QUALITY IMPROVEMENT IN DENTAL AND MEDICAL KNOWLEDGE, RESEARCH, SKILLS AND ETHICS FACING GLOBAL CHALLENGES

Edited by
Armelia Sari Widyarman, Muhammad Ihsan Rizal,
Moehammad Orliando Roeslan & Carolina Damayanti Marpaung

QUALITY IMPROVEMENT IN DENTAL AND MEDICAL KNOWLEDGE, RESEARCH, SKILLS AND ETHICS FACING GLOBAL CHALLENGES

The proceedings of FORIL XIII 2022 Scientific Forum Usakti conjunction with International Conference on Technology of Dental and Medical Sciences (ICTDMS) include selected full papers that have been peer-reviewed and satisfy the conference's criteria. All studies on health, ethics, and social issues in the field of dentistry and medicine have been presented at the conference alongside clinical and technical presentations. The twelve primary themes that make up its framework include the following: behavioral epidemiologic, and health services, conservative dentistry, dental materials, dento-maxillofacial radiology, medical sciences and technology, oral and maxillofacial surgery, oral biology, oral medicine and pathology, orthodontics, pediatrics dentistry, periodontology, and prosthodontics. This proceeding will be beneficial in keeping dental and medical professionals apprised of the most recent scientific developments.

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Quality Improvement in Dental and Medical Knowledge, Research, Skills and Ethics Facing Global Challenges

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Table of Contents

Preface xiii
Acknowledgements xv
Committee Members xvii

Behavioral, epidemiologic and health services

Characteristics of knowledge and attitude of Indonesian professional healthcare students toward Basic Life Support (BLS) courses 3
I. Gunardi, A. Subrata, A.J. Sidharta, L.H. Andayani, W. Poedjiastoeti & S. Suebnukarn

Bibliometric analysis of *imperata cylindrica* papers in Scopus database (2012–2021) 9
M.O. Roeslan, S. Wulansari & P. Monthanapisut

Development and validation of Indonesian version of OHIP-49 questionnaire using Rasch model 17
F.K. Hartanto, I. Gunardi, A. Kurniawan, A.J. Sidharta & W.M.N. Ghani

Knowledge regarding dental and oral health among pregnant women (study at Palmerah Community Health Center, West Jakarta) 24
P.A. Salsabila, L.H. Andayani & A.G. Soulissa

The xerostomia's effect on methadone therapy program patients' oral-health-related quality of life 31
T.T. Theresia, A.N. Fitri & W. Sudhana

The differences in work strategy and work fatigue between female and male dentists during the COVID-19 pandemic in Indonesia 42
D. Ranggaini, W. Anggraini, A.P. Ariyani, I. Sulistyowati & M.F.C. Musa

Dental students' perceptions and behaviors concerning oral hygiene and eating habits during the COVID-19 pandemic in Indonesia 49
A. Asia, L. Astuti, T.E. Astoeti, A.S. Widyarman & W. Sudhana

Analyzing teledentistry consultation during the pandemic Covid-19: A challenge of images in online consultation 56
M. Chandra & R. Tjandrawinata

Conservative dentistry

Mandibular first molar with radix entomolaris: An endodontic case report 67
F. Farasdhita, W. Widyastuti & E. Fibryanto

Walking bleach technique on endodontically treated caninus with tetracycline discoloration 73
J.D. Susanto, A.P. Dwisaptarini & S. Wulansari

Successful management of primary periodontal lesion with secondary endodontic involvement: A case report 77
F. Katrini, W. Widyastuti & Aryadi

Non-surgical treatment for extensive perapical lesion: A case report 84
M.P. Darmawanti, A.P. Dwisaptarini & D. Ratnasari

Monolithic zirconia endocrown: Indirect restoration for endodontically treated teeth 90
W. Wulandari, T. Suwartini & E. Fibryanto

Effect of air-abrasive particle and universal bonding to shear bond strength of zirconia 95
F. Witoko, M.F. Amin, D. Ratnasari & R. Tjandrawinata

Composite as a post-obturation restorative material on a non-vital tooth with endodontically treatment: A case report 101
R. Landy, W. Widyastuti & S. Wulansari

Caries detection effectiveness of two techniques assessed using FACE method 112
Y. Winardi & A.P. Dwisaptarini

Pluchea indica less leaves extract as a root canal irrigant against *Enterococcus faecalis* Colonies: *Ex vivo* study 116
E. Fibryanto, A. Tio, J.A. Gunawan, A. Hidayat & N.Z.M. Noh

Differences in resin polishing technique of nanofiller and nanohybrid composites 124
E.A.W. Yanti, A.P. Dwisaptarini, Elline & M.S. Jamil

Differences in the effect of two Nickel Titanium rotary files preparation toward the changes on root canal curvature 129
A. Darkim, W. Widyastuti, S. Wulansari & E.A. Budiyanti

Effect of high refractive index composite resin thickness on CIELAB value 136
A.P. Dwisaptarini, D. Ratnasari, I. Hadiutomo, R. Tjandrawinata & R. Trushkowsky

Single-visit retreatment in underfilled root canal of mandible second premolar: A case report 141
G. Jesslyn, B.O. Iskandar & T. Suwartini

Antibiofilm effect of avocado (*Persea Americana*) seed ethanol extract on *Streptococcus mutans* and *Enterococcus faecalis* (*ex vivo*) 146
S. Wulansari, A.S. Widyarman, R.U. Nadhifa & M.J. Fatya

Three-dimensional obturation in maxillary first molar with MB2: A case report 154
A. Sutanto, E. Fibryanto & A.E. Prahasti

Semi-direct composite overlay restoration as an alternative restoration for endodontically treated tooth: A case report 160
N. Brians, J.A. Gunawan, A.E. Prahasti, E. Istanto & S.M. Khazin

Comprehensive treatment of immature necrotic permanent teeth: A case report 166
A.E. Prahasti, E. Fibryanto, E. Elline & W. Widyastuti

Diastemas management using direct composite resin restoration: The digital smile design approach 173
E. Elline, D. Ratnasari, E. Fibryanto, A.E. Prahasti & R. Iffendi

Removal of broken file using ultrasonics at one-third apical second molar distal: A case report 178
Y. Sutjiono, B.O. Iskandar, A.E. Prahasti, A. Subrata & S.M. Khazin

