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

CRC Press
Taylor & Francis Group

PROCEEDINGS OF THE INTERNATIONAL CONFERENCE ON TECHNOLOGY OF DENTAL AND MEDICAL SCIENCES (ICTDMS 2022), JAKARTA, INDONESIA, 8–10 DECEMBER 2022

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 and Carolina Damayanti Marpaung
Universitas Trisakti, Indonesia

CRC Press
Taylor & Francis Group
Boca Raton London New York Leiden

CRC Press is an imprint of the
Taylor & Francis Group, an **informa** business
A BALKEMA BOOK

First published 2023
by CRC Press/Balkema
4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN

and by CRC Press/Balkema
2385 NW Executive Center Drive, Suite 320, Boca Raton FL 33431

CRC Press/Balkema is an imprint of the Taylor & Francis Group, an informa business

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

Library of Congress Cataloging-in-Publication Data
A catalog record has been requested for this book

ISBN: 978-1-032-51441-3 (hbk)
ISBN: 978-1-032-51466-6 (pbk)
ISBN: 978-1-003-40237-4 (ebk)

DOI: 10.1201/9781003402374

Typeset in Times New Roman
by MPS Limited, Chennai, India

Quality Improvement in Dental and Medical Knowledge, Research, Skills and Ethics Facing Global Challenges – Widyarman et al. (Eds)

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

Quality Improvement in Dental and Medical Knowledge, Research, Skills and Ethics Facing Global Challenges – Widyarman et al. (Eds)

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

Acknowledgements

Prof. Shinya Murakami, D.D.S., Ph.D. (*Department of Periodontology, Osaka University, Japan*)
Prof. Adrian Yap (*Department of Dentistry, Ng Teng Fong General Hospital, Singapore*)
Prof. Dr. Rosnah Binti Mohd Zain (*Department of Oro-Maxillofacial Surgical & Medical Sciences, Malaya University*)
Prof. Chaminda Jayampath Seneviratne, BDS (Hons)., M.Phil., Ph.D (*University of Queensland, Australia*)
Cortino Sukotjo, DDS, Ph.D., MMSc (*Department of Restorative Dentistry, University of Illinois at Chicago, United States*)
Prof. Dr. Nicola De Angelis (*Department of Periodontology, University of Genoa, Italy*)
Prof. Hirotaka Kuwata, D.D.S., Ph.D. (*Department of Oral Microbiology and Immunology, Showa University, Japan*)
Prof. Dr. drg. Tri Erri Astoeti, M.Kes (*Universitas Trisakti, Jakarta, Indonesia*)
Prof. drg. Rahmi Amtha, MDS, Ph.D, Sp.PM(K) (*Department of Oral Medicine, Universitas Trisakti, Jakarta, Indonesia*)
Prof. Dr. Siriwan Suebnukarn, D.D.S (*Thammasat University, Bangkok, Thailand*)

Committee Members

Scientific Committee

Prof. Dr. drg. David Buntoro Kamadjaja, Sp.BM(K) (*Oral Maxillofacial Surgeon, Universitas Hassanudin, Makasar, Indonesia*)
Prof. Dr. drg. Diah Savitri Ernawati, Sp.PM(K)., M.Si (*Oral Medicine, Universitas Airlangga, Surabaya, Indonesia*)
Prof. Dr. drg. Maria Francisca Lindawati Soetanto, Sp.Pros(K) (*Prosthodontic, Universitas Indonesia, Jakarta, Indonesia*)
Prof. drg. Boy Muchlis Bachtiar, M.S., Ph.D., PBO (*Oral Biology, Universitas Indonesia, Jakarta, Indonesia*)
Prof. Dr. drg. Inne Suherna Sasmita, Sp.KGA(K) (*Pediatric Dentistry, Universitas Padjajaran, Bandung, Indonesia*)
Prof. drg. Sondang Pintauli, Ph.D (*Public Health, Universitas Sumatera Utara, Indonesia*)
Prof. Dr. drg. Miesje Karmiati Purwanegara, S.U., Sp.Orto (*Orthodontic, Universitas Indonesia, Indonesia*)
Prof. Dr. drg. Sri Lelyati, S.U, Sp.Perio (K) (*Periodontic, Universitas Indonesia, Indonesia*)
drg. Diatri Nari Ratih, M.Kes., Ph.D., Sp.KG(K) (*Conservative Dentistry, Universitas Gadjah Mada, Indonesia*)

