## Systematic Reviews Pharmacy



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#### Research Article

Evaluation the Effect of Pulmicort Inhalation on Children with Acute Asthma Attack

Ahmad Bahrami, Shabahang Jafarnejad, Hamidreza khoshnezhad Ebrahimi, Seyedeh Mahsa Mahmoudinezhad Dezfouli, Rozhin Pahlevani.

SRP. 2020; 11(9): 905 - 912

#### **Research Article**

Elevated serum levels of Interleukin-13 and Interleukin-17A in Pediatric Asthma Sawsan M. Jabbar AL-Hasnawi, Abeer Thaher Naji AL-Hasnawi. SRP. 2020; 11(9): 229 - 223

» Abstract » PDF DOI: 10.31838/srp.2020.9.37

#### **Research Article**

Protein Isolation from Sponge Niphates sp. as an Antibacterial and Antioxidant

A Warsidah, Masrianih, Mega Sari Juane Sofiana, Ikha Safitri, Ajuk Sapar, Anthoni B. Aritonang, Yuges Saputri Muttalib, Dzul Fadly.

SRP. 2020; 11(9): 518 - 521

» Abstract >> PDF DOI: 10.31838/srp.2020.9.76

#### **Review Article**

Matrix Metalloproteinase-1 (MMP-1) Expression and Density of Collagen Fibers following Application of Haruan Fish (Channa striata) Extract in Inflamed Pulp of Wistar Rat

Luni Jekti Nugroho, Andi Sumidarti, Mufliha Siri, Muhammad Husni Cangara, Nurhayaty Natsir, Maria Tanumihardja, Noor Hikmah, Asrianti.

SRP. 2020; 11(9): 6 - 9

>>> Abstract >>> PDF DOI: 10.31838/srp.2020.9.02

#### **Research Article**

Did Servant, Digital and Green Leadership Influence Market Performance? Evidence from Indonesian Pharmaceutical Industry

Khaerul Fahmi, Temmy Kurniawan, Yoyok Cahyono, Afen Sena, Suhadarliyah, Popong Suryani, Agus Sugianto, Dahlia Amelia, Musnaini, Shofia Amin, Husni Hasbullah, M. Jihadi, Hadion Wijoyo, Agus Purwanto.

SRP. 2020; 11(9): 642 - 653

» Abstract » PDF DOI: 10.31838/srp.2020.9.95

#### **Research Article**

Juvenile Delinquency Measurement in Indonesian High Schools

🛔 Syariful, Akif Khilmiyah, Siswanto Masruri.

SRP. 2020; 11(9): 522 - 527

» Abstract » PDF DOI: 10.31838/srp.2020.9.77

#### **Research Article**

Prevention and Treatment Approaches in Children with the Coronavirus Shaqayeq Khosravi, Seyedeh Mahsa Mahmoudinezhad Dezfouli. SRP. 2020; 11(9): 913 - 919

» Abstract >> PDF DOI: 10.31838/srp.2020.9.133

#### **Research Article**

Comparative Study for Complications of Otoplasty between Patients under Ten Years and above Ten Years Old

🛔 Ahmed Miri saadoon, Ali Abd-Almer Jwad and Riyadh K. Madloum.

SRP. 2020; 11(9): 234 - 238

» Abstract » PDF DOI: 10.31838/srp.2020.9.38

#### **Research Article**

Extract Standardization in Ethyl Acetate Fraction from Sargassum Hystrix as Inhibitor of  $\alpha$ -Amylase and  $\alpha$ -Glucosidase

💄 Sovia Indah Nurkhanifah, Siti Ari Budhiyanti, Amir Husni.

SRP. 2020; 11(9): 528 - 534

» Abstract » PDF DOI: 10.31838/srp.2020.9.78

#### **Review Article**

A Review of the Presence of Antibiotic Resistance Problems on Klebsiella Pneumoniae Acquired from Pigs: Public Health Importance

🚔 Eka Dian Sofiana, Junianto Wika Adi Pratama, Mustofa Helmi Effendi, Hani Plumeriastuti, Freshindy Marissa Wibisono, Erwan Budi Hartadi, Akvyan Rafi Hidayatullah.

SRP. 2020; 11(9): 535 - 543

Synergistic Effect between Zingiber Officinale Volatile Oil and Meropenem against Acinetobacter Baumannii Producing-Carbapenemase Isolated from Neurosurgery in Iraq

💄 Safaa A.L. Al Meani, Mohammed M. Ahmed, Ali H. Abdulkareem. SRP. 2020; 11(9): 920 - 925

>> Abstract >> PDF DOI: 10.31838/srp.2020.9.134

#### **Review Article**

Distinctive Therapeutic Strategies against Corona Virus-19 (COVID-19): A Pharmacological Review 畠 Yousra A. Nomier, Devulapalli S. Rao, Ahmed H. Suhaqi, Rayan A. Ahmed. SRP. 2020; 11(9): 544 - 561

>> Abstract >> PDF DOI: 10.31838/srp.2020.9.80

#### **Research Article**

Effect of Diabetic Ketoacidosis on Some Biochemical and Immunological Variables 畠 Oqbah Abdul Halim, Qasim Khlaif Abdullah, Asmaa wajeh jumaa. SRP. 2020; 11(9): 239 - 242

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The Effect of Benzo [A] Pyrene on Changes in the Profile of CD11B + IL1 +, CD11B + IL17 +, CD4 + CD25 + in Mice (MUS MUSCULUS, L) after Getting Paramicsovirus Vaccine

🖀 Suwoyo, Lumastari Ajeng Wijayanti, Dwi Estuning Rahayu. SRP. 2020; 11(9): 926 - 930

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#### **Research Article**

Mechanisms for Managing Medical Institutions in Times of Crisis

L Anastasia Barzylovych, Bubalo Volodymyr, Nesterenko G. Valentyna, Rogachevskyi Oleksandr, Chornyi Oleg.

SRP. 2020; 11(9): 562 - 568

>>> Abstract >>> PDF DOI: 10.31838/srp.2020.9.81

#### **Research Article**

#### Platelets Profile Changes in Patients with COVID 19

畠 Safaa jawad kadhem, Ahmed Hasan Raheem, Hassan Salim aljumaily, Ahmed Abdul Haleem Al shammari, Ameer Kadhim Al-Humairi, Ali Baay.

SRP. 2020; 11(9): 569 - 574

>> Abstract >> PDF DOI: 10.31838/srp.2020.9.82

#### **Research Article**

Wives' Perceptions of Husbands with Erectile Dysfunction in Indonesia: The Fulfilment Pattern of the Wife's Sexual Partner Who Experiences Erectile Dysfunction due to Diabetes Mellitus

🖀 Abd. Nasir, Susilo Hariyanto, Nuruddin, Iswatun, Supatmi, Nuh Huda.

SRP. 2020; 11(9): 654 - 660

>> Abstract >> PDF DOI: 10.31838/srp.2020.9.96

#### **Research Article**

The Value of Standing X-ray in Detecting Physiological Spondylolisthesis in Patients with Single Disc Prolapse with Normal Intensity MRI Findings

🚨 Najat Adel Hashim, Raad Jawad Kadhim.

SRP. 2020; 11(9): 243 - 247

>> Abstract >> PDF DOI: 10.31838/srp.2020.9.40

#### **Research Article**

Effect of Career, Organizational Commitment on Turnover Intention through Mediation of Organizational Culture: Evidence from Indonesian Companies

🚨 Nico Alexander Vizano, Wiwik Utami, Sigmin Johanes, Aty Herawati, Havis Aima, Achmad H Sutawijaya, Agus Purwanto, Joko Supono, Puji Rahayu, Aris Setiyani, C Catur Widayati, Farida Elmi.

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#### **Research Article**

Social Network for Drug Circulation in Sidenreng Rappang Regency, Indonesia

🚨 Rahmat Pannyiwi, Andi Agustang, Tahir Kasnawi, Andi Tenri Pada, Ahmad Yani, Sadli Syam. SRP. 2020; 11(9): 575 - 577

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#### **Review Article**

The Mucosal Lesions on Removable Denture Wearers: A Systematic Review

🚨 Mohammad Dharma Utama, Acing Habibie Mude, Muhammad Ikbal, Vinsensia Launardo, Adriani Dachri.

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#### **Research Article**

Evaluation and Comparison of the Optimization Parameters Based on Univariate and Multivariate Techniques for Estimation Atorvastatin Calcium with Novel Reverse Indirect Spectrophotometric Method

🖀 Marwan A. Hasan, Rebwar O. Hasan, Khalid F. Al-Rawi.

SRP. 2020; 11(9): 248 - 259

» Abstract » PDF DOI: 10.31838/srp.2020.9.41

#### **Research Article**

Effect of pH, Temperature and Metal Salts in Different Storage Conditions on the Stability of Vitamin C Content of Yellow Bell Pepper Extracted in Aqueous Media

🚨 Husni S Farah, Jehad F Alhmoud, Atef Al-Othman, Khalid M Alqaisi, Ali M Atoom, Khalid Shadid, Ashok Shakya, Talal AlQaisi.

SRP. 2020; 11(9): 661 - 667

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#### **Research Article**

The Influence of Organizational Culture, Job Satisfaction, and Professional Commitment on Innovative Behavior of Flight Instructors at the Civil Flight School in Indonesia

🚔 Afen Sena, Yoyok Cahyono, Agus Purwanto.