Apis mellifera honey and miswak (*Salvadora persica*) effect on tooth color changes 182
N.D. Iskandar, D. Ratnasari & R. Stefani

Fiber reinforced composite in endodontically treated tooth: A case report 188
J. Setiawan, T. Ariwibowo & M.F. Amin

The management of post-endodontic treatment using fiber-reinforced composite: A case report 195
R. Lambertus, T. Suwartini, E. Elline, A.E. Prahasti & S.A. Asman

Management of crown-root fracture with pulp exposure: A case report 201
Y. Susanti, B. Iskandar & T. Ariwibowo

Management of molar with C-shape root canal configuration: Case reports 207
F. Antonius, T. Suwartini & J.A. Gunawan

Endodontic treatment on young age molar with pulp polyp and diffuse calcification finding in a radiograph 214
P. Andriani, A.P. Dwisaptarini & J.A. Gunawan

Cyclic fatigue of three heat-treated NiTi rotary instruments after multiple autoclave sterilization: An *in-vitro* study 221
S.A. Putri, W. Widyastuti, A. Aryadi & R. Amtha

Endodontic management of S-shaped root canal on mandibular first molar: A case report 226
N. Tanuri, M.F. Amin & S. Wulansari

Root canal treatment on the complex case using ultrasonics: A case report 231
L.H. Wibowo, E. Elline, E. Fibryanto, A.E. Prahasti & D. Qurratuani

Management of iatrogenic problems during root canal treatment 236
Y.N. Argosurio, M.F. Amin & E. Elline

Non-surgical endodontic retreatment of maxillary first premolar with direct composite restoration: A case report 243
A.R. Pradhista, B.O. Iskandar & Aryadi

Dental materials

The effect of soft drinks containing citric and phosphoric acid toward enamel hardness 249
A. Aryadi, D. Pratiwi & C. Cindy

Microhardness of a flowable bulk-fill resin composite in immediate and 24-hour storage 255
R. Tjandrawinata, D. Pratiwi, F.L. Kurniawan & A. Cahyanto

The effect of halogen mouthwash on the stretch distance of the synthetic elastomeric chain 261
M. Wijaya, R. Tjandrawinata & A. Cahyanto

Synthesis and characterization of β-tricalcium phosphate from green mussel shells with sintering temperature variation 267
M.R. Kresnatri, E. Eddy, H.A. Santoso, D. Pratiwi, D.L. Margaretta & T. Suwandi

The effect of immersion in 75% concentration tomato juice on the mechanical properties of nanohybrid composites resin 277
J. Kamad, D. Liliany & E. Eddy

Evaluation of setting time of glass ionomer cement mixed with ethanolic extracts of propolis 285
T.S. Putri, D. Pratiwi & A.E.Z. Hasan

The knowledge level of dental students on adequate composite resin polymerization in the COVID-19 pandemic era 290
O. Octarina & L.A.L. Ongkaruna

Dento-maxillofacial radiology

The role of dental record data in the mass disaster identification process: A case report of the Sriwijaya SJ-182 airplane crash 299
V. Utama, R. Tanjung, A. Quendangen, A. Fauzi, A. Widagdo, M.S. Haris & A.S. Hartini

Management of postmortem dental radiography procedure in mass disaster victim identification 305
R. Tanjung & I. Farizka

Radiomorphometric analysis of gonion angle and upper ramus breadth as a parameter for gender determination 312
I. Farizka & R. Tanjung

Medical sciences and technology

Artificial intelligence application in dentistry: Fluid behaviour of EDDY tips 321
H.H. Peeters, E.T. Judith, F.Y. Silitonga & L.R. Zuhal

MTHFR C677T, A1298C*, and its interaction in nonsyndromic orofacial cleft phenotypes among Indonesian 328
S.L. Nasroen & A.M. Maskoen

Oral and maxillofacial surgery

The effectiveness of giving forest honey (*Apis Dorsata*) and livestock honey (*Apis Cerana* and *Trigona*) on the number of fibroblast in wound healing after tooth extraction (*in vivo* research in Wistar rats) 341
T.A. Arbi, I.N. Aziza & T. Hidayatullah

Reconstruction of large post-enucleation mandibular defect with buccal fat pad 348
N.A. Anggayanti, A.D. Sastrawan & O. Shuka

Challenge and management of dental implant during COVID-19 pandemic: Bone formation on second stage implant surgery 354
D. Pratiwi, H. Pudjowibowo & F. Sandra

The evaluation of maxillary sinus for implant planning through CBCT 360
A.P.S. Palupi, W. Poedjiastoeti, M.N.P. Lubis, I. Farizka, B. Claresta & J. Dipankara

The jawbone quantity assessment of dental implant sites 366
W. Poedjiastoeti, M.N.P. Lubis, Y. Ariesanti, I. Farizka, J. Dipankara & S. Inglam

Comparative assessment of the distance between the maxillary sinus floor and maxillary alveolar ridge in dentulous and edentulous using panoramic radiography 372
A.S.D. Audrey, W. Poedjiastoeti, M.N.P. Lubis, J. Dipankara & S. Inglam

Comparison between impacted mandibular third molar against mandibular angle and canal 379
N. Marlina, W. Poedjiastoeti, I. Farizka, J. Dipankara & S. Inglam

Oral biology

Saliva as a diagnostic tool for COVID-19: Bibliometric analysis 387
M.I. Rizal, R.A. Hayuningtyas, F. Sandra, M.S. Djamil & B.O. Roeslan

Cytotoxicity activity of *Allium sativum* extracts against HSC-3 cells 393
I.J. Pardenas & M.O. Roeslan

Effectiveness of probiotic lozenges in reducing salivary microorganism growth in patients with fixed orthodontic appliances: A pilot study 399
A.S. Widyarman, S. Vilita, G.C. Limarta, S.M. Sonia & F. Theodorea

Potential anticancer properties of *Apium graveolens Linn.* against oral cancer 407
T. Hartono, F. Sandra, R.A. Hayuningtyas, S. Jauhari & J. Sudiono

Antibacterial activity of bromelain enzyme from pineapple knob *(Ananas comosus)* against *Streptococcus mutans* 414
D. Liliany, E. Eddy & A.S. Widyarman

