

- Home
- About
- Login
- Register
- Search
- Current
- Archives
- Announcements
- Ethical Publication

User

Username

Password

Remember me

Language

Select Language

English

- Notifications
- » View
 - » Subscribe

Journal Content

Search

Search Scope

All

- Browse
- » By Issue
 - » By Author
 - » By Title
 - » Other Journals

- Information
- » For Readers
 - » For Authors
 - » For Librarians

- Focus and Scope
- Editorial Board

Home / Archives / Vol 5, No 1 (2021)
 DOI: <http://dx.doi.org/10.30651/jqm.v5i1>

Table of Contents

Literature Review

The difference in severity and management between children and adult's cases of COVID-19	PDF 1-18
Mohammad Husin, Gina Noor Djalilah, R A Kaniraras, Afrita Amalia Laitupa	PDF
The role of gut microbiota in health and diseases	19-33
Deasy Fetarayani, Handoko Hariyono, Gatot Soegiarto	PDF
Roflumilast: A Review of Chronic Obstructive Pulmonary Disease (COPD) Treatment	PDF
Ita Octafia, Dwi Octamy Sari, Novi Wulandari, Sandra Annisa, Linda Wahyuni Wongkar, Ferdias Kurnia Bahari, Faiz	35-47
Farikhah, Moh Firmansah, Erfin Midhiawati, Fauna Herawati	PDF
Role of antioxidant to protect Leydig cells induced by reactive oxygen species: a literature review	49-60
Anak Agung Istri Dalem Cinthya Riris, Reny I'tishom, Siti Khaerunnisa	

Articles

Effects of acupressure therapy period towards blood sugar level in type 2 diabetes mellitus patients at Lumajang acupressure clinic	PDF 61-67
Anung Putri Illahika, Hean Safira	
Clinical and Functional Outcome of Cervical Degenerative Disc Disease after Operative Treatment at Dr. Soetomo General Hospital Surabaya In 2013-2018	PDF 69-75
Reyner Valiant Tumbelaka, Dwikora Novembri Utomo, I Ketut Martiana	
Association between gestational age and persistent pulmonary hypertension of the newborn (PPHN) severity in preterm babies at Sidoarjo Regional Hospital	PDF 77-85
Aisyah Faadhilah, M. Perdana Airlangga, Nurma Yuliyasari, Gina Noor Djalilah	
Solanum betaceum Extract as a Protective on Spermatozoa Morphology of Mice Exposed to Lead Acetate	PDF 87-94
Rima Wirenviona, Reny I'tishom, Siti Khaerunnisa, Anak Agung Istri Dalem Cinthya Riris, Nurul Fatimah Susanti, Nurul Jannatul Wahidah, Abadiyah Zakiah Kustantina	
Identification of Thalassemia Carrier in Anemic Pregnant Women at Puskesmas Kertapati Palembang:	PDF 95-101
Comparison of Five Erythrocyte Indices	
Mitayani Purwoko, Eriko Erenkwot	
Depression, anxiety, and stress levels in Denpasar community during the pandemic of Corona Virus Disease 2019 (COVID-19)	PDF 103-111
I Gusti Ngurah Bagus Rai Mulya Hartawan, I Gede Gita Sastrawan, Rovie Hikari Parastan, Luh Seri Ani	
The association between demographic and attitude factors with the practice of malaria prevention among the rural community in Purworejo district, Indonesia	PDF 113-124
Farindira Vesti Rahmasari, Winny Setyonugroho, I Ketut Swarjana, Desto Arisandi, Tri Wulandari	
Kesetyaningsih	
In vitro Alpha Lipoic Acid supplementation in freeze-dried human sperm: the impact on DNA fragmentation index	PDF 125-132
Rezia Octarina, M. P. B. Dyah Pramesti, Agustinus Agustinus	
The effectiveness of classic lecture and workshop as interventions to improve primary health care providers knowledge and skill on the management of pediatric emergencies: a case study	PDF 133-143
Ricky Indra Alfaray, Rahmat Sayyid Zharfan, Yudhistira Pradnyan Klopang, Yudith Annisa Ayu Rezkitha, Rafiqy Sa'adiy Faizun, Saruuljavkhan Batsaikhan, Ahmad Siddiq Muhajir, Bestya Presidiana, Umaimah Rosyidah, Khodijah Nidaul Chasanah, Delia Nur Aini, Naufal Fauzy, Kamal Musthofa, Nur Firdaos, Samsriyaningsih Handayani	