Organizing Committee

Drg. Aryadi Subrata, Sp.KG(K), (*Conservative Dentistry, Universitas Trisakti, Jakarta, Indonesia*)
Dr. drg. Armelia Sari W., M.Kes., PBO (*Microbiology Oral, Universitas Trisakti, Jakarta, Indonesia*)
Dr. drg. Anggraeny Putri Sekar Palupi, Sp.BM (*Oral Maxillofacial Surgeon, Universitas Trisakti, Jakarta Indonesia*)
Dr. drg. Muhammad Ihsan Rizal, M.Kes (*Oral Biology, Universitas Trisakti, Jakarta, Indonesia*)
drg. Isya Hanin, Sp.Pros (*Prosthodontic, Universitas Trisakti, Jakarta, Indonesia*)
drg. Muhammad Orliando Roeslan, M.Kes., PhD (*Oral Biology, Universitas Trisakti, Jakarta, Indonesia*)
drg. Dina Ratnasari, Sp.KG(K) (*Conservative Dentistry, Universitas Trisakti, Jakarta, Indonesia*)
drg. Carolina Damayanti Marpaung, Sp.Pros, PhD (*Prosthodontic, Universitas Trisakti, Jakarta, Indonesia*)

Quality Improvement in Dental and Medical Knowledge, Research, Skills and Ethics Facing Global Challenges – Widyarman et al. (Eds)

Potential anticancer properties of *Apium graveolens Linn.* against oral cancer

T. Hartono
Faculty of Dentistry, Universitas Trisakti, Jakarta, Indonesia

F. Sandra & R.A. Hayuningtyas
Department of Biochemistry and Molecular Biology, Faculty of Dentistry, Universitas Trisakti, Jakarta, Indonesia

S. Jauhari
Dentistry Programme, PAPRSB Institute of Health Sciences, Universiti Brunei Darussalam, Gadong, Brunei Darussalam

J. Sudiono
Department of Oral Pathology, Faculty of Dentistry, Universitas Trisakti, Jakarta, Indonesia

ABSTRACT: Background(s): Cancer represents one of the major healthcare issues worldwide with a rapid increase in cases but with limited cure. Oral cancer contributes about 3% of total cancer, with oral squamous cell carcinoma largely representing about 90% of all oral cancer. Given the high morbidity and mortality, finding effective ways that come with minimized side effects to treat cancer continues to be of great importance in the medical field. Plants, for instance, *Apium graveolens* Linn., are a rich source of novel chemical entities, which provide a promising line for research on cancer treatment. Objective(s): This review aimed to take an investigative approach to the possibility of future research on oral cancer using *A. graveolens*. Method(s): References for this review were identified through searches of PubMed, Google Scholar, and official reports and websites of global health organizations with the search terms "oral cancer", "anticancer", "*Apium graveolens*", and "apoptosis" from 2004 to 2022. References published in English and Indonesian language were considered for this review. Main finding(s): *A. graveolens* is widely cultivated for consumption and its uses in traditional medicine. Its pharmacological activities range from anticancer, antioxidant, antidiabetic, anti-inflammatory, hepatoprotective, and antihypercholesterolemia to antihypertensive. It is reported to possess many bioactive compounds with anticancer properties. Previous studies had shown the ability of *A. graveolens* to reduce the viability and induce apoptosis of several types of cancer such as prostate, rhabdomyosarcoma, and stomach cancer. Currently, there are no studies against oral cancer being reported. Conclusion(s): The current findings firmly support *A. graveolens* as a rich source of bioactive compounds and illustrate the importance of its pharmacological profile as an anticancer agent. Future research on the anticancer activity of *A. graveolens* against oral cancer should be encouraged.

1 INTRODUCTION

The rapid population growth has a significant impact on the existing healthcare system. With other possible risk factors accompanying the increasing and aging population, the

DOI: 10.1201/9781003402374-61

burden of cancer has also notably grown worldwide (Sung et al. 2021). The Global Cancer Observatory reported more than 19 million new cases and nearly 10 million deaths in 2020 (Globcan 2020-2021). The global cancer burden is projected to rise to more than 28 million cases in 2040, a substantial increase of 47% compared to 2020 (Sung et al. 2021). With significant morbidity and mortality, cancer cure remains a very difficult task in the medical field. The challenges include achieving the correct diagnosis at the early stage along with finding the most effective treatment to cure cancer (Al-Azri 2016).