SRP. 2020; 11(9): 938 - 952

Potential Impact of micro RNA-146a Gene Polymorphisms in Oxidative Stress of Diabetic Mellitus Type 1 🛓 Fulla Abd Alsattar Alriyahee, Noora M. Hameed, Israa Harjan Mohsen, Mona N. Al-Terehi.

SRP. 2020; 11(9): 260 - 263

#### **Research Article**

Testing the Role of Competence and Supervision of Job Satisfaction and Its Impact on Teacher Performance

🆀 Danang Hidayatullah, Anis Eliyana, Hamidah, Tuty Sariwulan, Agung Dharmawan Buchdadi. SRP. 2020; 11(9): 668 - 675

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#### **Research Article**

Effectiveness of Finger Held Relaxation on the Decrease in Intensity of Pain in Patient of Post-Sectio Caesarea in RSUD Sorong Regency

畠 Ariani Pongoh, Adriana Egam, Rizqi Kamalah, Anwar Mallongi.

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#### **Review Article**

Locator or Ball Attachment Systems for Mandibular Implant Overdentures: A Systematic Review

🛓 Muhammad Ikbal, Acing Habibie Mude, Irfan Dammar, Vinsensia Launardo, Ian Afifah Sudarman.

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» Abstract » PDF DOI: 10.31838/srp.2020.9.04

#### **Research Article**

Atomic Spectroscopy Technique Employed to Detect the Heavy Metals from Iraqi Waterbodies Using Natural Bio-Filter (Eichhornia crassipes): Thera Dejla as a Case Study

🖀 Ghalib Adrees Atiya Ali, Mohammed Nsaif Abbas.

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The Effect of Substitution of Purple Sweet Potato Flour and Tempeh on Organoleptic Quality of MP-ASI Biscuit

🖀 Radeny Ramdany, Yulia Rachmawati, La Supu, Anwar Mallongi.

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» Abstract » PDF DOI: 10.31838/srp.2020.9.139

#### **Research Article**

The Effect of Transformational Leadership on Employee Job Satisfaction with the Meditation of Trust to Supervisors

🖀 Bambang Raditya Purnomo, Anis Eliyana, Windra Alfatah Surya. SRP. 2020; 11(9): 676 - 686

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#### **Research Article**

Study the IL6 (C174G) Promoter SNP and Correlation with Physiological Growth Hormone and TNFA levels in Iraqi Subjects with Psoriasis

🖀 Shaimaa H. Ali, Rawaa S. A. AL-Azawi, Hamzah H. Kzar.

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» Abstract >> PDF DOI: 10.31838/srp.2020.9.44

#### **Research Article**

Effect of Organizational Citizenship Behavior, Work Satisfaction and Organizational Commitment toward Indonesian School Performance

🛔 Budi Sulistiyo Nugroho, Minnah El Widdah, Lukman Hakim, Muh. Nashirudin, Acep Nurlaeli, Joko Hadi Purnomo, Muhammad Aziz, Hendri Hermawan Adinugraha, Mila Sartika, Muhammad Khoirul Fikri, Abdul Mufid, Agus Purwanto, Mochammad Fahlevi.

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Democratic, Authocratic, Bureaucratic and Charismatic Leadership Style: Which Influence School Teachers Performance in Education 4.0 Era?

🖀 Wahidin, Basri, Teguh Setiawan Wibowo, Aufa Abdillah, Ahmad Kharis, Jaenudin, Agus Purwanto, Abdul Mufid, Suesthi Maharani, Alfi Qonita Badi`ati, Mochammad Fahlevi, Susila Sumartiningsih.

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Budi Sulistiyo Nugroho, Suheri, Lukman Hakim, Bambang Irawan, M. Sugeng Sholehuddin, Tatang Ibrahim, Mujib Ridlwan, Laily Hidayati, Gunawan Aji, Abdul Mufid, Nur Ihsan, Agus Purwanto, Mochammad Fahlevi.

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#### **Review Article**

Prosthetic Rehabilitation of Patient with Ocular Defects using Conventional Technique: A Systematic Review

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#### **Review Article**

#### A Review of Enterotoxigenic Escherichia coli Infection in Piglets: Public Health Importance

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Effect of Compensation and Organization Commitment on Tournover Intention with Work Satisfaction as Intervening Variable in Indonesian Industries

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#### **Research Article**

The Effect of Compensation Strategy Implementation on Knowledge Sharing through Affective Commitment and Psychological Contracts

Afzil Ramadian, Anis Eliyana, Hamidah, Agung Dharmawan Buchdadi, Randa Rakawuri.
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#### **Review Article**

Periodontal Status of Drug Abuser in Makassar

🚔 Nursyamsi Djamaluddin, Bagus Setiawan.

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New Paradigm for the Life Skills Development of Children and Youth in Elementary Education Schools in the Rural Highland of Omkoi District, Chiang Mai, Thailand: Towards Achieving the Sustainable Development Goals (SDGs)

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Moderating Role of IT Adoption and Mechanism of Dynamic Capabilities on Indonesian Pharmaceutical Firms Performance

**&** Juhriyansyah Dalle, Sandu Siyoto, Nita Dwi Astika, Danes Jaya Negara, Teddy Chandra, Khairul Anam.

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#### **Review Article**

The Prevalence of Temporomandibular Joint Disorders in Young Violin Players in Two Orchestras in Indonesia

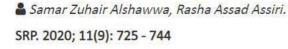
Like Damayanti Habar, Andi Adytha M.I.R, Mohammad Dharma Utama, Bahruddin Thalib, Acing Habibie Mude, Muhammad Ikbal, Eri Hendra Jubhari.

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>>> Abstract >>> PDF DOI: 10.31838/srp.2020.9.07

#### **Review Article**

mHealth Interventions for Cancer Care and Support A Systematic Literature Review



Impact of Complications after Surgical Treatment of Colon Cancer on Survival Bekisheva Aizhan, Makishev Abai, Yoshihiro Noso. SRP. 2020; 11(9): 993 - 1002

>>> Abstract >>> PDF DOI: 10.31838/srp.2020.9.143

#### **Review Article**

Quality of Dental Health Service in Indonesia: A Pilot Pathfinder Survey *Fuad Husain Akbar, Selistiani, Abd Hair Awang.* SRP. 2020; 11(9): 35 - 42

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#### **Research Article**

Did Transformational, Transactional Leadership Style and Organizational Learning Influence Innovation Capabilities of School Teachers during Covid-19 Pandemic?

Oding Supriadi, Zulkifli Musthan, Sa'odah, Rizki Nurjehan, Yuyun Dwi Haryanti, M. Rafid Marwal, Agus Purwanto, Abdul Mufid, Rohmad Adi Yulianto, Moh Farhan, Ahmad Asrof Fitri, Mochammad Fahlevi, Susila Sumartiningsih.

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The Role of Folic Acid on Some Physiological Parameters and Efficiency of Sperm in Male Rabbits

🚔 Rashad Fadhil Ghadhban, Nawras A. Alwan.

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#### Research Article

Tourism and Original Local Government Revenue in Indonesia Tourism Provinces: The Java Island Experience

Yustisia Kristiana, Rudy Pramono, Theodosia C. Nathalia, Vasco Adato H. Goeltom.
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Cytotoxicity Test of Tithonia diversifolia Leaf Extract on Bone Marrow Mesenchymal

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🖀 Hani Plumeriastuti, Agesti Veva Kalista, Budiastuti; Mustofa Helmi Effendi.

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#### **Research Article**

Boosting Organizational Commitment Through Visionary Leadership and Work Life Balance

Heni Kesumayani, Anis Eliyana, Hamidah, Maruf Akbar, Karuniana Dianta Sebayang.
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IN-VITRO EVALUATION OF THE ANTICANCER ACTIVITY OF Cu(II)AMINA(CYSTEINE)DITHIOCARBAMATE

Desy Kartina, Abdul Wahid Wahab, Ahyar Ahmad, Rizal Irfandi, Prihantono, And Indah Raya.
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THE ROLE OF FAMILIES CARING FOR PEOPLE WITH MENTAL DISORDERS THROUGH FAMILY RESILIENCE AT EAST JAVA, INDONESIA: STRUCTURAL EQUATION MODELING ANALYSIS

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Participation in-Service Teacher Training- Creativity Cultivation Program
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Observational Learning and Word of Mouth Against Consumer Online Purchase Decision during the Pandemic COVID-19

🛔 Juliana, Rudy Pramono, Arifin Djakasaputra, Innocentius Bernarto.

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The Role of Organizational Justice Dimensions: Enhancing Work Engagement and Employee Performance

🖀 Marisi Pakpahan, Anis Eliyana, Hamidah, Agung Dharmawan Buchdadi, Titis Ratih Bayuwati.

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HOW DOES APOPTOSIS OF OOCYTES AND GRANULOSA CELLS DUE TO CIGARETTE SMOKE EXPOSURE TO MICE BALB/C ? : EXPRESSION SMAD3, GDF9, APOPTOSIS

🚔 Eny Susanti, I Ketut Sudiana, Hendy Hendarto.

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#### **Review Article**

Construction and Preliminary Validation of the COVID-19 Pandemic Anxiety Scale V Vineeth Kumar, Geetika Tankha, Shelly, Sylvi Seth, Apeksha, Tanya S. Timple. SRP. 2020; 11(9): 1019 - 1024

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#### **Research Article**

ENHANCING EMPLOYEE PERFORMANCE WITH WORK MOTIVATION AS A MEDIATION VARIABLE

🚔 Qori Al Banin, Anis Eliyana, Eva Risalatul Latifiyah.