Case Report

Cardio-vocal Syndrome as a Complication Patient with Severe Mitral Regurgitation and Moderate Aortic Regurgitation with Pulmonary Hypertension

PDF
145-151

Adityo Basworo, Agus Subagjo

Characteristics of complaints and functional outcomes of conservatively treated clavicle fractures in Dr. Soetomo general hospital: A case series

PDF
153-161

Brilliant Citra Wirashada, Maghrizal Roychan, Teddy Heri Wardhana

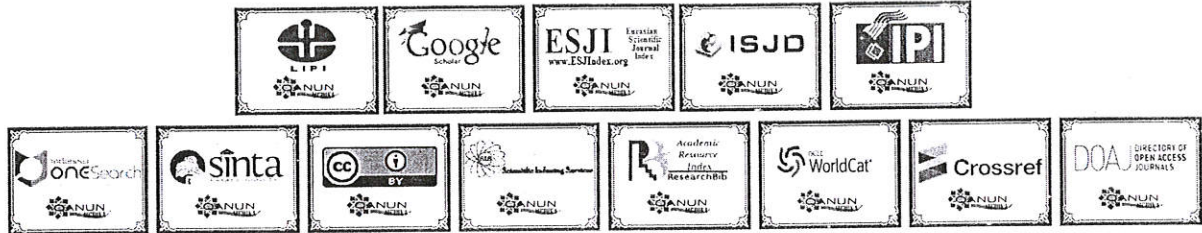
Index

Index and Acknowledgement
Yelvi Levani

PDF

0186992

View My Stat



Managed Hosting, Support, and OJS Responsive Theme by:
OpenJournalSystems.com



QANUN MEDIKA

Jurnal Kedokteran

Fakultas Kedokteran Universitas Muhammadiyah Surabaya

p-issn 254-2272 e-issn 2548-3526

website : <http://journal.um-surabaya.ac.id/index.php/qanunmedika>



- Home
- About
- Login
- Register
- Search
- Current
- Archives
- Announcements
- Ethical Publication
- Visitor Stat
- Template Download
- Author Guidelines
- Editorial Team
- Reviewer
- Focus and Scope

Home / About the Journal / Editorial Team

User

Username

Password

Remember me

Login

Language

Select Language

English

Submit

Notifications

» View

» Subscribe

Journal Content

Search

Search Scope

All

Search

Browse

» By Issue

» By Author

» By Title

» Other Journals

Information

» For Readers

» For Authors

» For Librarians

Focus and Scope

Editorial Board

Editor in Chief

» Yelvi Levani, (Scopus ID : 55200360700) (Sinta ID: 6689408) Faculty of Medicine Muhammadiyah University of Surabaya, Indonesia

Editor

» Jan L Nouwen, (Scopus ID : 7004057332) Erasmus MC University Medical Center Rotterdam, Netherlands

» Abdullah Al Tarique, (Scopus ID : 25960456000) Child Health Research Centre Faculty of Medicine, University of Queensland, Australia

» Prof Takashi Yashiro, (Scopus ID : 7007120815) JICHI Medical University School of Medicine, Japan

» Prof Murat Coskun, (Scopus ID : 24079683800) Istanbul University, Istanbul, Turkey, Turkey