Elephantopus scaber Linn.: Potential candidate against oral squamous cell carcinoma 424
T. Pang, F. Sandra, R.A. Hayuningtyas & M.I. Rizal

Effectiveness of gargling with 100% coconut oil to prevent plaque accumulation and gingival bleeding 429
A.G. Soulissa, M. Juslily, M. Juliawati, S. Lestari, N.P. Ramli, Albert & A. Ismail

Hydroxamate HDAC inhibitors potency in mediating dentine regeneration: A review 435
I. Sulistyowati, W. Anggraini, A.P. Ariyani & R.B. Khalid

Various compounds that are used as oxidative stress inducers on fibroblast cell 443
Komariah, P. Trisfilha & R. Wahyudi

Nano encapsulation of lemongrass leaves extract (*Cymbopogon citratus* DC) on fibroblast viability with oxidative stress 450
N. Ericka, K. Komariah, R. Wahyudi & T. Trisfilha

Arumanis mango leaves (*Mangifera indica* L.) extract efficacy on *Porphyromonas gingivalis* biofilm *in-vitro* 461
S. Soesanto, Yasnill, A.S. Widyarman & B. Kusnoto

A systematic review to evaluate the role of antibiotics in third molar extraction 468
R.A. Hayuningtyas, S. Soesanto, P. Natassya & S.B. Gutierez

Efficacy of epigallocatechin gallate gel on VEGF and MMP-9 expression on ulcerations 472
L.A. Porjo, R. Amtha & M.O. Roeslan

Oral medicine and pathology

Salivary interleukin (IL)-6 in elderly people with stomatitis aphthous and gingivitis associated with the occurrence of cognitive impairment 481
D. Priandini, A. Asia, A.G. Soulissa, I.G.A. Ratih, T.B.W. Rahardjo & E. Hogervorst

The uses of palm fruit (*Borassus flabellifer* L.) in dentistry 489
J. Sudiono & T.G.R. Susanto

Endodontic irrigation solution administration induces oral mucosal deformity: A case report 496
R. Amtha, D. Agustini, N. Nadiah, F.K. Hartanto & R.B. Zain

Profile of oral mucosa changes and perception of e-cigarettes smoker 502
R. Amtha, A.P. Rahayu, I. Gunardi, N. Nadiah & W.M.N. Ghani

Potency of *Solanum betaceum* Cav. Peel skin ethanol extract towards TNF-α blood level (Study in vivo on inflammatory rats model) 508
J. Sudiono & M.T. Suyata

Stomatitis venenata due to nickel as inlay materials in a 24-year-old woman: A case report 518
F. Mailiza, A. Bakar & U. Nisa

Treatment challenge of oral lichenoid lesion associated with glass ionomer cement restoration: A case report 526
F.K. Hartanto, I. Gunardi, M.L. Raiyon, N. Nadiah & H. Hussaini

Validity and reliability of the Indonesian version of COMDQ-26: A pilot study 531
J.V. Winarto, I. Gunardi, C.D. Marpaung, R. Amtha & W.M.N. Ghani

Orthodontics

Interceptive orthodontic treatment needs and its relating demographic factors in Jakarta and Kepulauan Seribu 539
Y. Yusra, J. Kusnoto, H. Wijaya, T.E. Astoeti & B. Kusnoto

Diastema closure and midline shifting treatment with standard technique (Case report) 543
H.F. Lubis & J.X. Ongko

Intrusion and uprighting using TADs in mutilated four first permanent molar case 548
H.F. Lubis & F. Rhiyanthy

Moringa and papaya leaf inhibit *Streptococcus mutans* and *Candida albicans* 554
H.F. Lubis & M.K. Hutapea

Intruding upper first molar using double L-Loop in an adult patient: A retreatment case 561
H.F. Lubis & Joselin

Profile changes in Class III malocclusion using protraction facemask in Indonesian patients (Cephalometric study) 565
H. Halim & I.A. Halim

Pediatric dentistry

Oral microbiome dysbiosis in early childhood caries (Literature review) 575
T. Putriany & H. Sutadi

Periodontology

Permanent splint using removable partial denture framework on reduced periodontium: A case report 587
V. Hartono, F.M. Tadjoedin, A. Widaryono & T.A. Mahendra

The effect of electric smoking on the severity of chronic periodontitis 594
A.P. Fathinah & M. Louisa

Periodontitis effects toward the extent of COVID-19 severity (Scoping review) 603
S.A. Arthur & M. Louisa

Scaffold-based nano-hydroxyapatite for periodontal regenerative therapy 614
N.A. Harsas, Y. Soeroso, N. Natalina, E.W. Bacthiar, L.R. Amir, S. Sunarso, R. Mauludin & C. Sukotjo

Defect management using hydroxyapatite and platelet-rich fibrin in advanced periodontitis 621
V. Wibianty, V. Paramitha & N.A. Harsas

The relationship between age with caries status and periodontal treatment needs on visually impaired individuals 630
P. Wulandari, M.A.L. Tarigan, K. Nainggolan, M.F. Amin & J. Maharani

Effects of COVID-19 on periodontitis (Scoping review) 638
A.R. Somawihardja & M. Louisa

Concentrated growth factor for infrabony defect in periodontitis treatment: A review 643
F.C. Maitimu & T. Suwandi

Subcutaneous emphysema after dental stain removal with airflow: A case report and anatomical review 651
A. Albert, W. Anggraini & W. Lestari

Bonding agents for dentine hypersensitivity treatment: A review 657
O.N. Komala, L. Astuti & F.C. Maitimu

Advantages and disadvantages of 2017 new classification of periodontitis (*Scoping review*) 668
R. Anggara & K. Yosvara

Comparison of periodontal disease severity in COVID-19 survivors and non-COVID-19 individuals 677
M. Louisa, R.A. Putranto, O.N. Komala & W. Anggraini

Aerosol spread simulation during ultrasonic scaling and strategies to reduce aerosol contamination 685
M. Sundjojo, V. Nursolihati & T. Suwandi

The effect of pineapple (*Ananas comosus* L.) juice on biofilm density of streptococcus sanguinis ATCC 10556 689
T. Suwandi & Y.V. Thionadewi

