was introduced. Here, NBO calculations also determined that all the hydrogen atoms were positively charged, but

**Table 3.** The difference of selected parameters of [RO—H—OOH] complex [1c] from M1. (a) is the torsion angle (degree), (b–f) are the interatomic distance (Å), (g) is the bond angle (degree). For (h), the relative electronic energy (eV), M1 is set to be the reference.

| parameter | | ROH | M1 | M2 | M3 | M4 |
|---|---|---|---|---|---|---|
| (a) | $\phi$ (3′, 4′, 0, H) | tR | 0.0 | +1.0 | +43.4 | −52.8 |
| | | gC | 0.5 | +0.3 | +43.1 | −55.5 |
| (b) | $R$ (H4′, Oa) | tR | 1.296 | −0.001 | −0.008 | −0.030 |
| | | gC | 1.307 | −0.002 | −0.010 | −0.034 |
| (c) | $R$ (H3′, Hb) | tR | 3.234 | −0.041 | +0.274 | +0.384 |
| | | gC | 3.231 | −0.040 | +0.278 | +0.338 |
| (d) | $R$ (H3′, Ob) | tR | 2.317 | −0.039 | +0.313 | +0.437 |
| | | gC | 2.314 | −0.038 | +0.319 | +0.460 |
| (e) | $R$ (Oa, Ob) | tR | 1.406 | 0.001 | −0.026 | −0.037 |
| | | gC | 1.406 | 0.001 | −0.027 | −0.039 |
| (f) | $R$ (Ob, Hb) | tR | 0.972 | 0.000 | +0.001 | 0.000 |
| | | gC | 0s.971 | 0.000 | +0.001 | 0s.000 |
| (g) | $A$ (Oa, Ob, Hb) | tR | 101.9 | 0.0 | +1.4 | +2.0 |
| | | gC | 101.9 | 0.0 | +1.5 | +2.1 |
| (h) | $E_{\mathrm{rel}}$ | tR | 0 | −0.69 | +12.21 | +11.11 |
| | | gC | 0 | −1.65 | +22.30 | +19.15 |

Note: Negative value of $\phi$ means that O4′—H bond rotates in a clockwise direction.

both oxygen atoms in $^{\bullet}$OOH were negatively charged. Therefore, coulombic interactions between the closest atoms in ring B and $^{\bullet}$OOH are the reason for the twisting. While Oa was attracted to H4′, Hb was repelled by H3′. The effect of repulsion and attractions can be seen from the interatomic distance between these atoms. Table 3(b) and (c) show that H4′—Oa distances decreased while H3′—Hb distances increased after the long-range correction was introduced.

While the long-range correction determined the orientation of $^{\bullet}$OOH, the dispersion correction affected the interatomic distance [table 3(c) and (d)]. The latter contracted the interatomic distance of H—H and H—O by about 1.3% and 1.7%, respectively. The correction did not affect the covalent bond parameters [table 3(b), (e), (f) and (g)], which is reasonable since the dispersion only works in the non-covalent region. These results complemented the report by Grimme *et al.* [25]. They reported that the effect began to arise at about 2.0 Å for C—C interatomic distance. Meanwhile, the contraction of H—H and H—O showed a critical difference between M1 and M2. Both methods resulted in a planar $^{\bullet}$OOH's orientation, but the dispersion correction stabilize the activated complex, as shown in their electronic energy [table 3(h)]. The stability of the activated complex naturally affected the energy barrier so it may affect the kinetic study or even the reaction pathways.

## 3.3. The radical-scavenging reaction

Figure 3 shows the reaction progress of scheme 1 with the transition state described in the previous section. All methods predicted that the reaction was exergonic. The experiment demonstrated that this reaction was indeed exergonic by showing its observable antioxidant activity [42]. Even though the reaction occurred in the solution experimentally, other studies using DFT with M05-2X functional in aqueous solution also obtained exergonic. [13,14] Therefore, our results can be accountable for further analysis.

Even though all methods obtained an exergonic reaction for scheme 1, the dispersion (M2) and long-range (M3) correction led to a different result. Since the activated complex determined the product, the exergonic difference level was aligned with the orientation of $^{\bullet}$OOH: the more twisting, the less exergonic. Since the twisting was due to the long-range correction as we discussed previously [table 3(a–d)], it implies that long-range correction also affects a reaction's exergonic level.