SRP. 2020; 11(9): 333 - 346

» Abstract » PDF DOI: 10.31838/srp.2020.9.50

#### **Research Article**

Identification of The Positive and Negative Emotions that Appeared among High School Students When Selecting University at Jakarta and Surrounding Area

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#### **Research Article**

An Empirical Examination of the Effect of TQM Practices on Hospital Service Quali An Assessment Study in UAE Hospitals

Ahmad Aburayya, Muhammad Alshurideh, Amina Al Marzouqi, Osama Al Diabat, Alanood Alfarsi, Roberto Suson, Mohammad Bash and Said A. Salloum.

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#### **Review Article**

The Impact of Motivation Mediation and Its Effect on the Level of Education and

Work Facilities on Employee Performance (Case Study of Education Office, West Sumatera Province)

Agussalim M, Novi Yanti, Hisar Sirait.

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A Review of the Opportunistic Pathogen Citrobacter Freundii in Piglets Post Weaning : Public Health Importance

Akvyan Rafi Hidayatullah, Mustofa Helmi Effendi, Hani Plumeriastuti, Freshindy Marissa Wibisono, Erwan Budi Hartadi, Eka Dian Sofiana.

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#### **Review Article**

### DISPARITIES OF THE USE OF HORMONAL AND NON-HORMONAL CONTRACEPTIVE DRUGS IN URBAN AND RURAL AREAS IN INDONESIA AND THE WORLD

Agustina Abuk Seran, Myrtati Dyah Antaria, Setya Haksama, Ema Setijaningrum, Agung Dwi Laksono, Anita Dewi Prahastuti Sujoso.

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#### **Research Article**

Antidiabetic Activity of Papaya Leaf Extract (Carica Papaya L.) Isolated with Maceration Method in Alloxan-Induces Diabetic Mice

Tridiganita Intan Solikhah, Boedi Setiawan, Dilian Ramdana Ismukada.
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#### **Review Article**

Health Care Professional Attitude and Motivation During COVID-19: A Case of Health Sector of Oman

La Ismail AlAbri, Rusinah bte Siron.

SRP. 2020; 11(9): 1035 - 1040

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#### **Research Article**

Develop Leadership Style Model for Indonesian Teachers Performance in Educatic

4.0 Era

Anissa Lestari Kadiyono, Rezki Ashriyana Sulistiobudi, Ikhfan Haris, Mohd Khaidir Abdul Wahab, Idan Ramdani, Agus Purwanto, Abdul Mufid, Muhammad Rikza Muqtada, M. Gufron, Mohamad Nuryansah, Lina Aris Ficayuma, Mochammad Fahlevi, Susila Sumartiningsih.

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🖀 Masruroh Masruroh, Soetrisno Soetrisno, Mahendra Wijaya, Sapja Anantanyu.

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#### Bioactivity of Amomum Compactum Soland Ex Maton (Java Cardamom) as a Natural Antibacterial

上 Tyagita Hartady, Roostita Lobo Balia, Mas Rizky Anggun Adipurna Syamsunarno, Sabri Jasni, Bambang Pontjo Priosoeryanto.

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Improving White Box Testing Using Bi ? Directional Symbolic Analysis and Test Case Slicing

🖀 P. Velmurugan, S. Ganesh Kumar

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Effect of Protecting Proteins from Degradation in the Rumen on Single Volatile Fatty Acid of Al Awassi Lambs

Br. Ibrahim S. Jasim.

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🖀 M.M. Elsahookie, Saddam H. Cheyed A.A. Dawood.

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🖀 Irfan Dammar, Acing Habibie Mude, Muhammad Ikbal, Yusalvi Rivai

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ANALYTIC STUDY OF ENDODONTIC WORKING LENGTH VARIATION OF MAXILLARY CANINE IN BASRAH GOVERNORATE

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nCD64, mHLA-DR: Sensitive Diagnostic Markers of Infection in Term Infants **Receiving Antibiotic Treatment** 

👗 Nguyen Thi Ngoc Tu, Le Thanh Hai, Truong Thi Mai Hong, Pham Thu Hien, Le Thi Ha, Doan Thi Mai Thanh.

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Develop Model of Transactional, Transformational, Democratic and Authocratic Leadership Style for Indonesian School Performance in Education 4.0 Era

💄 Irjus Indrawan, Evanirosa, Ramsah Ali, Indra, Ramadan, Muh. Hanif, Ihsan Harun, Lathifah Hanum, Agus Purwanto, Abdul Mufid, Siti Nurkayati, Mochammad Fahlevi, Susila Sumartiningsih.

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The Validity of CXR in the Screening & Detection of Endobronchial Lung Cancer in Iraqi Patients

🖀 Ameer Kadhim Al-Humairi, Safaa jawad Kadhem, Ahmed Hussein jasim, Shahad hamid mekki, Zainab Alaa abd-alhussein, Ali Baay.

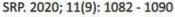
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Clinical study of Oral Lichen Planus for a selective sample in Basrah City south of Iraq between 2017-2019

💄 Ghaydaa Hashim Al Qudsi, Hussein Sh. Al-Essa and Sundus Abdul Wadood Aljazaeri.



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🖀 Hamid J. Mohammad, Israa I. Salih, Rabeah T. Mahmood.

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Effect of Stick Sweet Cherry (Prunus aviam) on the Reproductive System of Male
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Wasnaa H. Mohammed, Hamssa E. Abdul-Wahed, Zahraa A. Sharba.

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Relative Indicators and Predicative Ability of Some Biological Variables on Cardiac Neural Activity for Volleyball Players *Mohammed Nader Shalaby, Marwa Ahmed Fadl.* SRP. 2020; 11(9): 834 - 840

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Investigate the Strategy of Using Pharmacogenetics and Pharmacometabonomics to the Personalization of Ticagrelor Antiplatelet Therapy

Li Ng, Baharudin Ibrahim.

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Fronthea Swastawati, Putut Har Riyadi, Hersanti Sulistyaningrum, Sepsina Resky, Slamet Suharto.

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Defensive Effects of Breberine against Cypermethrin Induced Male Reproductive System Toxicity in Rabbits

Lawraa M. Murad, Shurooq Asaad Abdulameer, Dhuha Salman Asker Aljuboory, Dheyaa A. Neamah, Ali Hamza Maktouf.

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The Concept of Illness among Ethnic Groups in Indonesia: A Meta-Ethnographic Study

Agung Dwi Laksono, Ratna Dwi Wulandari, Zainul Khaqiqi Nantabah, Zulfa Auliyati Agustina, Ira Ummu Aimanah, Rukmini Rukmini, Yunita Fitrianti, Yurika Fauzia Wardhani, Diyan Effendi, Suharmiati Suharmiati, Lestari Handayani, Niniek Lely Pratiwi

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🚔 Oras Khalis yaseen, Mustafa Taha Mohammed.

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Vitamin D3 for Health and Muscle Functions of Athletes

🆀 Mohammed Nader Shalaby, Mona Mostafa Abdo Sakoury, Salman Mohammed Harthi, Faleh Mohammed Alshalawi, Marwa Mohammed Alhajji, Zahraa Hassan Alshaikh, Alhanouf Hassan Aljaber.

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🚔 Anwar A. Hussain, Khalid F. Al-Rawi, Aseel Khalid Hameed.

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🛔 Elly Usman, Ricvan Dana Nindrea.

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The Study of Genetic Variations of Human Testis-Expressed Protein 101(TEX 101) and Hormonal Levels of Fertile and Infertile (Oligospermia) Men

🖀 Baraa Ahmed Saeed, Rayah S. Baban, Usama Al-Nasiri. SRP. 2020; 11(9): 1108 - 1117

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The Relationship between Vitamin D Deficiency and Interleukins 8 and 10 in **Diabetes Mellitus** 🖀 Sura Mustafa Qasim, Alaa Zanzal Ra'ad Al-dorri, Mohanad Hasan Mahmood Al-Izzi. SRP. 2020; 11(9): 149 - 155

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🚔 Ali R Mulakhudair and Zahraa Reasan Kareem Shati.

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Do Servant Leadership Influence Market Performance? Evidence from Indonesian Pharmacy Industries

🍰 Yoyok Cahyono, M. Jihadi, Zainal Arifin, Wulan Purnamasari, Musnaini, Hadion Wijoyo, Fitriaty, Riyan Sisiawan Putra, Rizki Amalia Putri, Dadah Muliansyah, Popong Suryani, Agus Purwanto.

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Effect of Xanthium Strumarium Extract on Some Virulence Factor of Proteus Mirabilis Isolated from Patients in Ramadi Hospital 🖀 Ali Abd Sharad, Omar Almuharib, Najeeb Mohammed Hussein. SRP. 2020; 11(9): 1122 - 1124

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Assessment of Some Biomarkers Related with Recurrent Miscarriages in Iraq

🖀 Yahaya M. Jabber, Alaa Jawad Hassan, Hussein N. Abdullah.

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Penicillin for Secondary Prevention of Acute Rheumatic Fever and Rheumatic Heart Disease in Acehnese Children 🚔 HERLINA DIMIATI, SOFIA SOFIA, BASRI A. GANI. SRP. 2020; 11(9): 452 - 457

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The Effect of Microbiology Fertilization on the Nitrogen Fixation of Wheat Plant 🚔 Fawz A. Al.Saffar, Alaa Hussein Ali Al\_Shalal

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Distance Education as an Alternative Form of Learning During a Pandemic

🖀 Nataliia Kaliuzhka, Nelia Samoilenko, Larysa Zdanevych, Olesia Kyselova, Nataliia Terentieva, Diana Koval.