Prosthodontics

Prevalence and risk indicators of bruxism in Indonesian children 697
C. Marpaung, I. Hanin, A. Fitryanur & M.V. Lopez

Validity and reliability of temporomandibular disorders screening questionnaire for Indonesian children and adolescents 704
C. Marpaung, N.L.W.P. Dewi & M.V. Lopez

Effect of submersion of alginate molds in povidone iodine concentration of 0,47 % solution toward dimensional change 710
N. Adrian & I.G.P. Panjaitan

Effect of pure basil leaf extract on surface roughness of heat cured acrylic resin 715
I.G.P. Panjaitan & N. Adrian

Prosthetic rehabilitation after mandibular reconstruction in young adult patient with ameloblastoma history 720
I. Hanin & I. Setiabudi

Treatment of tooth supported magnet retained maxillary complete overdenture: Case report 725
I.G.A.R.U Mayun

Complete denture management with torus palatinus: A case report 730
E.S.I. Sari, I.K. Julianton & G.G. Gunawan

Management of rehabilitation for partial tooth loss with immediate removable dentures in the era of the COVID-19 pandemic: A case report 734
A. Wirahadikusumah

Management of anterior mandibular lithium disilicate crown fracture 742
J. Handojo & L.A. Halim

Author index 747

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Preface

Faculty of Dentistry Universitas Trisakti (Usakti) presents FORIL XIII 2022 Scientific Forum Usakti conjunction with International Conference on Technology of Dental and Medical Sciences (ICTDMS) on December 8th–10th 2022. The theme of the conference is "Quality Improvement in Dental and Medical Knowledge, Research, Skills and Ethics Facing Global Challenges".

The triennial conference has served as a meeting place for technical and clinical studies on health, ethical, and social issues in field medical and dentistry. It is organized around 12 major themes, including behavioral, epidemiologic, and health services, conservative dentistry, dental materials, dento-maxillofacial radiology, medical sciences and technology, oral and maxillofacial surgery, oral biology, oral medicine and pathology, orthodontics, pediatrics dentistry, periodontology, and prosthodontics.

The most recent findings in fundamental and clinical sciences related to medical and dental research will be presented in the conference that will be published as part of the conference proceeding. This proceeding will be useful for keeping dental and medical professionals up to date on the latest scientific developments.

Dr. Aryadi Subrata
Chairman FORIL XIII conjunction with ICTDMS

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Nano encapsulation of lemongrass leaves extract (*Cymbopogon citratus* DC) on fibroblast viability with oxidative stress

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ABSTRACT: During the wound healing process, fibroblasts may experience oxidative stress due to the high number of reactive oxygen species (ROS) produced by inflammatory cells, which, if out of control, may cause impaired fibroblast function, leading to a slow wound healing process. Nonenzymatic antioxidants as suppressors for oxidative stress are derived from secondary metabolites of natural ingredients such as lemongrass, which is unstable when reacting with the external environment and can be minimized by encapsulation using a natural polymer of chitosan. This research is aimed to find out the antioxidant activity of chitosan-encapsulated lemongrass leaves extract (EnChLg) and its effect on the viability of fibroblasts under oxidative stress. Antioxidant activity was measured using 2,2-diphenyl-2-picrylhydrazil (DPPH). Viability and proliferation tests were conducted using the Cell Counting Kit-8 (CCK-8) at a wavelength of 450 nm. The research was divided into 8 groups consisting of groups with hydrogen peroxide, ascorbic acid, groups without treatment, and EnChLg treatment with concentrations of 100 ppm, 200 ppm, 300 ppm, 400 ppm, and 500 ppm. EnChLg antioxidant activity test showed antioxidant activity with an IC_{50} value of 566.48 ppm, and administration of EnChLg with a concentration of 300 ppm was able to increase the viability of fibroblasts better than the concentrations of 100 ppm, 200 ppm, 400 ppm, and 500 ppm as well as the positive, negative, and comparison control groups. EnChLg has weak antioxidant activity. However, EnChLg is nontoxic and fibroblasts were able to survive well at a concentration of 300 ppm.

1 INTRODUCTION

Wound healing is the body's main defense mechanism through several phases, hemostasis, inflammation, proliferation, and remodeling (Thiruvoth et al. 2015). The hemostasis is the initial phase characterized by the vasoconstriction of blood vessels and coagulation (Putri 2020), aiming at preventing excessive blood loss (Tsiklidis et al. 2019) and maintaining tissue integrity (Jin et al. 2020). In the inflammatory phase, macrophages and neutrophils will move to the injured area and experience a respiratory burst (Rizwan et al. 2014) and reactive oxygen species (ROS) will be produced, (Nita & Grzybowski 2016), such as superoxide and hydrogen peroxide, which act as bactericidal (Arief & Widodo 2018). The low amount of ROS has favorable effects on several physiological processes of the body, such as the wound-healing process. However, too high levels of ROS can increase pro-oxidants and lead cells to experience oxidative stress (Bhattacharyya et al. 2014). Oxidative stress is a condition when there is an overproduction of ROS and a deficiency of enzymatic antioxidants, causing an

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imbalance (Phaniendra et al. 2015). This imbalance can interfere with the function of communication between cells and disrupt the wound healing process by prohibiting the proliferation process and collagen formation by fibroblasts (Pisoschi & Pop 2015).

Herbal medicines have been widely used in the wound-healing process. One of the herbal medicines is *Cymbopogon citratus* DC, known as lemongrass. Lemongrass is one of the spices growing in the tropics and is widely used in Southeast Asian countries, such as Indonesia (Felicia et al. 2022). Based on scientific studies, the lemongrass leaf has a higher content of active compounds than its stem (Andikoputri et al. 2021). The active compounds contained in lemongrass have antioxidant activities, such as flavonoids, tannins, saponins, alkaloids, and phenols (Oladeji et al. 2019). Natural ingredients with antioxidants have been proven to accelerate the wound-healing process (Comino-Sanz et al. 2021). One way to use natural ingredients with antioxidants is by reducing the production of ROS (Dunnill et al. 2017), which can cause oxidative stress to cells, thereby slowing the wound healing process (Süntar et al. 2012).