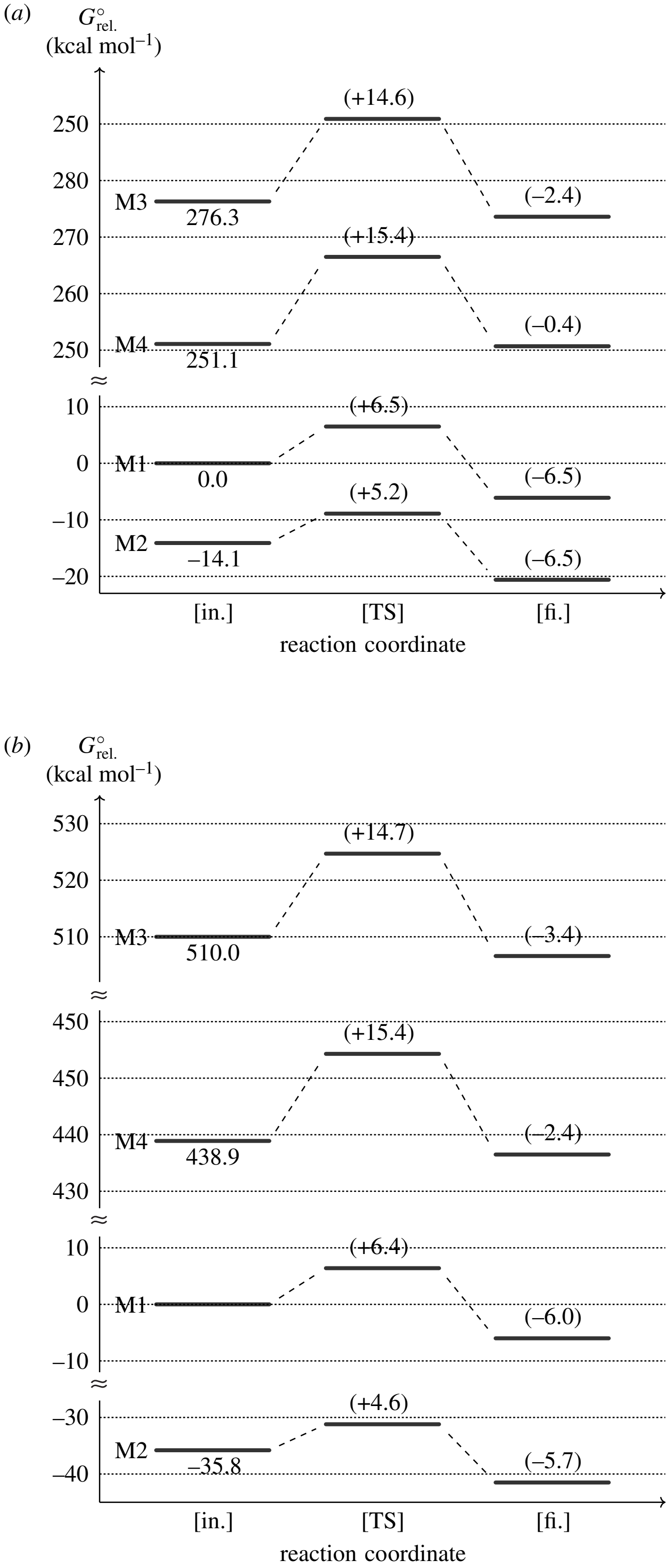


**Figure 3.** The reaction in scheme 1 in an energy level diagram. The *y*-axis is the relative free Gibbs energy at room temperature ($G^\circ_{\text{rel.}}$) with the total energy of reactant calculated by M1 as the reference. For clarity, only $G^\circ$ of reactants are written and the parenthesized numbers are the $\Delta G^\circ$ with respect to the reactant's total energy. (*a*) For trans-reveratrol scavenging, (*b*) For gnetin C scavenging.

Dispersion (M2) and long-range correction (M3) also result in a different activation energy ($\Delta^\ddagger G^\circ$). When compared with M1, the former decreased $\Delta^\ddagger G^\circ$ by more than 20%, while the latter increased $\Delta^\ddagger G^\circ$ by more than 120%. The trend of the activation energy is similar to that of the activation complex stability [table 3(h)]. It implies that the activated complex structure indeed determine the activation energy.

The increasing $\Delta^{\ddagger} G°$ by the long-range correction was remarkable. Regarding the planarity difference of H4′ with respect to Ring B between in the ground and the transition state, the former was plane [table 2(a.xiv)] and the later was twisted [table 3(a)]. The results suggest that the increasing $\Delta^{\ddagger} G°$ is due to the required energy to twist H4′ with respect to Ring B.

Overall, the similarity in the higher $\Delta G°$ and $\Delta^{\ddagger} G°$ calculations by M3 and M4 is a noteworthy results. It appears that the similarity originates from the Hatree–Fock exchange functional contribution to the selected calculation methods. B3LYP functional (M1) contained 20% of the Hartree–Fock exchange functional [43], CAM-B3LYP (M3) contained 19% for short-range and 65% for long-range exchange [23] and M06-2X (M4) contained 54% [29]. Therefore, the exact exchange such as Hartree–Fock functional plays a significant role in this study. It supported the study by Zhao & Truhlar [29] that recommends the use of M06-2X for studying the thermodynamic, kinetics and non-covalent interactions of the main-group element. Specifically, this study validates the study by Chai & Head-Gordon [44] that showed the importance of long-range corrected hybrid functional in thermochemistry, kinetics and non-covalent interactions calculations.

## 4. Conclusion

We have reported the effect of long-range and dispersion correction on the hydroperoxyl radical-scavenging reaction of trans-resveratrol and gnetin C. We found that long-range correction on the coulombic interaction, which was included in CAM-B3LYP, showed significant effects on the reaction. The effects predicted by CAM-B3LYP were similar to that of M06-2X. Both CAM-B3LYP and M06-2X predicted higher reaction and activation energy (in terms of Gibbs free energy) than B3LYP. The increase was 2.6–3.6 kcal mol$^{-1}$ (trans-resveratrol) and 3.7-5.7 kcal mol$^{-1}$ (gnetin C) for the reaction energy, while for activation energy, the increase was up to 8 kcal mol$^{-1}$. We argued that the higher values of reaction and activation energy were due to hydroperoxyl radicals' twisted orientation in the transition state. Hydroperoxyl radical was twisted up to 50° with respect to the phenyl ring attached to it. This twisted orientation of hydroperoxyl radical showed another similarity between CAM-B3LYP and M06-2X.

On the other hand, we noted that dispersion correction did not have a significant effect. B3LYP, without or with the Grimme's dispersion correction (GD3), obtained similar geometry and energy in the transition state. These results support other theoretical studies that reported the importance of long-range correction for the thermochemistry, kinetics and non-covalent interactions calculations. Therefore, our study verifies the significance of long-range correction in the hydroperoxyl radical-scavenging reaction of trans-resveratrol and gnetin C.

Data accessibility. The supporting data of this article has been uploaded as part of the electronic supplementary material.

Authors' contributions. V.K. carried out all simulations, participated in the design of the study, participated in data analysis and drafted the manuscript. F.R. conceived of the study, designed the methodology and critically revised the manuscript. L.S.P.B. and I.P. participated in data analysis. H.R. and H.K.D. critically revised the manuscript. All authors have read and agreed to the published version of the manuscript.