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Correlation between P53 and KI67 with Aggressiveness Factor in Recurrent **Respiratory Papillomatosis** 

💄 Rizka Fathoni Perdana, Sri Herawati, Muhtarum Yusuf, Irwan Kristyono, Puguh Setya Nugroho. SRP. 2020; 11(9): 163 - 168

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Assessment the Correlation of D-dimer and Ferritin Level in Patients Infected with Covid-19 in Anbar Governorate of Iraq

Safaa A.L. Al Meani, Ali H. Abdulkareem, Mohammed O. Ibrahim, Mohammed M. Ahmed, Mahmood Yassin Mukhlif.

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Intervention Model for Barotrauma Diseases to Improve Health and Safety Diving Behaviors in Traditional Fishermen in Small Islands in Makassar, Indonesia

Syamsiar S. Russeng, Lalu Muhammad Saleh, Awaluddin, M. Rum Rahim, Anwar Mallongi.
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Information and Innovative Technologies in Distance Learning in Higher Education Institutions of Ukraine

Inna Ivzhenko, Iryna Sokol, Valentyna Kochyna, Margaryta Noskova, Liliia Yeromina, Valentyna Blokhina.

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>>> Abstract >>> PDF DOI: 10.31838/srp.2020.9.65

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Effect of COVID-19 Virus on Biomass Index of Infected Patients

Safaa A.L. Al Meani, Mohammed M. Ahmed, Ali H. Abdulkareem, Nihad M. Hamid, Mohammed O. Ibrahim.

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» Abstract » PDF DOI: 10.31838/srp.2020.9.163

Effect of Adsorbent Composition Variation Quartz Sand/Andisol Soil/Zeolite/Activated Carbon Toward Cu, Pb, Coliform Total and E. coli Treatments on the Citarum River *Muhammad Sholeh, Pranoto, Sri Budiastuti, Sutarno.* 

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Pre-Exposure Prophylaxis for COVID-19 Infection: Current Concepts and Strategies Asmaa T Uthman, Noor N Al-Rawi, Natheer Al-Rawi. SRP. 2020; 11(9): 860 - 865

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The Effect of Treating Barley Straw with Fungus (Trichoderma Harzianum) (1): on Growth and Some Carcasses Characteristics of Awassi Lambs *S.N. Alwaeli, W.H. Al-Samaraee, M.J.H. Al-Tamemmy and Y.M. Al-Saadi.* SRP. 2020; 11(9): 601 - 605

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Investigation of the Trichomonas Hominis and Some other Parasites in Cases of Diarrhea Accompanying Children Arriving to the Obstetrics and Gynecology Hospital in Ramadi / Iraq

Abdulkhalik Alwan Mohemeed, Thaer Abdulqader salih, Qutaiba Ali Saleh Khalaf AL- juboori. SRP. 2020; 11(9): 1137 - 1142

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Six Sigma Benefit for Indonesian Pharmaceutical Industries Performance: A Quantitative Methods Approach

Layu Kartika, Defi Norita, Novera Elisa Triana, Iwan Roswandi, Abdul Rahim, Aulia Naro, Titia Izzati, Andary Asvaroza Munita, Didi Junaedi, Wiwit Suprihatiningsih, Agus Purwanto, Candra Setia Bakti.

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#### A Novel Pleiotropic Effect of Beta-Blockers: Useful or Not?

🚔 Tara Mandiricha, Maftuchah Rochmanti.

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Beta-Oxybutyrates: Biological and Pharmacological Effects

Bokov D.O., Morozova M.A., Beniashvili A.G., Bessonov V.V..

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Behavior of Growth and Yield Bread Wheat by the Influence of Fulvic Acid and Seeing Rate

💄 Hanaa Khudhaier Mohammed Ali Al-Haidary and Safaa A. Al-Zubaidy.

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Studies on microRNA in Pediatric Tuberculosis

Ayling Sanjaya, Dwi Yuni Nur Hidayati, Susanthy Djajalaksana, HMS Chandra Kusuma, Sumarno.

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» Abstract » PDF DOI: 10.31838/srp.2020.9.165

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PSMA-Specific Peptide with Inhibitor Cystine Knot for Prostate Cancer Treatment *Elena Iurova, Ivan Beloblov, Evgenii Beloborodov, Eugenia Rastorgueva, Evgenia Pogodina, Elizaveta Tazintseva, Aleksandr Fomin.* SRP. 2020; 11(9): 187 - 194

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Research Activity as a Technology of Activation of Cognitive Activity of Students of Higher Education Institutions

Tetiana Alieksieienko, Yuliia Pivnenko, Hanna Apalat, Lesia Vysochan, Viktoriia Mohilevska, Iryna Androshchuk.

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Study the Impact of Some Factors Associated with Hookah Smoking on Blood Standards *Amjad Adham Ahmed, Atheer Shehab Ahmed and Sara Fawzi Sahm.* SRP. 2020; 11(9): 613 - 616

>>> Abstract >>> PDF DOI: 10.31838/srp.2020.9.90

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Molecular analysis of virulence genes of UTI causing bacteria among pregnant women in Baghdad city, Iraq

🛔 Elaf Sameer and Rawa Abdul Redha Aziz.

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Does the Place of Residence Affect the Achievement of Exclusive Breastfeeding? A Study in Eastern Indonesia

🚔 Ratna Dwi Wulandari, Agung Dwi Laksono.

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Effect of Pedagogic, Professional Competency, and Work Motivation Toward Indonesian Primary School Teachers Performance

Lihaduddin, Nenden Suciyati Sartika, Desty Endrawati Subroto, Ratu Mauladaniyati, Eka Rosdianwinata, Rusdian Rifa'i, Asep Sujana, Zaenal Abidin, Muhamad Dadi Priadi, Eka Setiawati, Desri Yanti, Agus Purwanto.

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Factors Related to the Choice of Contraceptive Methods among the Poor in Indonesia

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Interactive Training Tools in the Modern Educational Process

La Nataliia Malinovska, Valentyna Borova, Valentuna Benera, Vadym Shemchuk, Iryna Gogol, Ihor Androshchuk.

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The Role Of Women In Maintaining The Environment Through Vegetable Development In Rural Agriculture Systems

🆀 Evi Feronika Elbaar, Beatrixia Barbara, M. Arief Fathuddien Hamdie, Yayuk Puji Lestari.

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» Abstract » PDF DOI: 10.31838/srp.2020.9.167

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Genotype of Potassium Inwardly Rectifying Channel, Subfamily J, Member 11 (KCNJ

11) Gene and Glycaemia Control in Diabetic Patients: A Narrative Review

Logah Aryani Perwitasari, Imaniar Noor Faridah, Haafizah Dania, Lalu Muhammad Irham, Fathia Vikri Salsabila, Rita Maliza.

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>>> Abstract >>> PDF DOI: 10.31838/srp.2020.9.92

#### **Research** Article

The Impact of Diabetes Mellitus on the Association of Endothelial Nitric Oxide Synthase Gene Polymorphisms (4a/4b, G894T, and T786C) with Clopidogrel Resistance in Coronary Artery Disease Patients Undergoing Percutaneous Coronary Interventions

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#### **Research Article**

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🖀 Dr. Ardianik, M.Kes., M.Pd, Dr. Edy Widayat, Drs., M.Si, Nailul Izzah, S.Pd., M. Kes, Dr. Kusmiyati, Dra., M. Pd.

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» Abstract » PDF DOI: 10.31838/srp.2020.9.34

#### **Research Article**

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🖀 Warqa a Muhammed Shariff Al-Sheikh.

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#### **Research Article**

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🛔 Saikhu Akhmad Husen, Muhammad Farraz Syadzha, Muhamad Frendy Setyawan, Pratiwi Pudjiastuti, Arif Nur Muhammad Ansori, Raden Joko Kuncoroningrat Susilo, Suhailah Hayaza, Dwi Winarni, Win Darmanto.

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& Wedad Salih Dawood.

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» Abstract >> PDF DOI: 10.31838/srp.2020.9.35

#### **Research Article**

Performance Achievement of Nutritional Programs in Mulyorejo Public Health Center, Surabaya, Indonesia in 2018

🛔 Shifa Fauziyah, Zukhaila Salma, Serius Miliyani Dwi Putri, Faradila Khoirun Nisa 🛛 Hakim, Hamidah Retno Wardani, Budi Utomo, Adi Pranoto, Pradika Gita Baskara, Teguh Hari Sucipto. SRP. 2020; 11(9): 893 - 898

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#### **Research Article**

Use of Natural Peptides with a Cysteine Knot of Arthropods as a Carrier of a Peptide Tropic to Glutamate Carboxypeptidase II

🛔 Elena Iurova, Ivan Beloblov, Evgenii Beloborodov, Eugenia Rastorgueva, Evgenia Pogodina, Elizaveta Tazintseva, Yuri Saenko, Aleksandr Fomin.

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#### **Research Article**

Scoring System in Prediction of Stunting Risk Among Children in West Sumatera Province, Indonesia 🖀 Masrul, Elly Usman, Amel Yanis, Ricvan Dana Nindrea. SRP. 2020; 11(9): 636 - 641

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#### **Research Article**

Transvaginal Ultrasound versus Saline Infusion Ultrasound for the Characterization of Intrauterine Lesions in Premenopausal Women with Abnormal Uterine Bleeding 🖀 Rana Hatem Matrood Alkhazraji, Mohammed Habeeb Hachim and Alaq Saeed Abdulhussain.