Oral cancer accounts for about three percent of all diagnosed cancer. The majority of oral cancers are oral squamous cell carcinoma (OSCC), accounting for more than 90% of all oral cancers (Oral Cancer 2022). OSCC has high morbidity and mortality rates, and the overall survival rate of OSCC patients remains unfavorable because of delay in early detection, poor prognosis, absence of specific biomarkers, and high costs of alternative therapies (Montero & Patel 2015). The long-term survival rate of OSCC is 50% despite having new treatment modalities (Gharat et al. 2016).

Treatment options for OSCC include surgery, target therapy, chemotherapy, and radiotherapy (Gharat et al. 2016). Chemotherapy is often used as a treatment for OSCC, but it has been reported to cause several side effects (Greenwell & Rahman 2015; Yu et al. 2011). Remission patients also have the risk of developing a second primary tumor, which makes it a continuous challenge to treat OSCC (Desai et al. 2008). Chemoprevention, which is the administration of medication to reduce the risk of cancer and its reoccurrence, becomes an increasingly important therapy in an effort to alleviate the cancer burden and reduce the morbidity and mortality rate of OSCC (Montero & Patel 2015).

Different molecular targets relevant to cancer therapy, such as the induction of apoptosis, can be exploited with chemoprevention. Plants offer a promising line of bioactive compounds reported to have the ability to modulate these molecular targets (Mroueh et al. 2020). Therapies using plant-derived substances for cancer treatment are reported to have minimal side effects (Greenwell & Rahman 2015; Yu et al. 2011). Indonesia is a country that boasts a high level of biodiversity and has more than 9,600 plant species that have medicinal properties (Aggarwal et al. 2004; Bahtiar et al. 2017). As a country with many potential medicinal plants, Indonesia has a good prospect in developing various types of medicine of natural origin (Aggarwal et al. 2004). Although several in vitro studies had reported many plant products with anticancer activity, only a few are used for cancer therapy (Greenwell & Rahman 2015).

Apium graveolens Linn., also known as celery, is one of the plants that had been previously identified for its anticancer property against various types of cancer. Studies have highlighted the anticancer properties of *A. graveolens*, indicating that it should be subject to further research as a promising chemopreventive agent (AL-Jumaily 2010; Bahtiar et al. 2017; Gao et al. 2011; Köken et al. 2016). Further research is needed to find out about the ability of *A. graveolens* as a chemopreventive agent for other cancer types (Al-Asmari et al. 2017), especially against oral cancer for which the effect of *A. graveolens* has never been reported.

2 METHODS

References for this review were identified through searches of PubMed, Google Scholar, and official reports and websites of global health organizations with the search terms "oral cancer," "anticancer," "*Apium graveolens*," and "apoptosis" from 2004 to 2022. References published in English and Indonesian language were considered for this review.

3 RESULTS AND DISCUSSION

3.1 *Oral cancer: Oral squamous cell carcinoma*

More than 200 types of different cancers have been discovered to this day. Each has its own character, marker, and treatment modality. While there is no one perfect marker that could be used to accurately identify the occurrence and/or recurrence of a particular type of cancer, there are multigene markers found in different cancers. Oral cancers in particular do not have a specific marker but do share some markers with other cancers such as p53 mutations (Rajguru et al. 2020).

OSCC histologically arises from the squamous cells, while the other types of oral cancer may originate from the epithelium, connective tissue, minor salivary glands, lymphoid tissue, and melanocytes or metastasize from a distant tumor (Tashakori-Sabzevar et al. 2016). The tongue, floor of the mouth, and lower lip are the most common sites of OSCC (Gharat et al. 2016).

There is a high correlation between OSCC and the lifestyle of a person (D'souza & Addepalli 2018; Tashakori-Sabzevar et al. 2016). The International Agency for Research on Cancer had reported on the constant use of carcinogenic substances being tantamount to high-risk lifestyles, which increase the risk of OSCC. These carcinogenic substances include both smoked or smokeless tobacco, alcohol, and betel nut with or without tobacco (Cancer 2010; Humans *et al.* 2004; Humans & Cancer 2007; International Agency for Research on Cancer 2020). Other risk factors of OSCC include dietary deficiencies, poor oral hygiene, socioeconomic status, and host factors (Oral Cancer 2022).