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# The significance of long-range correction to the hydroperoxyl radical-scavenging reaction of trans-resveratrol and gnetin C

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Density functional theory has been gaining popularity for studying the radical scavenging activity of antioxidants. However, only a few studies investigate the importance of calculation methods on the radical-scavenging reactions. In this study, we examined the significance of (i) the long-range correction on the coulombic interaction and (ii) the London dispersion correction to the hydroperoxyl radical-scavenging reaction of trans-resveratrol and gnetin C. We employed B3LYP, CAM-B3LYP, M06-2X exchange-correlation functionals and B3LYP with the D3 version of Grimme's dispersion in the calculations. The results showed that long-range correction on the coulombic interaction had a significant effect on the increase of reaction and activation energies. The increase was in line with the change of hydroperoxyl radical's orientation in the transition state structure. Meanwhile, the London dispersion correction only had a minor effect on the transition state structure, reaction energy and activation energy. Overall, long-range correction on the coulombic interaction had a significant impact on the radical-scavenging reaction.

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# 1. Introduction

Radical scavenging is an important property of antioxidants. It is the act of antioxidant to deactivate or remove free radicals to prevent oxidative damage in the biological system. A common radical scavenging example is the inhibition process of lipid peroxidation. In the inhibition process, an antioxidant scavenges the peroxyl radical to stop the chain reaction, which leads to lipid peroxidation. A phenolic antioxidant, such as resveratrol, is known to scavenge the peroxyl radical by donating its hydrogen atom [1]. The hydrogen donation can be affected by non-covalent interactions such as hydrogen bonding and steric repulsion in the system. Therefore, it is expected that non-covalent interactions significantly influence the activity of phenolic antioxidant [2].

The radical scavenging activity of antioxidants is widely studied theoretically using density functional theory (DFT) [1,3–16]. DFT has successfully predicted the antioxidant activity through thermodynamic quantities [1,17–19]. However, the limitation of exchange-correlation functionals in DFT for non-covalent interaction and barrier height calculations [20–22] are the challenges for studying the radicals scavenging reaction that leads to reaction kinetics and mechanism. Therefore, corrections to exchange-correlation functionals are needed to overcome the limitations.

One way to handle the limitation of exchange-correlation functionals in DFT is the long-range correction. It improves calculations by partitioning exchange interaction into two regions, Hartree–Fock exchange at long-range interaction and pure DFT at short-range interaction [23,24]. However, long-range correction cannot describe the correct asymptotic $R^{-6}$ potential for large intermolecular distances. The potential can be described by dispersion correction, which adds an empirical term to account for dispersion [25–27]. Another way to overcome the limitations is by applying the exchange-correlation functionals from Minnesota density functionals. M06-2X functional, one of the Minnesota density functionals, has been tested in many cases—it improved the accuracy for thermodynamic, kinetics and non-covalent parametric quantities of various simple chemical reactions [28,29].

In this study, we use four calculation methods for studying the hydroperoxyl radical-scavenging reaction of trans-resveratrol and gnetin C. We aim to examine the effect of long-range and dispersion correction on the transition state and activation energy of the two radical-scavenging reactions. We use B3LYP as a referenced functional since it is the most popular density functionals in chemistry [30] and has provided a good prediction in our previous studies [31–33]. We use a version of B3LYP that has been corrected using the Coulomb-attenuating method in CAM-B3LYP exchange-correlation functionals [23] and B3LYP with the D3 version of Grimme's dispersion [25] for performing long-range correction on the coulombic interaction and London dispersion correction, respectively. As a comparison, we also use M06-2X functional [29]. The two radical-scavenging reactions are the representative model for the inhibition process of lipid peroxidation by melinjo resveratrol.

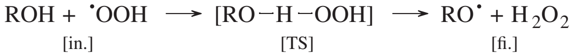
# 2. Model and computational details

## 2.1. Reaction model

We modelled the radical-scavenging reaction based on the hydrogen atom transfer (HAT) mechanism, as shown in scheme 1. In the initial and final states (abbreviated to [in.] and [fi.], respectively), molecules were in the ground state. The reactants were ROH (an antioxidant agent) and $^{\bullet}$OOH (hydroperoxyl, a model of peroxyl radicals in general). We used two antioxidant agents from melinjo–trans-resveratrol (tR) and gnetin C (gC)—as shown in figure 1*a*,*b* respectively. We only considered one active site of ROH for the hydrogen donation, which was $4'{-}OH$ site, as shown in figure 1*c*. It was the lowest bond dissociation energy among other sites [34,35]. Between [in.] and [fi.], we considered one transition state [TS], where we assumed the activated complexes, [RO—H—OOH], were formed.

## 2.2. Activation and reaction energy calculations

We constructed the reaction progress in an energy level diagram for scheme 1. It allowed us to calculate the reaction energy ($\Delta G^{\circ}$) and the activation energy ($\Delta^{\ddagger} G^{\circ}$) directly in terms of the standard Gibbs free



$$\underset{\text{[in.]}}{\mathrm{ROH} + {}^{\bullet}\mathrm{OOH}} \longrightarrow \underset{\text{[TS]}}{[\mathrm{RO{-}H{-}OOH}]} \longrightarrow \underset{\text{[fi.]}}{\mathrm{RO}^{\bullet} + \mathrm{H_2O_2}}$$

**Scheme 1.** The radical-scavenging reaction model, where [in.], [TS] and [fi.] are initial, transition and final states.