The active compounds in the body have limited bioavailability and absorption in the body, which can be restrained by encapsulation technology. Encapsulation is the trapping of active compounds to enhance bioavailability and stability (Kamel et al. 2017; Umawiranda & Cahyaningrum 2014), such as the protection of active compounds against oxidation to upgrade their therapeutic potential (Pateiro et al. 2021). The polymer material commonly used as a trapping matrix is chitosan (Triwulandari & Nurbayti 2019). Chitosan is a natural polymer compound obtained from chitin in the shells of marine animals and insects (Pratiwi 2014), such as the horned beetle (*Xylotrupes gideon*), which is a pest on coconut plants, but it has economic value by converting it into natural ingredients, such as chitosan (Veronica & Maria 2021). Chitosan is widely used due to its potential to be developed as a drug delivery because it is biocompatible, biodegradable, has a low level of toxicity, and has a simple preparation method (Ningsih et al. 2017). Physical modification of chitosan into smaller particles can increase absorption, diffusion, and penetration to the mucosal layer better than chitosan with regular size (Mardliyati et al. 2012).

Based on the description in the background, this study aimed to determine the antioxidant activity of nano-chitosan encapsulation of lemongrass leaf extract (EnChLg) on the viability of fibroblasts subjected to oxidative stress due to hydrogen peroxide induction.

2 METHODS

2.1 *Lemongrass leaf extraction*

Leaves of *C. citratus* and *X. gideon* were obtained from Bogor, West Java, Indonesia. The lemongrass leaves were dried for two weeks naturally. Extraction was conducted by maceration method using 70% ethanol solvent (1:10 w/v) (Dewi 2021) for 72 hours at room temperature (Lahague*et al.* 2020). Then, manual shaking was performed for three days. Shaking was executed every day for 15 minutes and repeated for eight hours. The extract was filtered using Whatman filter paper and evaporated using a rotary evaporator at a temperature of 50-60°C to concentrate the filtrate until a thick extract was obtained (Chairunnisa et al. 2019). The study was divided into eight groups, negative control, which is fibroblasts without treatment, fibroblasts given ascorbic acid as a positive control, fibroblasts given a stressor, and fibroblasts given EnChLg treatment with concentrations of 100, 200, 300, 400, and 500 ppm.

2.2 *Nano-chitosan encapsulation of lemongrass extract*

The making process of chitosan from *X. gideon* was carried out in several stages, namely demineralization, deproteinization, decolorization, and deacetylation. Nano-chitosan

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encapsulation was conducted by dissolving 0.5 grams of chitosan with 1% of acetic acid. One gram of lemongrass leaf extract was weighed and then dissolved with 10 mL of distilled water. A total of 150 mL of extract solution was mixed into 300 mL of chitosan solution, then stirred using a magnetic stirrer at a speed of 2500 rpm for 20 minutes. After that, the stirring was continued without heating for 100 minutes, then the solution was added with 40 mL of 0.1% tripolyphosphate dropwise. Then, the solution was stirred for one hour at a speed of 2500 rpm. After that, the tween 80 solution with 0.1% concentration was added and stirred again at 2500 rpm for one hour (Hadidi et al. 2020; Putri et al. 2019). The samples were centrifuged again at 7100 rpm for 15 minutes to obtain a precipitate, then dilution was carried out at concentrations of 100, 200, 300, 400, and 500 ppm.

2.3 *Antioxidant activity of EnChLg*

The antioxidant activity test of EnChLg was carried out using the 2.2-diphenyl-1-picrylhydrazyl method. The samples of EnChLg were prepared from 10,000 ppm stock solution and diluted with methanol. The DPPH solution was prepared by dissolving 20.2 mg of it in 126.25 mL of methanol in a volumetric flask. The extract solution was taken using a pipette (Eppendorf) and put into a test tube, then added with DPPH solution and methanol so that the volume of the solution reached 5 mL. The solution was shaken with a vortex mixer (Thermo Scientific) until homogeneous and then transferred to a test tube covered with aluminum foil. Subsequently, the solution was incubated in a dark room for 30 minutes. After that, the absorbance was measured at a wavelength of 516 nm (Chandra et al. 2019; Muthia et al. 2019). The percentage of inhibition can be calculated by the following formula (Sarraf et al. 2021):

$$Inhibition\ (\%) = \frac{Blank\ Absorbance - Sample\ Absorbance}{Blank\ Absorbance} \times 100 \quad (1)$$

The inhibitor concentration (IC_{50}) calculation is resolved from the results of the linear regression equation y = a + bx from various sample concentrations. The x-axis is the sample concentration, the y-axis is the percentage of inhibition, a is the intercept or the intersection of the y-line, and b is the slope. Then, IC_{50} can be calculated using the following formula (Fitriani et al. 2019):

$$\frac{50 - a}{b} \quad (2)$$

2.4 *Viability test*

Fibroblasts previously frozen in liquid nitrogen were warmed at 37°C in a water bath until thawed. After that, the fibroblasts were centrifuged at 1500 rpm for 15 minutes to obtain cell pellets (Fitriani et al. 2019). The precipitate from the centrifugation was stored in a laminar flow. Then, the cells were suspended again on a culture medium scaffold made with DMEM (Gibco), 10% FBS, and 1% antimycotic antibiotic in the form of penicillin-streptomycin (Chen et al. 2020). Then, the cells were grown with expansion using a T-flask and incubated for 48 hours at 37°C. The cultured cells were divided into eight groups. The fibroblast culture in the group expected to experience oxidative stress was added with a stressor in the form of 100 μM H_2O_2 and then stored in a 5% CO_2 (ESCO) incubator at 37°C for 60 minutes (Che Zain et al. 2020).