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» Abstract » PDF DOI: 10.31838/srp.2020.9.36

#### **Research Article**

Importance and Benefit of Application of Governance Risk and Compliance Principle

🖀 Bambang Leo Handoko, Ignatius Edward Riantono, Engelwati Gani.

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DOI: 10.31838/srp.2020.9.74 >> Abstract >> PDF

# Evaluation of the Effect of Massage by the Mother on the Pain of Term Infants after Care Measures

Lamidreza Khoshnezhad Ebrahimi, Soroor Sohrabi, Shabahang Jafarnejad, Saeideh Iranmanesh, Somayeh Esmaeilian.

SRP. 2020; 11(9): 899 - 904

>>> Abstract >>> PDF DOI: 10.31838/srp.2020.9.131

#### Research Article

Hepatoprotective Activity of Ethanolic Extract of Fresh and Fermented Clam Meretrix meretrix from Kalimantan, Indonesia

Logar Carlon Standi Bairil Alimuddin, Rukman Abdullah, Lili Amaliah, Rafdinal, Shifa Helena, Syarif Irwan Nurdiansyah, Warsidah.

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SRP. 2020; 11(9): 514 - 517
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## A Review of Enterotoxigenic *Escherichia coli* Infection in Piglets: Public Health Importance

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#### ABSTRACT

Diarrhea in piglets can cause health problems and even death. The cause is often infection by enterotoxigenic Escherichia coli (ETEC). This condition can have an impact on the growth of pigs and the economy of farmers, the cause can also be transmitted to humans which has an impact on public health. Diarrhea is one of the main health problems of piglets, because it attacks the digestive tract, especially the intestines. The main virulence factors are adhesin (fimbriae) and enterotoxins, with the most frequently found being ETEC F4 (K88) and F18. Fimbriae F4 (K88) ETEC causes diarrhea in neonatal pigs, while fimbriae F18 causes diarrhea in post-weaning pigs (PWD). Meanwhile, enterotoxin is divided into two types, namely heat labile enterotoxin (LT) and heat resistant enterotoxin (ST). After attaching it to the intestinal mucosa, E. coli will colonize and produce enterotoxins. Neonatal diarrhea is usually observed in piglets 1-4 days of age, while post-weaning diarrhea occurs in piglets 2-3 weeks after weaning with a peak diarrhea occurring 6-8 weeks post weaning, and even at 12 weeks. The large amount of water and electrolyte secretions causes dehydration, metabolic acidosis, osmotic diarrhea and a high probability of death before 2 weeks. Currently, there are many incidents of antibiotic resistance, so an alternative use of antibiotics is needed in pig farms to prevent ETEC infection. Alternative antibiotics that can be used to prevent infection with ETEC infection in piglets are immunoprophylaxis, antimicrobial minerals (such as zinci oxide and cupri sulfate), acidifiers, blood plasma, egg yolk antibodies, probiotics, nucleotides, bacteriophages and so on. These kinds of alternatives and feed additives can improve intestinal health and prevent diarrhea in piglets. This review contains the latest research from various journals discussing how ETEC can infect piglets and the management against the disease.

#### **INTRODUCTION**

The digestive tract (GIT) is an important channel in the metabolism and defense system of pigs. One of the important parts of this channel is the intestine. The intestine is responsible for digesting food, absorption of nutrients, and for protecting the body from toxins or pathogens. So that knowledge is needed in maintaining the health of piglets. The most common cases of piglets are neonatal diarrhea, post-weaning diarrhea (PWD) and edema. This is caused by enterotoxigenic Escherichia coli (ETEC) infection. ETEC can cause health problems and even death in piglets around the world (1,2). So that the pathogenesis of this infectious agent is important to be discussed in this review. ETEC attaches to the epithelium of the small intestine of pigs, then there is an increase in the secretion of water and electrolytes in the intestinal lumen. This is due to the production of enterotoxins and subsequent changes in enterocyte function. The large amount of water and electrolyte secretions causes dehydration, metabolic acidosis, osmotic diarrhea and a high probability of death before 2 weeks (3).

Diarrhea in pigs caused by E. coli is classified into six pathogenic strains based on virulence factors and pathogenic characteristics. Namely enterotoxigenic E. coli (ETEC), enterohemoragic E. coli (EHEC) or shigatoxicigenic E. coli (STEC), enteroagregative E. coli (EAEC), enteropathogenic E. coli (EPEC), enteroinvasive E. coli **Keywords:** enterotoxigenic Escherichia coli (ETEC), diarrhea, piglets, public health

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(EIEC), and diffusely attached E. coli. The most common and pathogenic strain in piglets is the ETEC strain (4,5).

The incidence of diarrhea in piglets is usually associated with the virulence factors of ETEC. Another very influential factor besides enterotoxin is fimbriae. The main fimbriae in pigs are F18 fimbrae in post-weaning piglets and F4 (K88) fimbrae in newborn pigs (neonates) (6-8). The large number of E. coli bacteria that are resistant to certain antibiotics has prompted research on preventive and control measures, one of which is finding a substitute for antibiotics. Abraham et al. (2014) stated that in their research, E. coli in pigs in Australia was resistant to several antibiotics including third generation cephalosporins and fluroquinolones (9). Another Australian study found E. coli resistance to colistin antibiotics, streptomycin spectinomycin, ampicillin and trimethoprimsulfamethoxazole (10). Another study, ETEC infection in swine in Switzerland, occurred resistance to antibiotics ampicillin, gentamicin, kanamycin, sulfonamide, streptomycin, tetracycline, and trimethoprim (11). In Kupang, Indonesia, the dominant resistance of E. coli isolates from pigs to erythromycin and cephalotin antibiotics (12). Even the research of Rosager et al. (2017) suggested that resistance was greater in E. coli ETEC strains than in non-ETEC (13). This indicates that it is difficult to control E. coli in piglets which causes diarrhea. With the incidence of diarrhea in piglets caused by ETEC,

knowledge of preventive and control measures against this problem is required. Furthermore, this review focuses on alternative strategies for preventing ETEC infection in piglets.

## Description of E. coli causing colisepticemia and pathogenesis

Enterotoxigenic E. coli disease (ETEC) in piglets causes huge economic losses with high morbidity, high mortality, growth retardation and high medical costs (13). Neonatal diarrhea is usually observed in piglets ages 1-4, while post-weaning diarrhea occurs in piglets 2-3 weeks after weaning with a peak diarrhea occurring 6–8 weeks post weaning, and even at 12 weeks. The period of ETEC infection to cause diarrhea is around 1 to 5 days depending on many factors, especially the success of bacterial colonization of the small intestinal mucosa (14).

Diseases caused by E. coli can cause diarrhea and septicemia in piglets. In addition, it can also cause diarrhea, edema during weaning, mastitis and cystitis in broodstock (15). Diarrhea in piglets often occurs as a result of a single infection or various types of E. coli, including ETEC, toxin-producing E. coli vero or shiga, necrotoxigenic E. coli, enteropathogenic E. coli, enterohemorrhagic E. coli, enteroaggregative E. coli, and enteroinvasive E. coli. Among these E. coli strains, ETEC is a common cause of severe and watery diarrhea in piglets (16). There are two important parts of ETEC infection in causing diarrhea, namely intestinal epithelial cells and the production of toxins from bacteria. The most well-known enterotoxin genes are the heat-labile enterotoxin LT and the heat-stable enterotoxins STa, STb. These toxins have the ability to cause diarrhea due to various changes in electrolyte balance (2,17).

#### Virulence Factors in Escherichia coli

The main pathotype of E. coli causing diarrhea in piglets is ETEC. These bacteria live and multiply in the intestinal epithelium. Diarrhea can cause health problems, death and economic decline for pig farmers. Enterotoxins produced by bacteria can also cause damage to enterocyte cell function so that they can interfere with fluid homeostasis (increasing fluidity and reducing water absorption) in the intestine (6,7). Apart from predisposing small environmental conditions and host factors, as well as high bacterial proliferation in the gut, virulence factors are very important in playing a role in the process of diarrhea. Virulence factor refers to the molecules produced by bacteria when interacting with the host (18). The main virulence factors of ETEC are adhesives with attachments such as fimbriae and enterotoxins. These fimbriae will help the bacteria attach to specific receptors. It is important for the pathoogenesis process are adhesins and enterotoxins. These specific receptors make the ETEC strain host specific (10).

The first step in the pathogenic process is an interaction between adhesins and ligands on the microvilli of the small intestine, this allows bacteria to attach to the microvilli (19). The relationship between ETEC and intestinal epithelium is caused by adhesive fimbriae such as F4 (faeG) and F18 (fedA), as well as F5 (fanC), F6 (fasA), and F41 (fim41A). ETEC classification in pigs at least in E. coli isolates found one enterotoxin gene (elt, sta, stb), along with one gene encoding fimbriae, including F4, F5, F6, F18, and F41 (2). The main fimbrae in pigs are F18 fimbrae in post-weaning pigs and F4 (K88) fimbrae in newborn pigs (7).