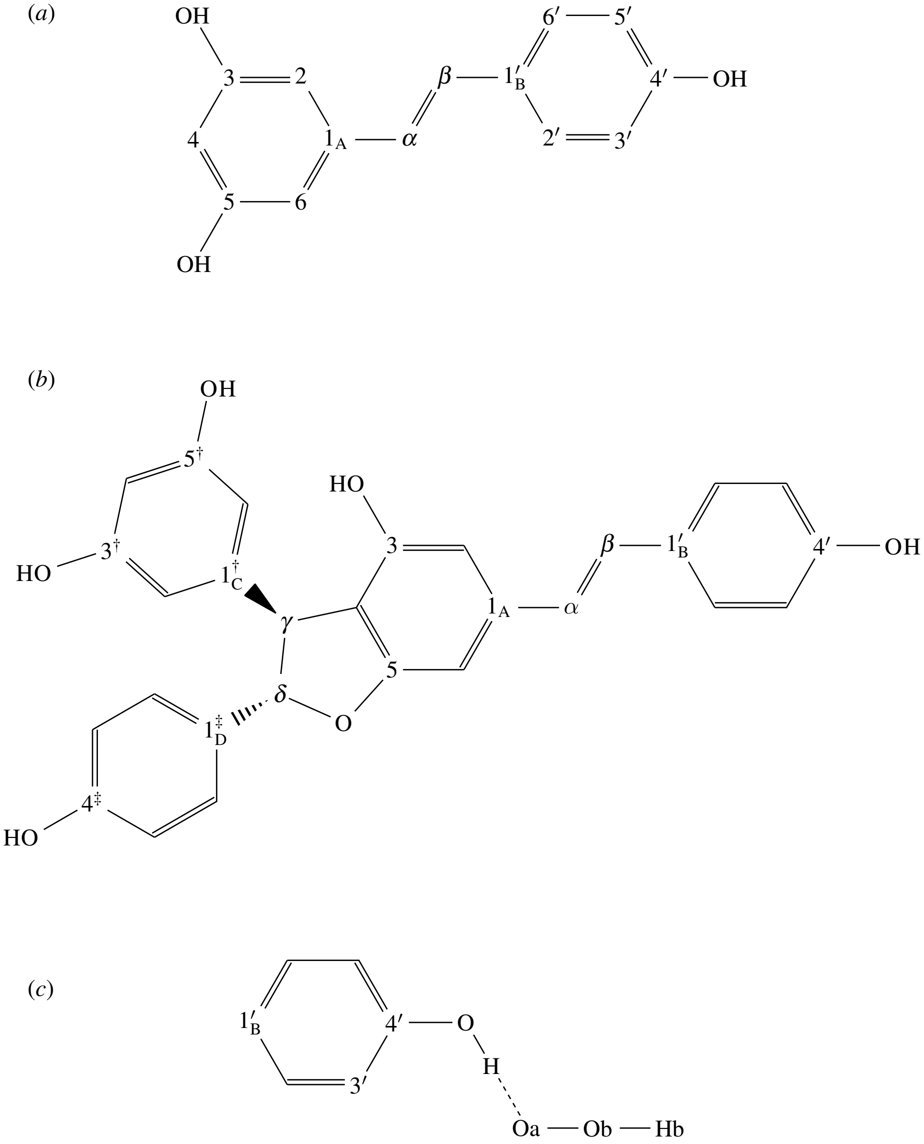


**Figure 1.** Molecular model for (*a*) trans-resveratrol (tR) in the ground state, (*b*) gnetin C (gC) in the ground state and (*c*) Ring B and hydroperoxyl in the [TS]. The nomenclature is used throughout the manuscript. The numbering of oxygen and hydrogen followed the numbering of its attaching carbon. The A, B, C and D indexes at the first carbon atom in each ring referred to phenyl ring's labels. The prime, dagger and double dagger symbols were for numbering ring B, C and D, respectively.

energy at 298.15 K. $\Delta G^{\circ}$ was the energy difference between [fi.] and [in.]

$$\Delta G^{\circ} = (G^{\circ}_{\mathrm{RO}^{\bullet}} + G^{\circ}_{\mathrm{H_2O_2}}) - (G^{\circ}_{\mathrm{ROH}} + G^{\circ}_{{}^{\bullet}\mathrm{OOH}}), \tag{2.1}$$

while $\Delta^{\ddagger}G^{\circ}$ was the energy difference between [TS] and [in.]

$$\Delta^{\ddagger}G^{\circ} = G^{\circ}_{\mathrm{TS}} - (G^{\circ}_{\mathrm{ROH}} + G^{\circ}_{{}^{\bullet}\mathrm{OOH}}). \tag{2.2}$$

$G^{\circ}$ is the total electronic energy with a correction from Gibbs free energy.

**Table 1.** List of methods and their notation.

| | | |
|---|---|---|
| M1 | B3LYP | the reference throughout the analysis |
| M2 | B3LYP with GD3 | London dispersion correction |
| M3 | CAM-B3LYP | long-range correction on the coulombic interaction |
| M4 | M06-2X | parameterization and evaluation for non-covalent interactions |

## 2.3. DFT calculation set-up

We used DFT calculations for obtaining the geometry in the ground and the transition states. In addition to the DFT calculations, we coupled it with frequency calculations at 298.15 K to determine the Gibbs free energy correction. Furthermore, we used natural bond orbital (NBO) calculations for the charge population analysis.

While we only used one basis set, which was 6-31++G(d,p), we performed all calculations using three different exchange-correlational functionals (XCs), namely B3LYP, CAM-B3LYP and M06-2X. We also performed the calculations using B3LYP with D3 version of Grimme's dispersion (GD3). Therefore, we were able to study the effect of long-range correction on the coulombic interaction and London dispersion correction in the transition state. List of methods and their notation is shown in table 1.

The routine calculations were as follows. First, we performed the geometry optimization to obtain the most stable spin-state. We considered singlet, triplet and quintet spin state for molecules with an even number of electrons. As for molecules with an odd number of electrons, the doublet and quartet spin state were considered. Second, we used the most stable spin-state for further calculations to obtain the optimized geometry and energy of molecules in the ground and transition state. We obtained the transition state by tracking a particular vibrational mode that decreased along the designed pathway, as demonstrated in our previous study [36]. We began the geometry optimization by employing B3LYP. The optimized structures were re-optimized with B3LYP + GD3, CAM-B3LYP and M06-2X. The relevant activated complex structures were the ones with the vibration of H atom between the 4′—OH site and $^{\bullet}$OOH having the imaginary frequency. All calculations were done in the gas phase using Gaussian 09 software [37].