Fibroblasts were planted on 96 well plates of 10,000 cells/well on culture media, which had been replaced with 200 μL centrifuged sample solution. Then, the fibroblasts were incubated for 24 hours. After being treated and incubated, the cells were washed using 10X PBS once. Then, 100 μL of CCK-8 (Dojindo) reagent was added to each well. The wells were incubated at 37°C for 90 minutes. Viability and cytotoxicity tests were observed after 24 hours. The

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percentage of cell viability can be calculated by the following formula (Mahardika MP & A. 2021):

$$Percentage\ of\ cell\ viability\ (\%) = \frac{Absorbance\ A - Blank\ Absorbance}{Absorbance\ B - \ Blank\ Absorbance} \times 100 \qquad (3)$$

3 RESULTS

This study aimed to determine the effect of lemongrass leaf extract entangled with a natural polymer in the form of horn beetle chitosan in particle size modified into nanoparticles to increase stability, solubility, and its effectiveness in influencing the activity of fibroblasts subjected to oxidative stress. The fibroblasts used in this study were human dermal fibroblasts (HDF) from the biorepository of Yarsi University. The lemongrass used was identified by the Biological Research Center of the Biological Sciences Organization of West Java No. B-112/V/DI.05.07/9/2021.

In this study, the effect of nano-chitosan encapsulation of lemongrass leaf extract (EnChLg) on the activity of fibroblasts under oxidative stress was examined. Oxidative stress of fibroblasts was obtained by giving H_2O_2 solution and incubating for 60 minutes indicated by the results of oxidative stress observations, namely the formation of ROS from fibroblasts.

3.1 *Antioxidant test of EnChLg*

The antioxidant activity of EnChLg was determined by performing the 2.2-diphenyl-1-picrylhydrazyl (DPPH) test. The DPPH test is a simple, easy, fast, reactive test method, and it does not require many samples to determine the antioxidant activity of a compound. Antioxidant activity can be identified by quantitative measurement of a compound in capturing free radicals from DPPH using UV-Vis spectrophotometry for absorbance measurement so that the value of the antioxidant activity of the compound is attained by reducing free radicals expressed by the IC_{50} value. The IC_{50} value is the concentration of a compound capable of reducing free radicals up to 50% (Nugrahani et al. 2020).

The results of the EnChLg antioxidant test with concentrations of 100, 200, 300, 400, and 500 ppm showed that the mean percentage of EnChLg inhibition was 10.48%, 19.16%, 25.89%, 36.71, and 31.42%, respectively, as can be seen in Table 1.

Table 1. Mean Percentage of Inhibition and IC_{50}.

	Inhibition (%)				
EnChLg	1	2	3	Mean	IC_{50} (ppm)
100	7.68	11.51	12.25	10.48 ± 2.45	566.48 ± 31.95
200	20.53	17.16	19.80	19.16 ± 1.77	
300	34.86	34.76	30.20	25.89 ± 2.67	
400	35.89	37.13	37.09	36.71 ± 0.70	
500	38.99	39.39	49.34	31.42 ± 5.87	

The IC_{50} value of chitosan encapsulation of lemongrass leaf extract was 566.48 ppm. The calculation of the IC_{50} value can be obtained from the calculation results of the linear regression equation, the regression equation with the values of y = 0.078x + 4.1972 and R^2 = 0.8712, y = 0.0757x+5.2709 and R^2 = 0.8847, and y = 0.0915x+ 2.2976 and R^2 = 0.9924 from the first, second, and third EnChLg tests, respectively. The results of the regression equation from EnChLg in three replications can be seen in Figure 1.

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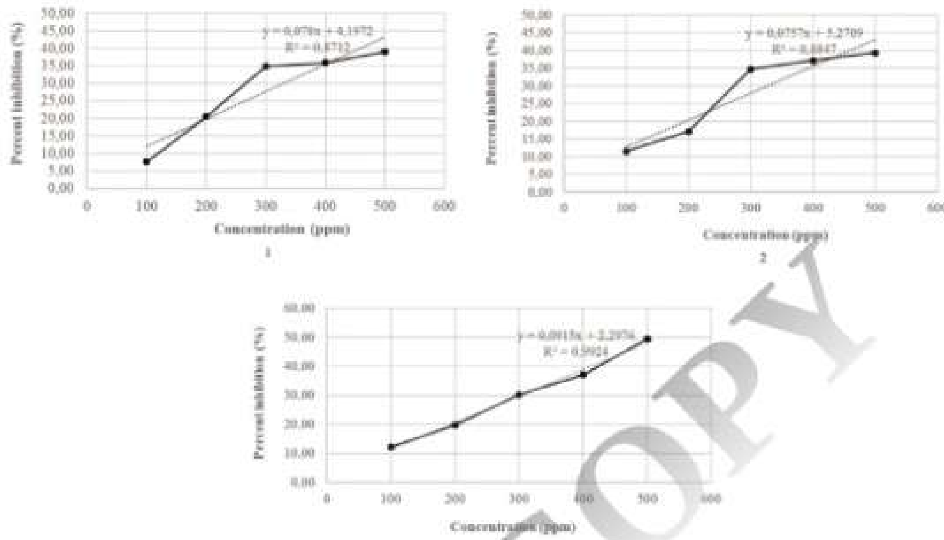

Figure 1. Curve of the relationship between the EnChLg concentration and the inhibition percentage.

3.2 *Fibroblasts cytotoxicity*

A cytotoxicity test was conducted to determine the value of IC_{50}, which is the concentration of compounds capable of inhibiting cell growth up to 50%. The smaller the IC_{50} value produced, the compound will be more toxic. Cytotoxicity test of EnChLg on fibroblasts subjected to oxidative stress showed an IC_{50} result of 1520 ppm. The calculation of the inhibition percentage in determining the IC_{50} value was obtained from the regression equation with the value of $y = 0.01x + 34.8$ and $R^2 = 0.7812$ (Figure 2).

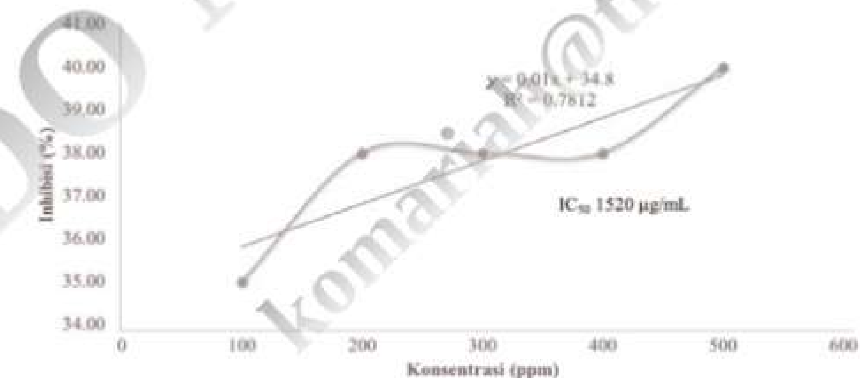

Figure 2. IC_{50} Value of Fibroblasts Cytotoxicity.