Morphologically, fimbriae can be classified into 2 categories, namely pili and fibrillae (20). Fimbriae are extracellular appendages  $0.5-10 \mu m \log 2-8 nm$ 

wide. Fimbriae are involved in adhesion and many other functions, including interactions with macrophages, biofilm formation, gut persistence, and bacterial aggregation (21). There are two antigenic variants that have been identified, namely F18ab (previously known as F107) and F18ac (previously known as 2134P and 8813), the word a means an antigen factor and the word b, c is a specific factor (22, 23). The majority of the ETEC F18 strains were capable of producing heat-resistant enterotoxins including STa and STb, whereas the ability to produce Shigatoxin was more related to F18ab (23). F18 is coded by the fed gene of five units, namely, fed A (major subunit), fed B (usher), fed C (chaperone), fed E (minor protein) and fed F (adhesin) (24).

Fimbriae F18 are filaments 1 to 2 mm long based on the main structural protein, called fed A (15.1 kDa) (16). The main structural subunit of F18 fimbriae is fed A, but the small adhesive fed F subunit also plays a central role in binding to the host receptor and is highly conserved among the F18 strains (25,26). F18ab is usually associated with strains that produce Stx2e (STEC) or shigatoxin E. coli, and F18ac is associated with ETEC causing diarrhea in post-weaning piglets (PWD) (27). The ETEC F18 + strain frequently produces heat-resistant enterotoxins including STa and STb, whereas heat labile (LT) enterotoxins are rarely produced in these strains (28, 29). ETEC colonization in the small intestine is initiated by the interaction of the fimbriae receptor, namely F18 fimbriae which binds to glycoproteins on the microvilli or brush border of the small intestine (24, 30). Genetically, some piglets do not have the F18 fimbriae receptor and thus these pigs may be resistant to F18 + ETEC colonization (31, 32).

Enterotoxigenic E. coli (ETEC) K88 expresses F4 fimbriae, which are proteinaceous filamentous adhesins consisting of repeated copies of the major fimbrial subunit fae G and several additional minor subunits (33). The ETEC strain expressing F4 fimbriae is associated with neonatal diarrhea and post-weaning diarrhea in piglets. Three variations of the F4 fimbriae antigen are F4ab, F4ac, and F4ad, with the most popular being F4ac. These antigen variants differ in amino acid composition from the main subunit, fae G, and each has a related but different receptor binding profile (34, 35).

Amino acids along the 125 - 163 subunits of FaeG are effectively essential to the binding of fimbrial F4. Amino acid residues 140-145 and 151-156 were identified as functional sites for F4ab fimbriae. Meanwhile, other amino acids, namely 148–150 and 156–158, were reported to inhibit the attachment of F4ab to the host cell. F4ac has an amino acid length of 147 to 160, this being the defining epitope that controls the fimbrial binding capacity (36). In contrast to the ab and ac variants, the F4ad FaeG subunit interacts with the minimal galactose-binding epitope via the D'-D"- $\alpha$ 1- $\alpha$ 2 binding domain, resulting in different structural and attachment properties (34). Recent studies have shown that oral inoculation of ETEC / VTEC / EPEC F4 ab or ac in freshly weaned piglets causes enteritis and a severe systemic inflammatory response (37). In another study, in vitro enterotoxigenic binding of F4 + E. coli (ETEC) to piglet enterocytes was partially blocked by dose-specific neoglycans (38). FaeG is the main fimbriae subunit and adhesion for F4 fimbriae compared to F18 fimbriae. All adhesins F4 bind to carbohydrate glycoproteins in intestinal epithelial cells and intestinal mucus. F4ad adheres more to glycolipids, whereas adhesins F4ab and F4ac tend to bind glycoproteins more (36)

Other associated fimbriae that have a lower prevalence are F5 (K99), F6 (987P), F17 (Fy / Att25) and F41, with the number of active receptors in intestinal epithelial cells decreasing as the pigs and cows age. This fimbrae is usually found in post weaning piglet diarrhea (PWD) together with F18 and / or F4, or individually (6). The results of the most recent study regarding colonization factors identified among the ETECs isolated from swine neonatal diarrhea were F4, F5 + F41, and F6 (40.5, 16.7, and 11.9%, respectively), whereas in post-piglet diarrhea, weaning (PWD) there were no positive isolates for F5, F6, and F41 (8).

#### Enterotoxin Characteristics

Enterotoxins are extracellular proteins or peptides secreted by bacteria, one of which is ETEC. ETEC can cause disease by colonizing the small intestine or colonization factors (CFs), the production of heat-resistant or labile toxin (LT) and / or heat-resistant or stable toxin (ST) toxins. The proportion of ETEC strains producing single LT, single ST, or both toxins (LT + ST) varies depending on geographic location and seasonality. However, overall, the majority of ETEC produced ST and LT (17,39).

LT is an 84-kDa polymer protein consisting of enzymatically active A subunits (28 kDa) which are noncovalently linked to pentameric B subunits (11.5 kDa each). Subunit A consists of two components, A1 and A2. The A1 subunit (21 kDa), the enzymatically active portion of the toxin, is noncovalently linked to pentamer B via peptide A2 (7 kDa) (40,41). STp or stabile toxin produced by pigs is a short peptide, consisting of 18 or 19 amino acids, originally produced as 72-structure amino acids by bacteria (17). The STa gene encodes 72 precursors of prepro-peptide amino acids. Just like STa, STb is synthesized as 71 amino acid prepeptides, consisting of a signal peptide and an adult STb enterotoxin namely 48 amino acids (5.2 kDa) (42).

Labile enterotoxin (LT) is a member of the AB5 toxin family, which is similar to the cholera toxin secreted by Vibrio cholerae. These toxins have structural similarities and mechanisms of action. The LT structure consists of one catalytic subunit A and a pentameric ring of subunit B as a receptor binding. The subunit is encoded by genes from plasmids eltA and eltB, and then transcribed as operons (41,42,43). Subunit A contains 240 amino acids, while subunit B contains 103 amino acids (16).

Subunit A is enzymatically active, divided into A1 and A2. Domain A1 is enzymatically active, domain A2 is shorter active and five B subunits mediate binding of glycolipid and glycoprotein receptors to host cells. Pentamer GM1binding B subunit (LTB) (11.5 kDa) interacts with A subunit (28 kDa) via noncovalent binding of the A2 domain to form the holotoxin AB5 structure. The B subunit binds primarily to the monocialotetrahexosylganglioside (GM1) receptor on the cell surface. Domain A1 is responsible for ADP-ribosylating stimulation of G protein. A1 will translocate to the endoplasmic reticulum and activate the cyclic adenylate system to increase cellular cyclic adenosine monophosphate then the intracellular cAMP concentration is uncontrolled. As a result, the ions open, then the chloride anion and then the water molecules are released. This is a characteristic feature of diarrhea caused by ETEC infection, namely increased secretion of fluids and electrolytes followed by decreased water absorption (44,45). In addition to its enterotoxicity function, LT also acts as an adhesin, which binds bacteria to GM1 in the plasma membrane of small intestinal epithelial cells. Elimination of the LT gene can reduce the

severity of diarrhea and ETEC colonization in the small intestine of pigs (46,47).

Heat resistant enterotoxin (ST) produced by ETEC is a peptide which is divided into two types, namely STa and STb. STb is more deadly in animals, especially in postweaning piglets (PWD). Then the STa enterotoxin is more relevant for diarrhea in humans, newborn piglets and calves. These peptides are encoded by two genes, estA (STI) and estB (STII), which are located in plasmids, and can be differentiated from one another by their solubility in methanol and their protease sensitivity (42).

STa has poor resistance due to its small size (19 amino acids with 3 disulfide bonds), but STa is a very strong enterotoxin (48). Enterotoxin STa is soluble in methanol and resistant to proteolytic enzymes. According to the host species, STa is further classified into two subtypes, known as STp and STh, which were initially isolated from the ETEC strains of pigs and humans. While STb is a peptide consisting of 48 amino acids with 4 cysteine residues included in 2 disulfide bonds (42).

Serogroups and serotypes in diarrhea caused by ETEC ETEC has many variations of the toxin coding genes, so that scientists classify them based on specific serogroups and specific serotypes. ETEC specific serogroups, namely O and H serogroups, were determined based on lipopolysaccharide and flagella. The O antigen consists of repeating subunits that extend over the surface of the bacteria. Research in China, the most O antigen found in pigs is 08, 064, 0141 and 0149 (49-51). This is in line with research in Vietnam, where the O8 antigen found the most (52). Other serogroups that cause diarrhea are 02, 06, 09, 0, 11, 020, 026, 040, 045, 048, 054, 086, 087, 0115, 0101, 0138, 0139, 0147, 0152, 0157 and 0161. Meanwhile, serogroup O causes edema, namely 0138, 0139 and 0141 (49,51). Specific serogroup H are determined by the flagella antigen, which also serves as an antigenic marker. This antigenic will be useful as a component of the ETEC vaccine. When compared with serogroup O, serogroup H has less association, namely 0141: H4, O2: HNM, O139: H1, O26: H11 and O2: H40 antigens (8). In addition, fimbrial adhesins which also play an important role in diarrhea caused by ETEC in pigs are F4 (K88), F5, F6, F18 and F41 (53).

#### Pathogenesis of Enterotoxigenic E. coli (ETEC).

Adhesins and enterotoxins in the pathogenesis of ETEC play an important role as virulence factors. Adhesin in ETEC is useful for facilitating binding to specific receptors of small intestinal epithelial cells. Adhesin also plays an important role in the colonization, proliferation and development of ETEC infection. Enterotoxins are also considered to be direct virulence factors that cause disease and may also play a role in the colonization process. (54).