# 3. Results and discussions

## 3.1. The ground state structures

The optimization geometry calculations for trans-resveratrol and gnetin C using three XCs obtained spin-singlet state was the lowest in energy level. The energy difference between the singlet and triplet states was about 2.0 eV (trans-resveratrol) and 6.5 eV (gnetin C); while between the singlet and quintet states was about 6.2 eV (trans-resveratrol) and 10.4 eV (gnetin C). The differences are significant, which indicates that the spin-singlet state is very stable. The result agrees with most organic compounds that are stable in the spin-singlet state, with carbenes as the exception [38,39]. Therefore, we only considered the spin-singlet state for further calculations. As for hydroperoxyl, the spin-doublet was the ground state and the next spin state was a quintet with energy difference 2.8 eV on average.

Overall, the obtained ground state geometries of trans-resveratrol and hydroperoxyl were in good agreement with the experimental result, as shown in table 2(a.i)—(a.xii) and (b.xv)—(b.xvii). The discrepancies were less than 0.017 Å and 1.4 degrees, which were considered accurate for DFT calculations [30]. The higher discrepancies were for C4′—O bond length and Oa—Ob—Hb bond angle by M3 and M4. However, when we considered the experimental error, these values were still in the range. Therefore, all methods were capable to determine an accurate geometric structure for trans-resveratrol and hydroperoxyl. It implies we can use all methods for further calculations.

In detail, there was a significant difference in the dihedral angles of trans-resveratrol [table 2(a.xiii)]. The calculations obtained phenyl ring A and B were twisted, while experimental showed they were preferably planar. The NBO calculations determined that all hydrogens were positively charged (see electronic supplementary material, table S1); hence the coulombic repulsions of H2′—H$\alpha$ and H2—H$\beta$ were responsible for *D*(A, B). However, the coulombic repulsions were unlikely to play a dominant role in the experiment. As Zarychta *et al.* [40] reported, trans-resveratrol was prepared in crystal form, where one trans-resveratrol was surrounded by six others. Each trans-resveratrol formed hydrogen

**Table 2.** The selected geometric parameters of (a) trans-resveratrol and (b) hydroperoxyl in the ground state, the bond length ($R$, in Å), the bond angle ($A$, in degrees) and the dihedral angle ($D$, in degrees). Parameter (i)—(xii) and (xv)—(xvii) are the discrepancy from the experimental values. Parameter (xiii) is the difference between ring A and ring B calculated with the same method. Parameter (xiv) is the absolute value (without any reference).

| | parameter | Expr. | M1 | M2 | M3 | M4 |
|---|---|---|---|---|---|---|
| (a) | trans-resveratrol | | | | | |
| (i) | $R(3, 2)$ | 1.387 | +0.006 | +0.006 | +0.001 | +0.004 |
| (ii) | $R(2, 1)$ | 1.404 | +0.002 | +0.002 | −0.006 | −0.005 |
| (iii) | $R(1, \alpha)$ | 1.471 | −0.003 | −0.003 | −0.001 | 0.000 |
| (iv) | $R(\alpha, \beta)$ | 1.338 | +0.012 | +0.012 | +0.002 | +0.004 |
| (v) | $R(\beta, 1')$ | 1.462 | +0.003 | +0.003 | +0.006 | +0.007 |
| (vi) | $R(1', 2')$ | 1.400 | +0.009 | +0.009 | +0.000 | +0.001 |
| (vii) | $R(2', 3')$ | 1.385 | +0.007 | +0.007 | +0.003 | +0.005 |
| (viii) | $R(5, \mathrm{O})$ | 1.378 | −0.008 | −0.008 | −0.014 | −0.016 |
| (ix) | $R(4', \mathrm{O})$ | 1.381 | −0.011 | −0.011 | −0.017 | −0.019 |
| (x) | $A(4, 5, 6)$ | 121.1 | 0.0 | 0.0 | 0.0 | +0.1 |
| (xi) | $A(1, \alpha, \beta)$ | 126.0 | +0.8 | +0.6 | +0.2 | −0.7 |
| (xii) | $A(3', 4', 5')$ | 120.3 | −0.6 | −0.6 | −0.5 | −0.3 |
| (xiii) | $D(\mathrm{A}, \mathrm{B})$ | 8.7 | 17.4 | 21.2 | 30.5 | 39.6 |
| (xiv) | $D(3', 4', \mathrm{O}, \mathrm{H})$ | 32.0 | 0.0 | 0.0 | 0.1 | 0.7 |
| (b) | hydroperoxyl | | | | | |
| (xv) | $R(\mathrm{Oa}, \mathrm{Ob})$ | 1.335 | −0.001 | −0.001 | −0.014 | −0.023 |
| (xvi) | $R(\mathrm{Ob}, \mathrm{Hb})$ | 0.977 | +0.004 | +0.004 | +0.001 | −0.001 |
| (xvii) | $A(\mathrm{Oa}, \mathrm{Ob}, \mathrm{Hb})$ | 104.1 | +1.4 | +1.4 | +1.7 | +1.7 |

Note: Experimental values: trans-resveratrol from [40]; hydroperoxyl from [41].

bonds with its six neighbour molecules through OH—O. The hydrogen bonds were predominant over the coulombic repulsions; hence the measured dihedral angle showed the rings were preferably planar.

We also showed the planarity of H4′ in term of the dihedral angle $D(3', 4', \mathrm{O}, \mathrm{H})$ [table 2(a.xiv)]. This particular H atom would be interacting with $^{\bullet}$OOH in the transition state. The experimental value showed that it was not planar. It was due to the aforementioned experimental condition. However, all methods obtained planar H4′ with respect to ring B. We shall recall this quantity later in the activation energy discussion.