» Muhammad Anas, (Scopus ID : 57192299850) Medical Faculty University Muhammadiyah of Surabaya, Indonesia

» Suhartono Taat Putra, (Scopus ID : 57194008862) Departemen Patobiologi Universitas Airlangga Surabaya, Indonesia, Indonesia

» Azis Alimul Hidayat, (Scopus ID : 57203654137) Universitas Muhammadiyah Surabaya, Indonesia

Section Editor

» Syafarinah Akil, Faculty of Medicine, Universitas Muhammadiyah Surabaya, Indonesia

» Ayu Lidya Paramita, Faculty of Medicine Muhammadiyah University of Surabaya, Indonesia

Layout Editor

» Dede Nasrullah, (Scopus ID : 57212390877) Departement Nursing Faculty of Health, University Muhammadiyah of Surabaya, Indonesia

0186997

View My Stat



Managed Hosting, Support, and OJS Responsive Theme by:
OpenJournalSystems.com



Literature Review

Role of antioxidant to protect leydig cells damage induced by reactive oxygen species: a literature review

Anak Agung Istri Dalem Cinthya Riris^{1*}, **Reny I'tishom²**, Siti Khaerunnisa³

- 1) Graduate Student of Reproductive Health Science, Faculty of Medicine Universitas Airlangga
- 2) Biomedical Department, Faculty of Medicine Universitas Airlangga
- 3) Biochemistry Department, Faculty of Medicine Universitas Airlangga

ARTICLE INFO

Submitted : April 2020
Accepted : January 2021
Published : January 2021

Keywords:

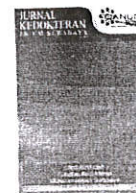
Leydig cell, antioxidant, reactive oxygen species, infertility

*Correspondence:

a.a.istri.dalem-cinthya2017@
 fk.unair.co.id

ABSTRACT

The Leydig cells play a crucial role in steroidogenesis and spermatogenesis. Those processes need complex communication in hormonal and testicular to maintain male reproductive function. Abnormal conditions induced by reactive oxygen species reduce cell viability through lipid peroxidation and apoptotic pathway that disrupt specific cells. Antioxidant ameliorates ROS elevation and prevents cell damage. Specifically, Leydig cells are vulnerable to ROS exposure and decline their function in mediating spermatogenesis. The imbalance of antioxidant and ROS level triggers oxidative stress and start damaging the Leydig cells. Loss of Leydig cells' functions in the testicular can lead to severe steroidogenic and spermatogenic impairment, which can contribute to male infertility. Therefore, it is needed to improve Leydig cells viability with antioxidant supplementation. This study aimed to determine the protective effect of antioxidants on Leydig cells induced by reactive oxygen species. This type of study is an integrative literature review. Various studies have been reviewed through critical appraisal tool Olsen-Baisch Scoring for integrated review. The online databases for all articles were found in different journals such as Nature, SAGE Journal, Scopus, and Springer Link. This study retrieved 295 titles, and 17 articles were qualified after the qualitative synthesis. Furthermore, this study highlighted the importance of the mechanism of antioxidants as a protective agent of Leydig cells. Numerous antioxidants can be found naturally, however, there are some factors with the compounds related to its antioxidant activity. Supplementation of antioxidants with the correct administration, dosage, and duration can balance reactive oxygen species level and protect Leydig cells.



INTRODUCTION

Infertility has become a world issue for reproductive health. Approximately 8-12% of couples of reproductive age experienced the inability to conceive spontaneous pregnancy. Moreover, up to 40% are related to male infertility, and most cases are the reproductive age group (Bisht et al., 2017). In Indonesia, the number of infertility couples of productive ages 20 to 40 years is 12-15%. Moreover, men influenced 40% of the infertility cases (Agustina, Budihastuti and Murti, 2018). Abnormal semen analysis has been reported in many infertile men, but the etiology is still poorly understood. Male infertility factors are genetic, dietary, physiologic, medical, and environmental factors. Recently, reactive oxygen species have been described to be a secret agent of male infertility. A previous study showed that 30-80% of male infertility is caused by reactive oxygen species (Wagner, Cheng and Ko, 2018).