There are four main fimbriae in ETEC as fimbrial adhesins, namely F4 (K88), F5 (K99), F6 (987P), and F41. One particular ETEC strain usually only expresses one fimbrial type, so that each strain has a different fimbrial type. ETEC possessing fimbrial adhesins F4 which release enterotoxins is a characteristic pathogen causing diarrhea in piglets (55). The ETEC strain expresses two main types of enterotoxins as previously described, namely heatlabile (LT) enterotoxins and heat-stable (ST) enterotoxins. Enterotoxin ST is subdivided into STa and STb according to differences in protein structure and pathogenesis. Since each section targets a specific site, it is necessary to develop vaccinations against ETEC targeting fimbriae and enterotoxins. How much bacteria colonize can determine the severity of the disease. Fimbriae attach to specific receptors for small intestinal epithelial cell membranes and non-specific on the epithelial mucous membrane of the small intestine, in this case the jejunum (56). The molecular epidemiology of diarrhea in pigs showed that the ETEC F4 receptor was expressed in the small intestine of newborn to adult pigs, whereas the ETEC F18 receptor was expressed increased in 3 weeks old pigs (57). Therefore, the F18 receptor does not cause diarrhea in newborn pigs.

Immunoglobulin G (IgG) antibodies or immunoglobulin A (IgA) piglets were obtained from the colostrum of sows that developed E. coli in their intestines. However, this only applies to weaning (54,58). As previously explained, piglets with ETEC usually show watery diarrhea in the first week after infection with ETEC. Some piglets died suddenly without symptoms of diarrhea, when necropsy was performed, intestinal edema occurred. The diarrhea causes significant dehydration due to impaired intestinal absorption. The pathogenetic mechanism of LT and ST enterotoxins, namely damaging the function of small intestinal epithelial cells which results in increased secretion of water and electrolytes (Na + and Cl-), decreased fluid absorption and dehydration, and even acidosis.

The mechanism of action of LT is divided into 2 subunits, namely, the A subunit is enzymatically active and five B subunits which mediate the binding of glycolipids and glycoprotein receptors to host cells. Pentamer GM1binding B subunit (LTB) interacts with the subunit via noncovalent binding of the A2 domain. The B subunit binds to the monocialotetrahexosylganglioside (GM1) receptor on the cell surface. Domain A1 is responsible for ADP-ribosylating stimulation of G protein. Then A1 will translocate to the endoplasmic reticulum and activate the cyclic adenylate system to increase cellular cyclic adenosine monophosphate then intracellular cAMP concentration is not controlled. Furthermore, protein kinase A is stimulated by cAMP which phosphorylates the cystic fibrosis transmembrane conductance regulator (CFTR). As a result, the ions open, then the chloride anion and then the water molecules are released. This is a characteristic feature of diarrhea caused by ETEC infection, namely increased secretion of fluids and electrolytes (Cl-) followed by decreased water absorption (44,45).

STa binds and activates guanylyl cyclase C (GC-C) in the brush border of the intestinal epithelium. It then induces intracellular cGMP accumulation and activates several interrelated signal transduction routes resulting in an uncontrolled osmotic flow of water to the intestinal lumen (Na + and Cl-) (4,59). The STb transduction pathway does not involve cyclic nucleotides as secondary messengers. Research shows that STb binds to the sulfatide receptor (3-O-sulfogalactosylceramide) and is internalized into small intestinal epithelial cells. Subsequently, the protein G cascade was activated, and the intracellular calcium concentration increased. This makes a number of enzymes active. The first phase is calmodulin dependent PKII, which opens a specific chloride pathway and activates PKC. The result is phosphorylation of CFTR and inhibits absorption of Na +. Next is the activation of phospholipase A2 and C enzymes. The function of this enzyme is to catalyze the release of arachidonic acid from the phospholipid membrane and the formation of prostaglandins E2 and serotonin, which are known as secretory agents from enterochromaffin cells (60).

#### Incidence of diarrhea caused by ETEC in piglets.

There were cases of antibiotic resistance to ETEC strains in Switzerland with certain characterizations (11). In Brazil, ETEC strains were also found with the types LT, STa and STB, with the most cases being the type STb (61). In addition, there were cases of diarrhea in neonatal pigs in Spain, one of which is due to ETEC infection. The ETEC patotypes that often occur are STa and STb, with fimbriae F4 (62). In Spain, out of 122 pigs to be studied for antibiotic resistance, 94 were stricken with ETEC diarrhea (63).

Furthermore, in South Africa, the dominant STb type ETEC case appeared with high frequency in newborn and postweaning piglets. A total of 74.4% of ETEC cases presented with diarrhea symptoms and 69.2% without diarrhea (14). A recent study in Korea from 2008 to 2016, found cases of diarrhea in piglets with a percentage of 61.3% ETEC, with various types of enterotoxins (27). Until now, there are still many cases that occur in piglets caused by ETEC. In addition, ETEC has a specific coding gene with a specific target which can be used as a reference for research related to vaccination of this disease. This encourages research to conduct research on how to prevent and control diseases caused by ETEC infection (11).

**Preventive measures against diarrhea caused by ETEC** The diagnosis of diarrhea in piglets must take into account clinical signs and lesions, as well as epidemiological patterns and detection of infectious agents (64). However, it would be difficult to diagnose diarrhea caused by ETEC on the basis of clinical signs and necropsy lesions alone, which are considered non-specific. Isolation and identification of E. coli still does not prove the relationship of disease, because E. coli is a normal bacterial flora in the intestines of animals. Thus, a phenotypic or genotypic description of the isolated strains is needed to recognize bacterial fimbriae. Furthermore, it can be carried out characterization of genes encoding fimbrial proteins and enterotoxins (65).

Virulence factors such as adhesins and enterotoxins can be detected by ELISA (Enzyme-linked Immunosorbent Assay) (66, 67). More recently, DNA-based molecular detection methods for determining serotypes, such as enterotoxins and fimbrial genes, can use PCR with samples from the faecal or internal organs of the intestine. Until recently detection using PCR was more effective and simplest for diagnosis in pigs (68, 69). Another study using PCR multiplex has proven useful for the rapid, sensitive and specific detection of enteric pig pathogens (70).

Neonatal pigs can form immune reactions such as tolerance or mucosal defense against certain antigens (71). Vaccination of weaned piglets can be used to control diarrhea due to ETEC infection. Continuous supply of SIgA to piglets via milk is required for passive immunity. Piglets must have active immunity to ETEC after weaning because passive immunity cannot continuously protect against ETEC infection (72). So that targeted vaccination is needed to protect the intestinal mucosa. The vaccine must activate the immune system in the intestinal mucosa as well as immunoglobulin specific to the antigen, namely IgA and IgM.

There are several methods of applying the ETEC vaccine to pigs. The first is via intramuscular injection. Economically, injection vaccines tend to be expensive. This vaccine stimulates a systemic immune response rather than the mucosal barrier needed to prevent ETEC infection in the small intestine (73). The injection site is usually done in the neck. After the first vaccine injection, a booster is carried out 2 weeks later (54).

Next is the oral vaccine with live attenuated vaccines. It is also possible with the live wild strain E. coli vaccine, which is non-enterotoxigenic, which carries the fimbrial adhesin. Attenuated live vaccines can protect pigs from the ETEC K88 + LT + STb + strains (74). Oral vaccination of piglets with recombinantly produced FaeG can induce specific mucosal and systemic immune responses (73). Several studies have shown that oral vaccination with purified F4 fimbriae is an antigen that can induce mucosal immunity in pigs (72). Oral vaccination of fimbriae F18 encapsulated into weaned pigs may not produce a significant serum antibody response, or in other words no decrease coli colonization. However, in Canada, the live vaccine F4 + ETEC has been commercialized, and has been shown to protect pigs from ETEC infection (58,73).

Other vaccines include the inactivated, multi-adhesins, intact cell ETEC bacterin mixture, or the purified ETEC fimbrial subunit vaccine (54). This purification of fimbriae F4ac is a vaccine that has strong immunogenicity (58). This purification involves many processes, one of which is chemical conjugation which is long and complicated, especially when the toxoid STa or STa is to be purified from wild strains. Basically, the latest research has been able to clone wild-strain STa, making the purification process easier (74, 75). The orally purified fimbriae are introduced into the small intestine in a pellet form with an enteric coating. Although the interaction of the purified fimbriae with the coating polymer reduces the biological activity of the purified fimbriae, this is not a problem. However, this requires further research to find an effective way for purified fimbriae to target the small intestine without losing its biological activity (76).

Recent studies suggest that the addition of zinc oxide (ZnO) at a level of 3100 mg / kg in feed resulted in a decrease in the number of ETEC isolated from pig faeces. This addition was associated with small intestinal morphology, increased the number of goblet cell villi and resulted in favorable changes in the ratio of lactic acid bacteria to coliforms (77,78). Another study, namely the addition of zinc oxide (ZnO) to post-weaning pig feed as much as 2,000 to 3,000 ppm can reduce diarrhea and growth increase intestinal morphological and performance (79). So that the presence of free zinc ions continuously in the luminal compartment is very important for intestinal protection, decreasing the inflammatory response and reducing the small intestinal morphological damage to ETEC K88 infection (80,81). Zinc (Zn) is a mineral that is important as a micronutrient for pigs. Zinc deficiency can lead to growth retardation and reduced overall enzyme activity in tissues (82).