We remarked that the dihedral angle calculation was sensitive to the calculation method. The comparison results among four calculation methods showed that dispersion (M2) and long-range correction (M3) increased the twisting $D(\mathrm{A}, \mathrm{B})$. Both simultaneous corrections (M4) increased $D(\mathrm{A}, \mathrm{B})$ even further. This trend was consistent for the case of gnetin C (see electronic supplementary material, table S2). The results suggest the long-range correction plays a dominant role in the twisting compared with the dispersion correction.

## 3.2. The transition state structures

Figure 2 shows the optimized structures in the [TS] of scheme 1 obtained from all calculation methods for both trans-resveratrol and gnetin C. All structures possessed a single imaginary frequency, which was the O4′—H—OOH vibration. The magnitudes of imaginary frequency were more than 1300 $\mathrm{cm^{-1}}$ for trans-resveratrol and 1200 $\mathrm{cm^{-1}}$ for gnetin C. These magnitudes were strong, which indicated that the O4′—H—OOH vibration encouraged the displacement of H4′. The displacement of H4′ can also be seen from the elongation of O4′—H bond length, which was about 0.140 Å (or, 15% longer than in its ground state). Meanwhile, the Oa—Ob bond of $^{\bullet}$OOH was not significantly elongated (only about

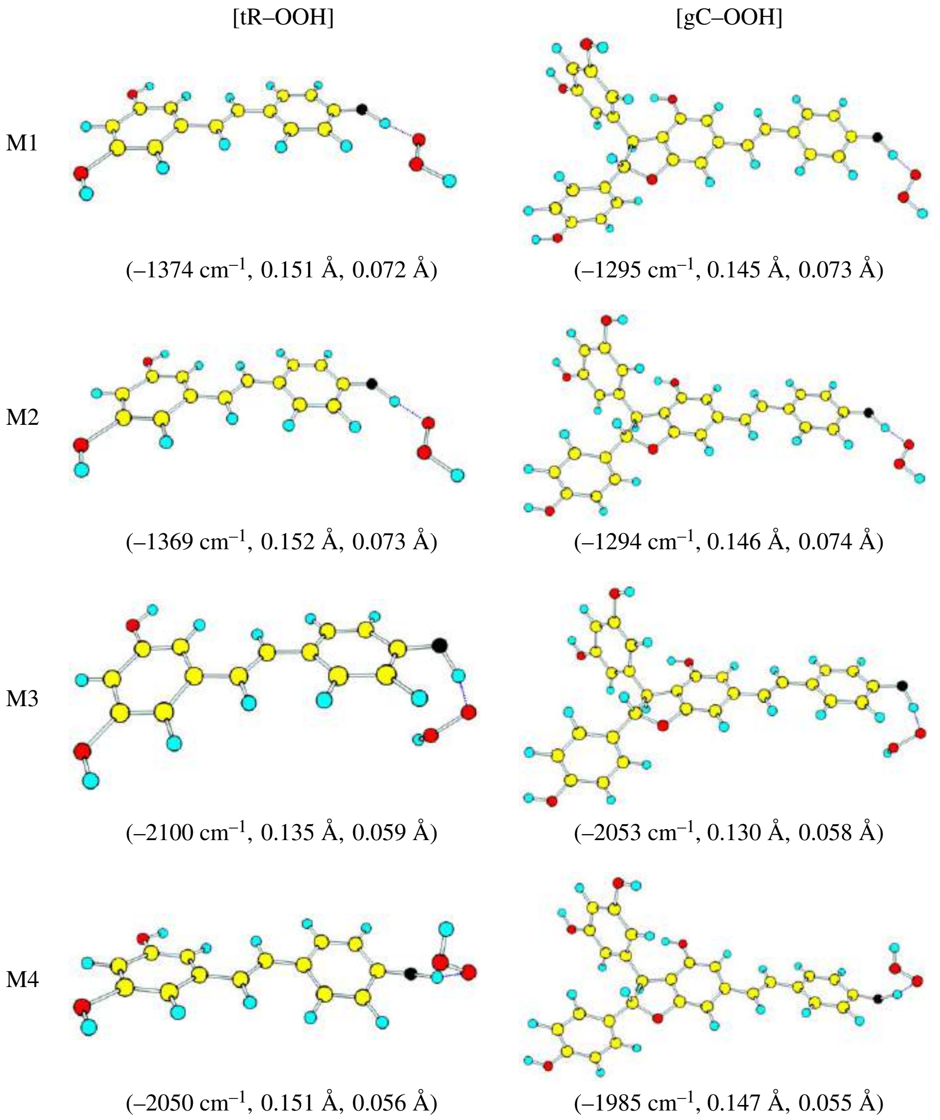


**Figure 2.** Optimized activated complex structures for trans-resveratrol and gnetin C with •OOH. Blue, red, yellow atoms represent H, O and C atoms. The black atom is O at the active site 4′, written as O4′ in the texts. The numbers in parentheses represent the required imaginary vibrational frequency for a transition state, the elongation of O4′—H and Oa—Ob bonds with respect to its ground state bond length.

5%). It means •OOH is attracting H4′. Therefore, the obtained structures are the activation complex of the radical-scavenging reaction in scheme 1.

The optimized [TS] structures revealed the different orientation of •OOH with respect to the ring B in the activated complexes. The presence of ring C and D did not contribute to the orientation, as the orientation was alike between [tR-OOH] and [gC-OOH]. However, the change in calculation methods altered the orientation. The significant alteration was obtained by M3 and M4, which implies that long-range correction plays a significant role in the orientation.

The orientation of •OOH in the activated complexes can be measured as a torsion angle of 3′— 4′—O—H, or $\phi$ (in degree). Table 3(a) shows the value of phi for all computational methods. Both M1 and M2 obtained phi was about zero, or •OOH was planar with respect to the ring B. However, •OOH was twisted up to 50 degrees according to M3 and M4 results. It implies that long-range correction was the reason for the twist. Therefore, the long-range correction plays a significant role both in the ground and the transition states of trans-resveratrol and gnetin C.