Reactive oxygen species (ROS) is needed in some physiological processes, include capacitation and apoptotic processes. ROS sources in sperm, such as activation of leukocytes in the seminal plasma and the mitochondria in the spermatozoa. The higher level of ROS will cause an imbalance of endogenous antioxidant capacity that is defined as oxidative stress (Redza-dutoroir and Averill-bates, 2016). Oxidative stress is a potential contributor to reproductive cell dysfunction. The elevation of ROS level can damage sperm and testes. Low oxygen tensions in the testes are due to its poor vascularization, and it makes incredibly intense competition for the vital element within the testes. In addition, excessive ROS production in testicular tissue cells stimulated lipid peroxidation then trigger spermatogenesis and steroidogenesis perturbation. Leydig cell plays an important role in testosterone synthesis in male, which can be damaged by higher ROS level in the testicular tissue (Zirkin and Papadopoulos,

2018). Supplementation of exogenous antioxidant is needed to cover the imbalance of ROS level.

Antioxidant capacity can inhibit ROS-induced cell injury by natural or synthetic compounds to protect the Leydig cell. Antioxidant administration has been reported to protect and maintain Leydig cells induced by oxidative stress (Kumar and Neeraja, 2019). However, antioxidants' protective effect to Leydig cells damaged by ROS exposure should be investigated for a better understanding. This literature review aimed to determine the antioxidant's role in protecting Leydig cell induced by reactive oxygen species. This review specifically explores in Leydig cell and its damage through elevation of ROS level. Furthermore, this present study distinguish the important role of antioxidant system in Leydig cells to maintain spermatogenesis and steroidogenesis.

LITERATURE REVIEW

This integrative literature review based on four databases included Nature, Sage Journal, Scopus, and Springer Link. Based on the original research article keywords used in this study were "Leydig cells AND antioxidant AND reactive oxygen species AND protective". The articles have been selected by inclusion and exclusion criteria. In this study, the inclusion criteria were articles published in 2014 till 2019 range, written in English, available and accessible to the entire article. Only original article with true experimental study and laboratory study design will be included. Article without of involvement of Leydig cell will be excluded. Quality of the article defined by critical appraisal tool Olsen-Baisch Scoring for integrated review. The literature tracing scheme can be seen in Figure 1.



Antioxidant as protective agent evidence

This literature review selected 17 research articles. The article must be an original article with true experiment or laboratory research. This

present review explored and analyzed the type of antioxidant, doses, and antioxidant effect to counter ROS as Leydig cells protection. The details of the evidence can be seen in Table 1.