It has been reported that the risk of developing OSCC is thrice more in smokers than nonsmokers (Greenwell & Rahman 2015). Furthermore, the risk of OSCC increased proportionally with the number of years a person uses tobacco. This risk can decrease after tobacco cessation, but it will not be fully diminished (Oral Cancer 2022). Involuntary smokers also face an increased risk of 87% in developing OSCC compared with those who never smoked and have not been exposed. In addition, studies have emphasized the synergistic effect that tobacco and alcohol cause in the development of OSCC (Gharat et al. 2016). The risk of developing OSCC is three to nine times greater in smokers and drinkers and up to 100 times greater in heavy smokers and drinkers/alcoholics (Coletta et al. 2020). However, alcohol consumption and abuse are linked to an increased risk of OSCC even in nonsmokers (Montero & Patel 2015).

Oral carcinogenesis is an extremely complex process involving many different elements. There are numerous elements essential for carcinogenesis to occur, which make up the hallmarks of cancer such as a limitless replicative potential, self-sufficiency in growth signals, lack of sensitivity to anti-growth signals, the ability to evade apoptosis, increased angiogenesis, invasion, and metastasis. The tumor microenvironment (TME) comprising cancer-associated fibroblasts (CAFs), immune cells, and other supporting cells contributes to the development of cancer by making cancer cells more adaptable to their surroundings, enabling survival and proliferation above their normal neighboring cells, leading to their perpetuation. Chronic exposure of normal epithelial cells to all risk factors will lead to an initial impetus for the transformation of these cells, beginning with the disruption of homeostasis and genetic alterations through cytogenic and epigenetic processes that alter cell cycle progression, DNA repair mechanisms, cell differentiation, and apoptosis. The cells consequently escape the normal growth control pattern and undergo malignant neoplastic changes, which can then be inherited by their clones (Gharat et al. 2016).

Early diagnosis and treatment are key to a better prognosis and survival for OSCC patients (Sharan et al. 2012). OSCC is usually treated by one or a combination of treatment modalities depending on the location, size, and stage of the primary tumor (Montero & Patel 2015). Additionally, the patient's comorbidity, history, nutritional status, ability to tolerate treatment, and willingness to face therapy also play a role in treatment choices (Gharat et al.

2016). Initial evaluation using tools such as the Tumor-Lymph Node-Metastasis (TNM) staging system is typically employed to assess and evaluate the primary tumor characteristics. In tumors that can be operated on, surgery is the treatment of choice as it enables accurate pathologic staging, providing information about the status of margins, tumor spread, and histopathologic characteristics, aiding the assessment of the most appropriate method for subsequent management. Reconstructive surgery such as bone grafting and surgical flaps may be necessary to rebuild the structures removed during surgery and restore function (Oral Cancer 2022).

In contrast, for tumors that are not able to be surgically removed, chemotherapy and radiotherapy are usually the treatment option. It has been reported that chemotherapy and radiotherapy (chemoradiotherapy) have a synergistic effect against oral cancer including OSCC when used at the same time (Montero & Patel 2015). However, chemoradiotherapy is reported to cause several side effects and is very toxic to both normal and tumor cells (Nurgali et al. 2018; Pfeffer & Singh 2018; Rhodus et al. 2014).

Apoptosis is a normal physiologic process that constantly takes place in multicellular organisms through the formation of programmed cell death (Ribeiro et al. 2018). Apoptosis is finely regulated at the gene level resulting in the genetically determined elimination of cells. The dysregulation of apoptosis can be seen in many diseases and is deemed one of the hallmarks of cancer. Such deregulation of apoptosis is associated with unchecked cell proliferation, the development and progression of cancer, and cancer resistance to drug therapies (Xu et al. 2019).

3.2 *Plant-derived cancer treatment*

Cancer chemoprevention is becoming more common in cancer treatment (Montero & Patel 2015). The goal of chemoprevention is to overturn any premalignant transformations, prevent cancer reoccurrence, and prevent the occurrence of a second primary tumor (Palmer & Grannum 2011). There are numerous molecular targets of chemoprevention relevant to cancer therapy such as the activation of apoptosis, suppression of growth factor expression or signaling, downregulation of antiapoptotic proteins, and angiogenesis.