3.3 *Fibroblasts viability*

Based on the results of observations and readings of the absorbance values of the viability test from EnChLg concentrations of 100, 200, 300, 400, and 500 ppm on fibroblasts, the results of the normality test using Shapiro-Wilk showed that the data had a normal distribution with $p>0.05$. The test was continued with the Oneway ANOVA parametric test demonstrating that there was a significant difference in the study group ($p<0.05$). Next,

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Duncan's test was conducted to find out which groups had differences. The results of Duncan's test indicated that there were significant differences between the untreated group and the encapsulated group of lemongrass leaf extract with chitosan.

The viability test results showed that the group without treatment as negative control did not indicate a significant difference ($p>0.05$) from the positive control group given ascorbic acid and the group given EnChLg with a concentration of 300 ppm with viability values of 87.67%, 87.67%, and 90.00%, respectively. However, the EnChLg concentration of 300 ppm had a higher percentage of 2.66% compared to the negative and positive control groups. The negative control group, positive control group, and EnChLg had 300 ppm significant differences from the group given the H_2O_2 stressor, EnChLg 100, and EnChLg 500 ppm with viability values of 68.33%, 70.50%, and 71.33%, respectively. The group that was given stress, although it did not show a significant difference, had the lowest viability value compared to the EnChLg 100 and 500 ppm groups, namely 3.18% and 4.39%, respectively. Although the EnChLg 400 ppm group was not significantly different from the other groups, it had higher viability than the group given the stressor, EnChLg 100, and EnChLg 500 ppm. Meanwhile, EnChLg 400 ppm had low viability when compared to the EnChLg 200, EnChLg 300 ppm, positive control, and negative control groups. The calculation results of the viability values can be seen in Table 2. The results of microscopic viability test observations in all study groups showed the persisted fibroblasts and fibroblasts undergoing apoptosis. The results of microscopic observations at 100x magnification can be seen in Figure 3.

Table 2. Fibroblasts viability mean.

Group	Number (N)	Viability ± SD (%)	*p Value*
Fibroblast	3	87.67 ± 6.51^{a}	$p<0.05$
H_2O_2	3	68.33 ± 7.64^{c}	
Ascorbic acid	3	87.67 ± 1.53^{a}	
EnChLg 100	3	70.50 ± 5.50^{bc}	
EnChLg 200	3	85.00 ± 6.56^{ab}	
EnChLg 300	3	90.00 ± 4.36^{a}	
EnChLg 400	3	81.67 ± 11.59^{abc}	
EnChLg 500	3	71.33 ± 13.50^{bc}	

[a-c]the different columns show significant differences ($p<0.05$)

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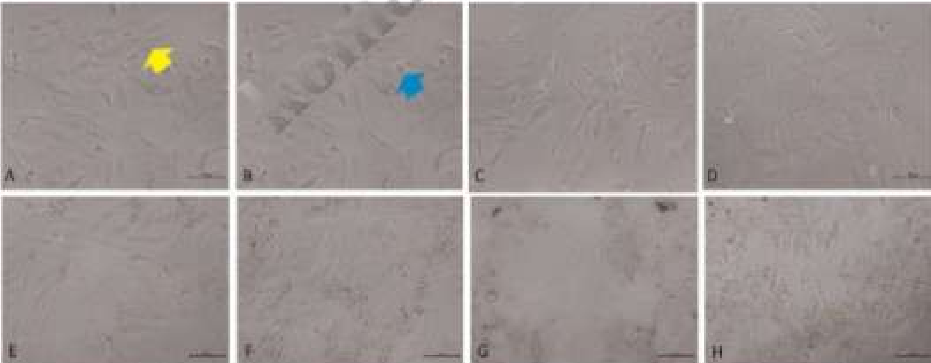

Figure 3. Effect of EnChLg administration on fibroblast viability. Yellow arrows display live fibroblasts with clearly visible cell nuclei and blue arrows express dead fibroblasts with clumping of cells. Observation of fibroblast morphology structure in the groups: A. Negative control, B. H_2O_2, C. Positive control, D. EnChLg 100 ppm, E. EnChLg 200 ppm, F. EnChLg 300 ppm, G. EnChLg 400 ppm, H. EnChLg 500 ppm. Observations were at 100x magnification.

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4 DISCUSSION

The success of the wound healing process is supported by mutually coordinated and overlapping healing phases, namely hemostasis, inflammation, proliferation, and remodeling, as well as various mediators, growth factors, and cells involved in this process, one of which is fibroblasts. Fibroblasts are cells whose populations are mostly found in connective tissue and are one of the cells playing a significant role in the wound healing process, especially in the proliferative phase. Fibroblasts are stimulated by various mediators and growth factors to proliferate and migrate to the wound area, which then plays a role in depositing collagen fiber proteins and the ground substance forming an extracellular matrix (ECM) to facilitate cell migration and forming new tissue (Dewi 2018; Wallace et al. 2021).

In the wound-healing process, the role of oxygen (O_2) is required to produce adenosine triphosphate (ATP) by the mitochondria, thereby increasing the energy needed for the formation of new tissue. However, O_2 molecules are having unpaired electrons so they become very reactive molecules, namely ROS. The most common forms of ROS are superoxide (O_2-), hydrogen peroxide (H_2O_2), and hydroxyl (OH-) anions. Too low levels of ROS in the body can induce a halt in the cell cycle, whereas normal levels of ROS can maintain cell function, and excessive levels of ROS can result in the activation of pro-apoptotic proteins causing the death of cells (Dunnill et al. 2017). Therefore, the amount of ROS in the body needs to be balanced with the presence of antioxidants that will work synergistically in balancing ROS in the inflammatory process (Andarina & Djauhari 2017).