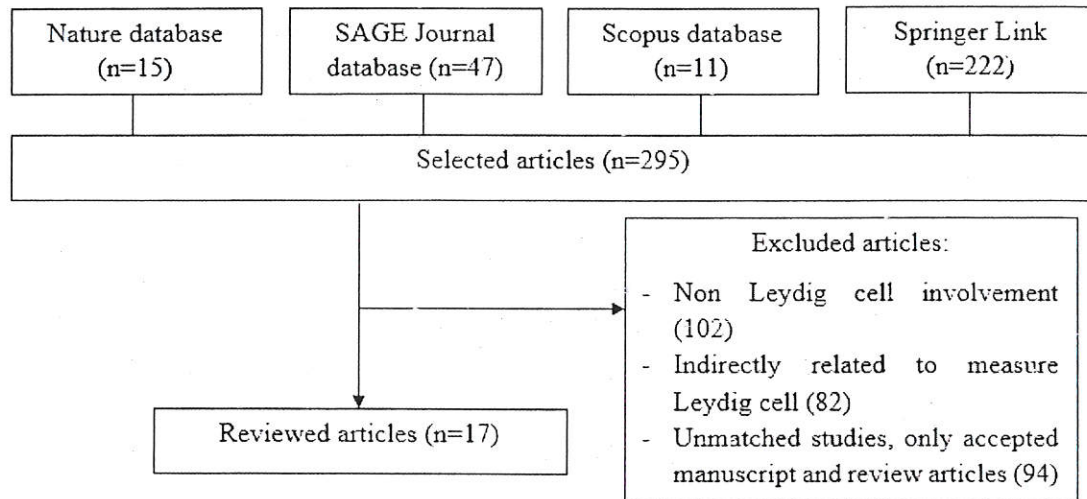


Figure 1. Literature review tracing scheme

Table 1. List of antioxidant protect Leydig cells induced by ROS evidence

No	Title and Author	Type of Antioxidant	Result
1	Adrenomedullin protects Leydig cells against lipopolysaccharide - induced oxidative stress and inflammatory reaction via MAPK/ NF-κB signalling pathways (Hu et al., 2017)	Adrenomedullin (ADM)	Addition of 100 nM ADM were significantly increased Leydig cell viability and advanced cell proliferation compare to control. 10 nM ADM, 50 nM ADM, and 300 nM ADM.
2	Vitamin D alleviates lead induced renal and testicular injuries by immunomodulatory and antioxidant mechanisms in rats (Basalamah, Abdelghany and El-boshy, 2018)	Vitamin D (VD ₃)	Administration of VD ₃ 1,000 IU/Kg in 3 days per week decreased apoptotic index of Leydig cell and maintain cell viability due to lead toxicity.



3	Protective role of <i>Nigella sativa</i> oil against reproductive toxicity, hormonal alterations, and oxidative damage induced by chlorpyrifos in male rats (Mosbah et al., 2016)	<i>Nigella sativa</i> oil (NSO)	Administration of 1 ml/kg/day NSO increased diameter of Leydig cells and decreased ROS level in testicular.
4	Prevention of carbon tetrachloride (CCl ₄)-induced toxicity in testes of rats treated with <i>Physalis peruviana</i> L. fruit (Moneim, 2016)	<i>Physalis peruviana</i> L.	P. peruviana juice supplementation significantly increased the testicular glutathione and significantly decreased the level of lipid peroxidation and the nitric oxide production compared with the CCl ₄ group. P. peruviana juice also prevented the degeneration of germ and Leydig cells along with deformities in spermatogenesis induced after CCl ₄ .
5	Vitamin C ameliorates the adverse effects of dexamethasone on sperm motility, testosterone level, and spermatogenesis indexes in mice (Sadeghzadeh, Mehranjani and Mahmoodi, 2019)	Vitamin C	Supplementation of 100 mg/kg/day Vitamin C showed significant differences between control and DEX group. Vitamin C reduce testicular toxicity induced by ROS and protect Leydig cells number.
6	Zinc sulphate and vitamin E alleviate reproductive toxicity caused by aluminium sulphate in male albino rats (Rawi, Seif and Nassr, 2015)	Zinc sulphate and vitamin E	Administration of 50 mg/kg/day Zinc sulphate and Vitamin E 15 mg/kg/day individually or combination have been proven to maintain Leydig cells due to ROS caused by aluminium sulphate.
7	Cerium oxide nanoparticles protect Cyclophosphamide-induced testicular toxicity in mice (Hamzeh et al., 2019)	Cerium oxide nanoparticles (NC)	Supplementation of 100 µg/kg NC prevented Leydig cells destruction induced by ROS generated by Cyclophosphamide.