Apoptosis plays an important role in the inherent tumor-suppression mechanism and is subject to an array of research. Many drugs and therapeutic measures are founded on the current understanding of it (Palmer & Grannum 2011; Ribeiro et al. 2018; Xu et al. 2019). Gaining control of or terminating the uncontrolled proliferation of cancer cells by using the cell's own mechanism for death is one strategy to treat cancer. Because apoptosis evasion is a hallmark of cancer, targeting it is useful for many types of cancer. This apoptosis-targeting is the most effective nonsurgical cancer treatment. Many anticancer medications target distinct phases in both the intrinsic and extrinsic apoptotic pathways. Numerous plant-derived substances have also been discovered to be capable of inducing apoptosis in cancer cells and are typically nontoxic to normal cells (Pfeffer & Singh 2018). Due to their pharmacological safety, these substances can either be employed alone to prevent cancer or in conjunction with chemotherapy or radiotherapy to treat cancer (Ribeiro et al. 2018).

3.3 *Apium graveolens Linn.*

A. graveolens belonging to the family of *Apiaceae* (Agriculture 2021), originates from Southern Europe, Asia, and Africa; it can also be found in North and South America. It is widely cultivated as a popular vegetable for consumption (Al-Asmari et al. 2017). High levels of moisture and low temperature are essential for its growth, hence *A. graveolens* of the highest quality can be easily spotted growing in cold and mild environments (Kooti & Daraei 2017). In Indonesia, *A. graveolens* can be found in large quantities in Cipanas, Pangalengan dan Badungan (Sukohar & Arisandi 2016).

A. graveolens has gradually become a popularly cultivated crop not only for consumption but also for medicinal benefits in many parts of the world. Owing to its many benefits, the growing popularity of *A. graveolens* on the markets over the years is undoubtable (Bruznican *et al.* 2020). *A. graveolens* has many different health benefits because it contains various bioactive compounds such as flavonoids, organic acid, organic acid ester, coumarins, furanocoumarins, fatty acids, and phthalides (Al-Asmari et al. 2017).

All parts of *A. graveolens* can be consumed (Gupta et al. 2019). It has also been used in traditional medicine, and as a diuretic to decrease blood pressure. It reduces glucose, blood lipids, and blood pressure, which play a vital role in a healthy heart (Al-Asmari et al. 2017). Its use in medicine is attributed to its pharmacological activities such as anticancer, antioxidant, anti-inflammatory, hepatoprotective, antidiabetic, antihypercholesterolemic, and antihypertensive activities (Emad et al. 2020; Gao et al. 2011; Gupta et al. 2019; M.M. *et al.* 2018; Tala'a 2020; Tashakori-Sabzevar et al. 2016).

3.4 *Apium graveolens Linn. for cancer*

A. graveolens has been researched for many types of cancer including prostate cancer, rhabdomyosarcoma, and stomach cancer. Research on prostate cancer was done using lymph node carcinoma of the prostate (LNCaP) cell line, and results showed that the ethanolic extract of *A. graveolens* was able to prevent cell proliferation and expression of vascular endothelial growth factor as well as trigger the induction of apoptosis (Köken et al. 2016). Meanwhile, aqueous, ethanolic, and hexane extracts of *A. graveolens* were evaluated against the rhabdomyosarcoma (RD) cell line where these extracts were seen to have significant cytotoxic and inhibitory effects on the growth of the cell line (AL-Jumaily 2010). The celery seed extract was also tested against the human gastric cancer cell line and reported to have reduced the viability of the cancer cells and brought about the induction of apoptosis (Gao et al. 2011). With all these benefits for other types of cancer, *A. graveolens* has yet to be researched on its effect on any type of oral cancer. It will be beneficial to study whether *A. graveolens* is beneficial in the treatment of oral cancer, especially OSCC.

4 CONCLUSION

A plethora of plants have been found to possess promising anticancer activity. While *A. graveolens* being one of the aforementioned plants is shown to be useful for the treatment of several cancer types, studies on its anticancer activity against oral cancer have not been made available. Because different types of cancer are likely to share similar hallmarks and mechanisms of death, further studies on *A. graveolens* against oral cancer could be pursued to discover more of its uses in the field of cancer therapy.

REFERENCES

Aggarwal, B.B., Takada, Y., & Oommen, O. V. 2004. From chemoprevention to chemotherapy: common targets and common goals. *Expert Opinion on Investigational Drugs* 13(10): 1327–1338.