Ascorbic acid is a nonenzymatic antioxidant from natural ingredients that have been known as the gold standard of antioxidants. Ascorbic acid can balance the amount of ROS by neutralizing superoxide anions and hydroxyl radicals and activating other antioxidants in the body (Andarina & Djauhari 2017). Apart from ascorbic acid, other natural antioxidants are obtained from active compounds in almost all plants, one of which is lemongrass leaf or *Cymbopogon citratus*. Extracts from lemongrass leaves are proven to contain active compounds of flavonoids, phenols, tannins, saponins, and alkaloids known as natural nonenzymatic antioxidants (Trang et al. 2020). To enhance the stability and protect the active compounds from the extract of lemongrass leaf, trapping is carried out with natural polymers in the form of chitosan (Raza et al. 2020), physically modified into nanoparticles. The chitosan used is derived from the horned beetle or *Xylotrupes gideon*, which is a plant pest but has beneficial properties, such as biocompatible, biodegradable, mucoadhesive, and low toxic, and it has good diffusion and penetration capabilities (Mardliyati et al. 2012).

The DPPH value indicates the antioxidant activity of a compound with the magnitude of the free radical scavenging activity of DPPH indicated by the IC_{50} value. The smaller the IC_{50} value produced by a compound, the higher the antioxidant activity (Martiningsih & Gede Agus Beni WIdana 2016) The DPPH test results showed that EnChLg has antioxidant activity with a strong low IC_{50}. This is based on the classification of IC_{50} values of 10-50 ppm containing strong antioxidant activity, 50-100 ppm containing moderate antioxidant activity, and IC_{50} of more than 100 ppm containing strongly low antioxidant activity (Jadid et al. 2017), The antioxidant activity of EnChLg occurs when the EnChLg active compound donates a hydrogen atom to an unpaired electron in the free radical strand indicated by a change in the color of DPPH from purple to yellow (Ismail et al. 2017). Hence, the active compound of lemongrass leaf extract encapsulated with nano chitosan can be a natural alternative to antioxidants to help balance the number of free radical molecules with a better delivery and absorption system in the body. Research conducted by Husniati (2019) revealed that the antioxidant activity of the anthocyanin extract of *Euphorbia milii* flower encapsulated with chitosan could be maintained for good storage and delivery. Also, research by Sari et al. (2017) identified that lemongrass leaf

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extract had antioxidant activity as a free radical scavenger and secondary antioxidant because it could reduce redox potential and stabilize the oxidized form of metal ions (Sari et al. 2017).

The antioxidant activity with an extremely IC_{50} from EnChLg indicated a cytotoxicity value with a nontoxic IC_{50}, where an active compound is considered to be toxic if it has an IC_{50} category value of less than 1000 ppm (Rusanti et al. 2017). This is supported by the fibroblasts' viability results, where exposure to EnChLg at 300 ppm allowed for a 90% survival rate.. The high cell viability value showed that EnChLg administration could not only reduce oxidative stress due to hydrogen peroxide administration (stressor) but could also escalate fibroblast viability as indicated by a higher viability value than the negative control. Furthermore, the EnChLg administration had better viability than the positive control given a synthetic nonenzymatic antioxidant in the form of ascorbic acid. In this study, observations of fibroblast viability showed that the viability value of the EnChLg treatment indicated a higher number than the control, especially at a concentration of 300 ppm giving the highest viability value. This is in line with research carried out by Sari et al. (2017), revealing that the ethanolic extract of lemongrass leaves showed capable antioxidant activity in scavenging hydrogen peroxide and hydroxyl, where hydroxyl can cause a direct effect on lipid peroxidation and hydroxyl is the most damaging ROS for cell components.

Research undertaken by Pan et al. (2022) found that antioxidant activity could enhance cell viability and proliferation by reducing oxidative stress caused by high amounts of ROS and lipid peroxidation. Research conducted by Roriz et al. (2014) identified that lemongrass could reduce lipid peroxidation in brain cells due to the high concentration of flavonoids contained in the brain cells. Moreover, lemongrass shows an antioxidant effect by increasing the activity of the enzyme superoxide dismutase (SOD) and decreasing the production of ROS in macrophages (Ajuru et al. 2017). In the wound healing process, by decreasing oxidative stress and ROS production in cells, inflammatory cells will be stimulated to release various mediators and growth factors, such as interleukin-1β, platelet-derived growth factor (PDGF), and basic fibroblast growth factor (BFGF), which will stimulate the proliferation of fibroblasts.

5 CONCLUSION

Nano chitosan encapsulation of lemongrass leaf extract contains active compounds playing a role as antioxidants effective in accelerating the wound healing process by reducing the level of oxidative stress from fibroblasts, through high viability. The concentration of EnChLg having the best and most significant effect on fibroblast viability was the concentration of 300 ppm.

CONFLICT OF INTEREST

The authors certify that they have no affiliations in any organization with any financial interest or nonfinancial interest.

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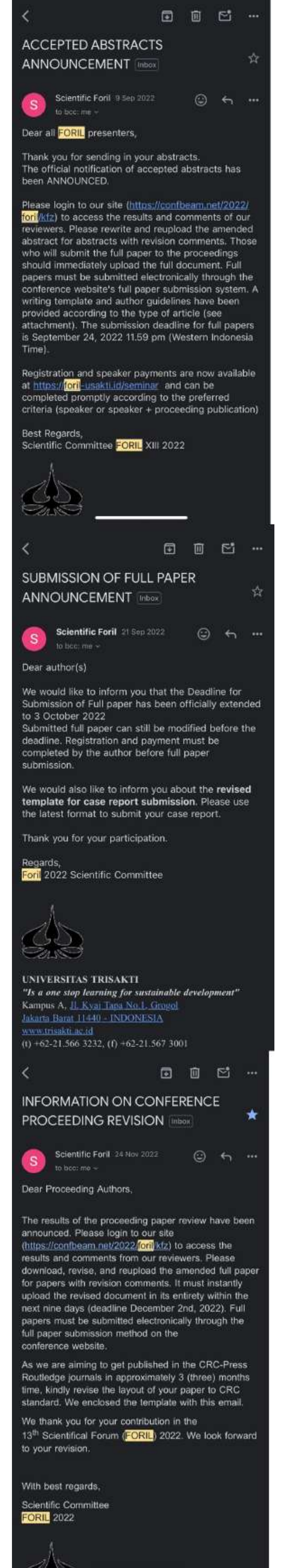

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