The origin of •OOH orientation is probably the same with the aforementioned ring A and B twisting origin in the ground state. The twisting presented after the long-range correction was introduced. Here, NBO calculations also determined that all the hydrogen atoms were positively charged, but both oxygen

**Table 3.** The difference of selected parameters of [RO—H—OOH] complex (figure 1*c*) from M1. (a) is the torsion angle (degree), (b–f) are the interatomic distance (Å), (g) is the bond angle (degree). For (h), the relative electronic energy (eV), M1 is set to be the reference.

| | parameter | ROH | M1 | M2 | M3 | M4 |
|---|---|---|---|---|---|---|
| (a) | $\phi$(3′, 4′, O, H) | tR | 0.0 | +1.0 | +43.4 | −52.8 |
| | | gC | 0.5 | +0.3 | +43.1 | −55.5 |
| (b) | *R*(H4′, Oa) | tR | 1.296 | −0.001 | −0.008 | −0.030 |
| | | gC | 1.307 | −0.002 | −0.010 | −0.034 |
| (c) | *R*(H3′, Hb) | tR | 3.234 | −0.041 | +0.274 | +0.384 |
| | | gC | 3.231 | −0.040 | +0.278 | +0.338 |
| (d) | *R*(H3′, Ob) | tR | 2.317 | −0.039 | +0.313 | +0.437 |
| | | gC | 2.314 | −0.038 | +0.319 | +0.460 |
| (e) | *R*(Oa, Ob) | tR | 1.406 | 0.001 | −0.026 | −0.037 |
| | | gC | 1.406 | 0.001 | −0.027 | −0.039 |
| (f) | *R*(Ob, Hb) | tR | 0.972 | 0.000 | +0.001 | 0.000 |
| | | gC | 0.971 | 0.000 | +0.001 | 0.000 |
| (g) | *A*(Oa, Ob, Hb) | tR | 101.9 | 0.0 | +1.4 | +2.0 |
| | | gC | 101.9 | 0.0 | +1.5 | +2.1 |
| (h) | $E_{\mathrm{rel}}$ | tR | 0 | −0.69 | +12.21 | +11.11 |
| | | gC | 0 | −1.65 | +22.30 | +19.15 |

Note: Negative value of $\phi$ means that O4′—H bond rotates in a clockwise direction.

atoms in •OOH were negatively charged. Therefore, coulombic interactions between the closest atoms in ring B and •OOH are the reason for the twisting. While Oa was attracted to H4′, Hb was repelled by H3′. The effect of repulsion and attractions can be seen from the interatomic distance between these atoms. Table 3(b) and (c) show that H4′—Oa distances decreased while H3′—Hb distances increased after the long-range correction was introduced.

While the long-range correction determined the orientation of •OOH, the dispersion correction affected the interatomic distance [table 3(c) and (d)]. The latter contracted the interatomic distance of H—H and H—O by about 1.3% and 1.7%, respectively. The correction did not affect the covalent bond parameters [table 3(b), (e), (f) and (g)], which is reasonable since the dispersion only works in the non-covalent region. These results complemented the report by Grimme *et al.* [25]. They reported that the effect began to arise at about 2.0 Å for C—C interatomic distance. Meanwhile, the contraction of H—H and H—O showed a critical difference between M1 and M2. Both methods resulted in a planar •OOH's orientation, but the dispersion correction stabilized the activated complex, as shown in their electronic energy [table 3(h)]. The stability of the activated complex naturally affected the energy barrier so it may affect the kinetic study or even the reaction pathways.

## 3.3. The radical-scavenging reaction

Figure 3 shows the reaction progress of scheme 1 with the transition state described in the previous section. All methods predicted that the reaction was exergonic. The experiment demonstrated that this reaction was indeed exergonic by showing its observable antioxidant activity [42]. Even though the reaction occurred in the solution experimentally, other studies using DFT with M05-2X functional in aqueous solution also obtained exergonic [13,14]. Therefore, our results can be accountable for further analysis.

Even though all methods obtained an exergonic reaction for scheme 1, the dispersion (M2) and long-range (M3) correction led to a different result. Since the activated complex determined the product, the exergonic difference level was aligned with the orientation of •OOH: the more twisting, the less exergonic. Since the twisting was due to the long-range correction as we discussed previously [table 3(a–d)], it implies that long-range correction also affects a reaction's exergonic level.