Agriculture, U.S.D. of. 2021. Apium graveolens L. https://plants.usda.gov/java/ClassificationServlet?source=display&classid=APGR2

Al-Asmari, A.K., Athar, M.T., & Kadasah, S.G. 2017. An updated phytopharmacological review on medicinal plant of Arab region: Apium graveolens linn. *Pharmacognosy Reviews* 11(21): 13.

Al-Azri, M.H. 2016. Delay in cancer diagnosis: causes and possible solutions. *Oman Medical Journal* 31(5): 325.

AL-Jumaily, R.M.K. 2010. Evaluation of anticancer activities of crude extracts of Apium graveolens L. seeds in two cell lines, *RD and L20B in vitro. Iraqi Journal of Cancer and Medical Genetics* 3(2).

Bahtiar, A., Vichitphan, K., & Han, J. 2017. Leguminous plants in the Indonesian archipelago: traditional uses and secondary metabolites. *Natural Product Communications* 12(3): 1934578X1701200338.

Bruznican, S., De Clercq, H., Eeckhaut, T., Van Huylenbroeck, J., & Geelen, D. 2020. Celery and celeriac: a critical view on present and future breeding. *Frontiers in Plant Science* 10: 1699.

Cancer, I.A.for R. on. 2010. *Alcohol Consumption and Ethyl Carbamate*. (Vol. 96). IARC Press, International agency for research on cancer.

Coletta, R.D., Yeudall, W.A., & Salo, T. 2020. Grand challenges in oral cancers. *In Frontiers in Oral Health* (Vol. 1, p. 3). Frontiers Media SA.

D'souza, S., & Addepalli, V. 2018. Preventive measures in oral cancer: An overview. *Biomedicine & Pharmacotherapy* 107: 72–80.

Desai, A.G., Qazi, G.N., Ganju, R.K., El-Tamer, M., Singh, J., Saxena, A.K., Bedi, Y.S., Taneja, S.C., & Bhat, H.K. 2008. Medicinal plants and cancer chemoprevention. *Current Drug Metabolism* 9(7): 581–591.

Emad, A.M., Ali, S.F., Abdel-Rahman, E.A., Meselhy, M.R., Farag, M.A., Ali, S.S., & Abdel-Sattar, E.A. 2020. Anti-inflammatory and antioxidant effects of Apium graveolens L. extracts mitigate against fatal acetaminophen-induced acute liver toxicity. *Journal of Food Biochemistry* 44(10): e13399.

Gao, L.-L., Feng, L., Yao, S.-T., Jiao, P., Qin, S.-C., Zhang, W., Zhang, Y.-B., & Li, F.-R. 2011. Molecular mechanisms of celery seed extract induced apoptosis via s phase cell cycle arrest in the BGC-823 human stomach cancer cell line. *Asian Pac J Cancer Prev* 12(10): 2601–2606.

Gharat, S.A., Momin, M.M., & Bhavsar, C. 2016. Oral squamous cell carcinoma: current treatment strategies and nanotechnology-based approaches for prevention and therapy. *Critical Reviews™ in Therapeutic Drug Carrier Systems* 33(4).

Globcan 2020. 2021. *International Agency for Research on Cancer*. WHO Chronicle. https://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf

Greenwell, M., & Rahman, P. 2015. Medicinal plants: their use in anticancer treatment. *International Journal of Pharmaceutical Sciences and Research* 6(10): 4103.

Gupta, J., Gupta, R., & Mathur, K. 2019. Pharmacognostical, pharmacological and traditional perspectives of apium graveolens an ethnomedicinal plant. *International Journal of Life Science and Pharma Research* 9 (3): 38–47.

Humans, I.W.G.on the E. of C.R. to, & Cancer, I.A. for R. on. 2007. *Smokeless tobacco and some tobacco-specific N-nitrosamines* (Vol. 89). World Health Organization.

Humans, I.W.G.on the E. of C.R. to, Organization, W.H., & Cancer, I.A. for R. on. 2004. *Tobacco Smoke and Involuntary Smoking* (Vol. 83). Iarc.