Another mineral that has a pharmaceutical effect to inhibit bacterial development is cupric sulfate (CuSO4). Cupric sulfate is actually a mineral to stimulate growth, but also has antimicrobial properties. A concentration of 175 mg / kg in pig feed is required. It is also based on the Cu inclusion rates currently allowed in EU countries. This dose can also affect the level of bacterial development in the digestive tract, in this case the fecal coliform bacteria and E. coli (83,84). E. coli is damaged and even killed due to oxidation of the membrane, which causes loss of membrane integrity. This bactericidal effect occurs due to the fusion of cupri alloy with cupric sulfate (CuSO4) (85). Several feed additives that can function as antimicrobials, one of which is an acidifier. Acidifier-based feed when given to pigs with diarrhea, has a significant effect. In recent studies, the use of fatty acids (medium chain fatty

acids) in pigs induced enterotoxigenic  $\beta$ -hemolytic E. coli (ETEC), serotype 0149: K91: K88, has antibacterial effects (86). It has also been recognized in recent studies that volatile fatty acids (VFAs), such as acetic, propionic, butyric, valeric and lactic acids, have antibacterial activity. Propionic and butyric acid are very important metabolites because they have a specific inhibitory effect against enteric bacteria, such as E. coli in pigs (87). Hydrochloric acid secreted from the stomach can also act as an antibacterial. After weaning piglets, solid feed can increase the pH of the digestive tract. So that feeding with organic acid supplementation can be an effective way to control the pH of the gastrointestinal tract, in order to control the growth of bacteria in the stomach and intestines.

Diets containing blood plasma have been shown to inhibit the development of ETEC in pigs. Recent studies have shown that natural IgG purified directly from pig plasma and given in the form of a feed additive can be used to increase pig production. This is because IgG has a positive effect on reducing the colonization of ETEC bacteria and can be an alternative use of antibiotics (88). This product can be used given 5 days before weaning and 10 days after weaning.

chicken Recently. egg yolk antibody called immunoglobulin Y (IgY) from chickens that were immunized against a specific pathogen was effective in preventing and controlling disease. Specific IgY acts to effectively inhibit various intestinal pathogens including Salmonella, coronavirus, rotavirus, viral gastroenteritis and ETEC (89). Oral administration of specific IgY has great potential to control diarrheal diseases and increase pig growth. This can be an alternative to antibiotics (90,91). There is research that egg yolk antibodies may be ineffective in pigs 3 to 4 weeks of age. This is because gastric pH and digestive enzymes can break down the antibodies in GIT thereby reducing the amount of egg antibodies available to protect pigs from E. coli infection (92). Antibodies must also remain in the intestines continuously. A total of 1.5 g per day per piglet is sufficient to prevent diarrhea caused by infection with 1010 ETEC. The addition of 0.2% egg yolk antibody to feed can prevent diarrhea in commercial pig farms (91). However, research on how many doses are needed for the effectiveness of egg yolk antibodies is still being done to date.

Probiotics or Direct fed microbials (DFM) are live microorganisms which, when given in sufficient quantities, provide health benefits to the host. These microbes are categorized into 3 main groups, including lactic acid-producing bacteria, yeast, and Bacillus (93). Probiotics can work against various pathogenesis processes. The main thing is to inhibit the invasion of pathogens to target cells. Blockade of this process is important, because it is the first step in the pathogenesis process of ETEC. Furthermore, it prevents the colonization of bacteria in the intestinal mucosa. It has also been proven related to the inhibition of enterotoxin production from ETEC. Moreover, it reduces the inflammatory process in the intestine due to ETEC infection (94). However, these results can be effective at the end of the probiotic administration. This may be due to decreased appetite, dehydration and a lack of cytokine response in the pig's body (95).

A recent study, when pigs were induced by ETEC F18, then treated with DFM1, it seemed that no change had occurred. But with DFM2 therapy can provide effectiveness by decreasing colonization of ETEC in the intestine. In addition to colonization, ETEC induction also results in impaired intestinal barrier integrity, disruption of OCLN and ZO-1 junction proteins, decreased intestinal mucosal sIgA, and activation of the immune response, namely increased local and systemic IL-8 production. DFM1 contains 3 strains of Bacillus amyloliquefaciens, while DFM2 contains 2 strains of Bacillus amyloliquefaciens (96).

Other probiotics such as Lactobacillus also provide antimicrobial benefits. One of them is L. plantarum ZLP001. This probiotic can prevent the growth of ETEC by producing certain antimicrobial substances which are then combined to produce a relatively acidic environment. L. plantarum ZLP001 adheres to IPEC-J2 cells and inhibits ETEC adhesion primarily through exclusion and induces HDP expression and secretion in intestinal epithelial cells (97,98). The Bacillus subtilis DSM25841 strain also has an antimicrobial effect against ETEC F4ac infection in weaned pigs. B. subtilis can improve intestinal health of pigs by reducing the abundance of Enterobacteriaceae. It also increases the regulation of genes related to immunity, increases metabolism and utilization of amino acids (99). Overall, given the good potential in the use of probiotics to treat diarrheal disease in pigs, it can be said that probiotics are an alternative as a substitute for antibiotics and can avoid bacterial resistance to antibiotics.

Plant extracts, also known as phytobiotics, have been widely researched and have many benefits as a nutritional enhancer for animal feed, as an antimicrobial, antiinflammatory, antioxidant, and anti-parasitic. Some studies consider that plant extracts at minimum inhibitory concentrations (MICs) of 100 - 1000 µg / ml in in vitro bacterial susceptibility tests have antibacterial activity. Until now, there are several kinds of phytobiotics, such as phenolics / polyphenols, terpenoids / essential oils, alkaloids and lectins / polypeptides. There are many variations in the composition of phytobiotics based on several influencing factors, namely biological factors (type of plant, location of growth and harvest conditions), manufacturing (extraction, distillation and stabilization), and storage conditions (light, temperature, oxygen tension, and time) . These phytobiotics have different antimicrobial activities (100.101). Previous research. tannic acid can inhibit the growth of bacteria in the intestine, one of which is E. coli. Alkaloids can inhibit DNA synthesis by killing the topoisomerase enzyme. In addition, saponins can be antimicrobial by forming sterol complexes and damaging the bacterial membrane. Usually these phytobiotics become feed additives (102).

Phytobiotics have now become a trend as a substitute for the growth promoter antibiotic (AGP), whose use has been banned. Like the Labiatae family plants, namely thyme, oregano and sage can reduce the number of E. coli bacteria in the small intestine of animals (103). Macleaya cordata extract can increase pig palatability, body weight and amino acid concentration. In addition, it has the effect of increasing immunity by regulating phagocytes, haptoglobin and amyloid A. Another effect is that it is an important barrier to breast milk with the action of the ZO-1 and claudin-1 proteins (104). The effectiveness of phytobiotics and any plants that can be antimicrobial needs to be studied further, because until now there are so many plants that can be used as antimicrobials.

Nucleotide feed supplements have a role as bioactive molecules in the functions of metabolism and the immune system. Recent studies suggest that giving pig feed supplements containing nucleotides has shown positive effects. Namely the increase in growth, by increasing the effectiveness of intestinal absorption, controlling the concentration of bacteria in the intestine, reducing the severity of diarrhea, increasing the performance of enzymes in the ileum and immune stimulation (105,106). Feeding supplements to pigs containing 0.2 to 1 gram / kilogram of feed, can have a positive effect in pigs (107). There are still many studies related to how nucleotides can be used as feed additives for the prevention of diarrhea in piglets.

Bacteriophage is a kind of virus that has the effect of inhibiting growth and even killing bacteria. Virulent bacteriophages can be isolated from sources such as pig manure, wastewater and soil indicating that these phages are widely distributed in the environmental areas of pigs. Bacteriophage therapy has good potential for control of infections in pigs, such as diarrhea caused by ETEC (108). Pork feed containing bacteriophages can inhibit the development of ETEC F4 + infection. It is characterized by decreased bacterial adhesion in the ileum and cecum. It can also improve villi morphology (109). There is still much that needs to be deepened regarding how bacteriophages can become feed supplements and antimicrobial substitutes.

Preventive methods were used to avoid improper use of antibiotics. In the field of veterinary medicine, there have problems related with antimicrobial resistance such as in livestock (110-117), pets (118- 122), poultry (123-128) and in fisheries (129-132). The concept of antimicrobial replacement treatment is needed, not only to overcome the problem of diarrhea in piglets caused by ETEC, but also to prevent transmission to humans. So that public health is maintained properly.

#### CONCLUSION

The intestines are responsible for digestion, absorption of nutrients and protection of the body from toxins or pathogens. The incidence of diarrhea in piglets that has been rife recently has resulted in health problems and even death. The diarrhea is caused by E. coli enterotoxigenic infection (ETEC). An understanding of the disease features, virulence factors, ETEC characteristics and pathogenesis of the disease is required. Antibiotics are expected to be an effective way to prevent and manage infections. However, the more recent continuous use of antibiotics has resulted in E. coli resistance to some antibiotics. Preventive action and control strategies are needed against this disease, one of which is the use of alternative antibiotic substitutes. Alternative antibiotics that can be used to prevent infection with ETEC infection piglets in are immunoprophylaxis (vaccines). antimicrobial minerals (such as zinci oxide and cupri sulfate), acidifiers, blood plasma, egg volk antibodies, probiotics, nucleotides, bacteriophages and so on. These kinds of alternatives and feed additives can improve intestinal health and prevent diarrhea in piglets. This review contains the latest research from various journals discussing the pathogenesis of ETEC in infecting piglets and the management of disease, which also benefits to public health.

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