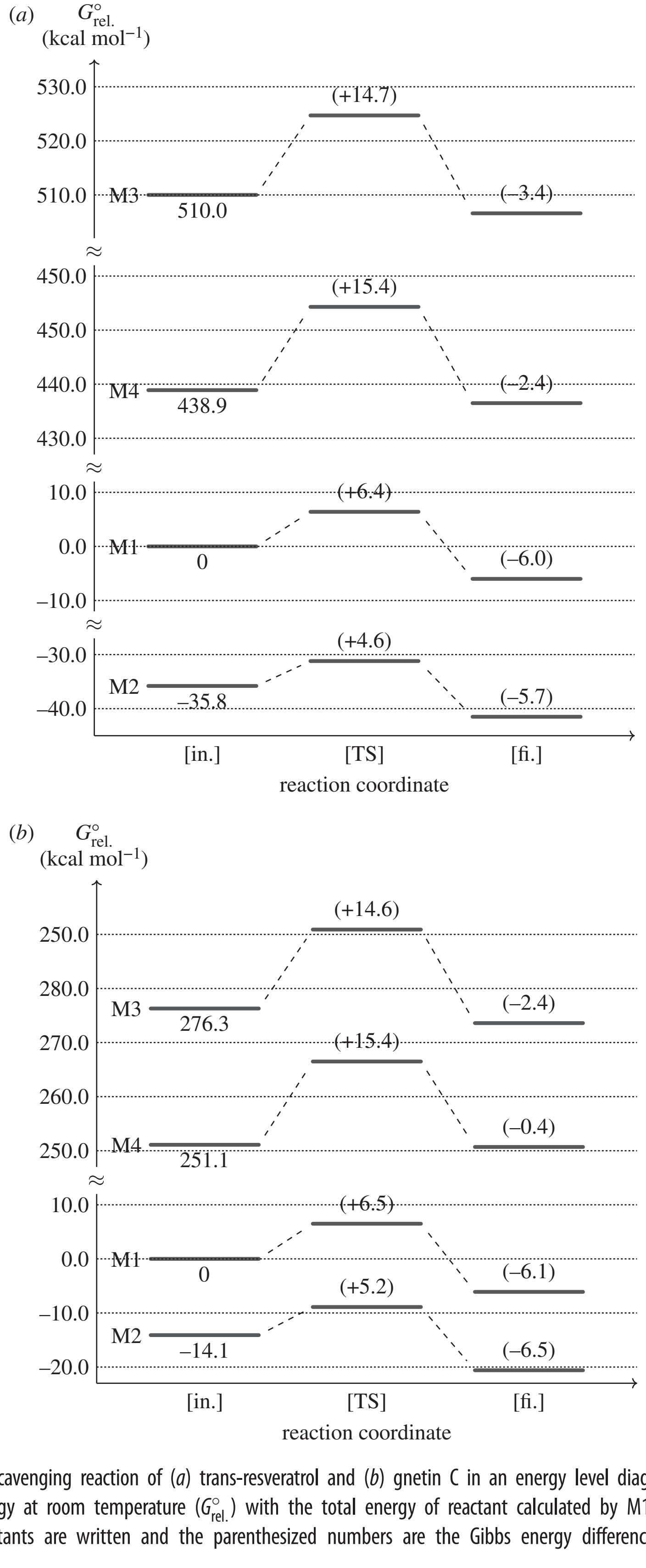


**Figure 3.** The radical-scavenging reaction of (*a*) trans-resveratrol and (*b*) gnetin C in an energy level diagram. The *y*-axis is the relative free Gibbs energy at room temperature ($G^\circ_{\text{rel.}}$) with the total energy of reactant calculated by M1 as the reference. For clarity, only $G^\circ$ of reactants are written and the parenthesized numbers are the Gibbs energy difference with respect to the reactant's total energy.

Dispersion (M2) and long-range correction (M3) also result in a different activation energy ($\Delta^\ddagger G^\circ$). When compared with M1, the former decreased $\Delta^\ddagger G^\circ$ by more than 20%, while the latter increased $\Delta^\ddagger G^\circ$ by more than 120%. The trend of the activation energy is similar to that of the activation complex stability [table 3(h)]. It implies that the activated complex structure indeed determine the activation energy.

The increasing $\Delta^{\ddagger}G^{\circ}$ by the long-range correction was remarkable. Regarding the planarity difference of H4′ with respect to ring B between in the ground and the transition state, the former was plane [table 2(a.xiv)] and the latter was twisted [table 3(a)]. The results suggest that the increasing $\Delta^{\ddagger}G^{\circ}$ is due to the required energy to twist H4′ with respect to ring B.

Overall, the similarity in the higher $\Delta G^{\circ}$ and $\Delta^{\ddagger}G^{\circ}$ calculations by M3 and M4 is a noteworthy result. It appears that the similarity originates from the Hartree–Fock exchange functional contribution to the selected calculation methods. B3LYP functional (M1) contained 20% of the Hartree–Fock exchange functional [43], CAM-B3LYP (M3) contained 19% for short-range and 65% for long-range exchange [23] and M06-2X (M4) contained 54% [29]. Therefore, the exact exchange such as Hartree–Fock functional plays a significant role in this study. It supported the study by Zhao & Truhlar [29] that recommends the use of M06-2X for studying the thermodynamic, kinetics and non-covalent interactions of the main-group element. Specifically, this study validates the study by Chai & Head-Gordon [44] that showed the importance of long-range corrected hybrid functional in thermochemistry, kinetics and non-covalent interactions calculations.

## 4. Conclusion

We have reported the effect of long-range and dispersion correction on the hydroperoxyl radical-scavenging reaction of trans-resveratrol and gnetin C. We found that long-range correction on the coulombic interaction, which was included in CAM-B3LYP, showed significant effects on the reaction. The effects predicted by CAM-B3LYP were similar to that of M06-2X. Both CAM-B3LYP and M06-2X predicted higher reaction and activation energy (in terms of Gibbs free energy) than B3LYP. The increase was 2.6–3.6 $\mathrm{kcal\,mol^{-1}}$ (trans-resveratrol) and 3.7–5.7 $\mathrm{kcal\,mol^{-1}}$ (gnetin C) for the reaction energy, while for activation energy, the increase was up to 8 $\mathrm{kcal\,mol^{-1}}$. We argued that the higher values of reaction and activation energy were due to hydroperoxyl radicals' twisted orientation in the transition state. Hydroperoxyl radical was twisted up to 50 degrees with respect to the phenyl ring attached to it. This twisted orientation of hydroperoxyl radical showed another similarity between CAM-B3LYP and M06-2X.

On the other hand, we noted that dispersion correction did not have a significant effect. B3LYP, without or with the Grimme's dispersion correction (GD3), obtained similar geometry and energy in the transition state. These results support other theoretical studies that reported the importance of long-range correction for the thermochemistry, kinetics and non-covalent interactions calculations. Therefore, our study verifies the significance of long-range correction in the hydroperoxyl radical-scavenging reaction of trans-resveratrol and gnetin C.

Data accessibility. The supporting data of this article has been uploaded as part of the electronic supplementary material.

Authors' contributions. V.K. carried out all simulations, participated in the design of the study, participated in data analysis and drafted the manuscript. F.R. conceived of the study, designed the methodology and critically revised the manuscript. L.S.P.B. and I.P. participated in data analysis. H.R. and H.K.D. critically revised the manuscript. All authors have read and agreed to the published version of the manuscript.

Competing interests. We declare we have no competing interests.

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