International Agency for Research on Cancer. 2020. IARC Monographs on the Identification of Carcinogenic Hazards to Humans: List of Classifications by Cancer Site. https://monographs.iarc.who.int/wp-content/uploads/2019/07/Classifications_by_cancer_site.pdf

Köken, T., Koca, B., Özkurt, M., Erkasap, N., Kuş, G., & Karalar, M. 2016. Apium graveolens extract inhibits cell proliferation and expression of vascular endothelial growth factor and induces apoptosis in the human prostatic carcinoma cell line LNCaP. *Journal of Medicinal Food* 19(12): 1166–1171.

Kooti, W., & Daraei, N. 2017. A review of the antioxidant activity of celery (Apium graveolens L). *Journal of Evidence-Based Complementary & Alternative Medicine* 22(4): 1029–1034.

M.M., A., H.S., E.-R., & M.S., M. 2018. Evaluation of the potential anti-diabetic effect of apium graveolens and brassica oleracea extracts in alloxan induced diabetic rats. *Int J Pharm Sci Rev Res* 49(2): 39–44.

Montero, P.H., & Patel, S.G. 2015. Cancer of the oral cavity. *Surgical Oncology Clinics* 24(3): 491–508.

Mroueh, R., Nevala, A., Haapaniemi, A., Pitkäniemi, J., Salo, T., & Mäkitie, A.A. 2020. Risk of second primary cancer in oral squamous cell carcinoma. *Head & Neck* 42(8): 1848–1858.

Nurgali, K., Jagoe, R.T., & Abalo, R. 2018. Adverse effects of cancer chemotherapy: Anything new to improve tolerance and reduce sequelae? *In Frontiers in pharmacology* (Vol. 9, p. 245). Frontiers Media SA.

Oral Cancer. 2022. Nidcr.nih.gov. https://www.nidcr.nih.gov/health-info/oral-cancer

Palmer, O., & Grannum, R. 2011. Oral cancer detection. *Dental Clinics* 55(3): 537–548.

Pfeffer, C.M., & Singh, A.T.K. 2018. Apoptosis: a target for anticancer therapy. *International Journal of Molecular Sciences* 19(2): 448.

Rajguru, J.P., Mouneshkumar, C.D., Radhakrishnan, I.C., Negi, B.S., Maya, D., Hajibabaei, S., & Rana, V. 2020. Tumor markers in oral cancer: A review. *Journal of Family Medicine and Primary Care* 9(2): 492.

Rhodus, N.L., Kerr, A.R., & Patel, K. 2014. Oral cancer: leukoplakia, premalignancy, and squamous cell carcinoma. *Dental Clinics* 58(2): 315–340.

Ribeiro, I.P., Rodrigues, J.M., Mascarenhas, A., Kosyakova, N., Caramelo, F., Liehr, T., Melo, J.B., & Carreira, I.M. 2018. Cytogenetic, genomic, and epigenetic characterization of the HSC-3 tongue cell line with lymph node metastasis. *Journal of Oral Science* 60(1): 70–81.

Sharan, R.N., Mehrotra, R., Choudhury, Y., & Asotra, K. 2012. Association of Betel Nut with Carcinogenesis: Revisit With a Clinical Perspective.

Sukohar, A., & Arisandi, R. 2016. Seledri (Apium graveolens L) sebagai agen kemopreventif bagi kanker. *Jurnal Majority* 5(2): 95–100.

Sung, H., Ferlay, J., Siegel, R.L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. 2021. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians* 71(3): 209–249.

Tala'a, A.A. 2020. Protective Effects of Celery Extracts on Hepatic Tissues in Rats Consumed a Concentrated Feed.

Tashakori-Sabzevar, F., Razavi, B.M., Imenshahidi, M., Daneshmandi, M., Fatehi, H., Sarkarizi, Y.E., & Mohajeri, S.A. 2016. Evaluation of mechanism for antihypertensive and vasorelaxant effects of hexanic and hydroalcoholic extracts of celery seed in normotensive and hypertensive rats. *Revista Brasileira de Farmacognosia* 26: 619–626.

Xu, X., Lai, Y., & Hua, Z.-C. 2019. Apoptosis and apoptotic body: disease message and therapeutic target potentials. *Bioscience Reports* 39(1).

Yu, F.-S., Yang, J.-S., Yu, C.-S., Lu, C.-C., Chiang, J.-H., Lin, C.-W., & Chung, J.-G. 2011. Safrole induces apoptosis in human oral cancer HSC-3 cells. *Journal of Dental Research* 90(2): 168–174.