8	Effect of Cistanche Tubulosa extracts on male reproductive function in streptozotocin–nicotinamide-induced diabetic rats (Kong et al., 2018)	Cistanche tubulosa extracts (CTE)	Administration of 160 mg/kg CTE decreased ROS level induced by diabetes mellitus in rats and it can maintain Leydig cells due to testicular toxicity.
9	Anti-apoptotic and anti-oxidant effects of caffeic acid phenethyl ester on cadmium-induced testicular toxicity in rats (Erboga et al., 2016)	Caffeic acid phenethyl ester (CAPE)	Therapy with 10 µmol/kg b.w. CAPE had significantly prevented oxidative stress due to ROS level and increased the number of Leydig cells viability.
10	Ameliorative effect of VE, IGF-I, and hCG on the fluoride-induced testosterone release suppression in mice Leydig cells (Yu et al., 2018)	Vitamin E (VE), IGF-1, and hCG	Leydig cells viability were maintained through ameliorative effect of VE, IGF-1, and hCG due to ROS induced testicular toxicity with the most powerful antioxidant showed in VE.
11	Malathion induced testicular toxicity and oxidative damage in male mice: the protective effect of curcumin (Ali and Ibrahim, 2018)	Curcumin	Administration of 200 mg/kg/day of curcumin showed normal histological structure, no Leydig cell hyperplasia, and decreased ROS level induced by malathion.
12	Testicular antioxidant mechanism of cultivated wild ginseng extracts (Ok, Kang and Kim, 2016)	Wild ginseng extracts	Supplementation of 50 mg/kg/day wild ginseng extracts increased Leydig cells viability and eliminated ROS level cause by Bisphenol-A.
13	Antioxidant activity of Spirulina platensis alleviates doxorubicin-induced oxidative stress and reprotoxicity in male rats (Eleiwa et al., 2018)	Spirulina platensis	Prevention effect of Spirulina platensis at a dose 300 mg/kg showed improvement in Leydig cells number and ameliorated ROS caused by doxorubicin.
14	Ameliorative effect of taurine-chloramine in azathioprine-induced testicular damage; a deeper insight into the mechanism of protection (Schaalan, Ramadan and Elwahab, 2018)	Taurine-chloramine (TAU-CL)	Supplementation of TAU-CL increased Leydig cells viability, decreased distortion in interstitial area, and prevented cell damage induced by ROS level.



15	Testicular toxicity and sperm quality following copper exposure in Wistar albino rats: ameliorative potentials of L-carnitine (Khushboo et al., 2018)	L-carnitine	Supplementation of 100 mg/kg L-carnitine showed significantly restored Leydig cells number induced by copper exposure.
16	Comparative analysis of the protective effects of curcumin and N-acetyl cysteine against paracetamol-induced hepatic, renal, and testicular toxicity in Wistar rats (El-Maddawy and El-Sayed, 2018)	Curcumin (CUR) and N-acetyl cysteine (NAC)	Administration of 200 mg/kg b.w. CUR and 150 mg/kg b.w. NAC increased the integrity of cellular membrane and stimulated regeneration of damaged cells. It showed that CUR has stronger ability to protect Leydig cells rather than NAC to improve reproductive function.
17	Bisphenol A exposure and healing effects of Adiantum capillus-veneris L. plant extract (APE) in bisphenol A-induced reproductive toxicity in albino rats (Yousaf et al., 2016)	Adiantum capillus-veneris L. plant extract (APE)	Administration of 25 mg/kg/day APE prevented Leydig cells damaged induced by Bisphenol-A.

Leydig cells

The Leydig or interstitial cells lie in the connective tissue between the seminiferous tubules. This cell-synthesized male sexual hormone testosterone makes Leydig cell the endocrine cells of the testes (Ji et al., 2015). Testosterone secreted by Leydig cells has various functions in men’s reproductive health system. Those functions were needed before birth, such as testosterone secretion by the Leydig cells of the fetal testes masculinizes the reproductive tract and external genitalia and promotes the descent of the testes into the scrotum. After birth, when initiated at puberty, testosterone secretion and spermatogenesis occur continuously throughout the male’s life. Ongoing testosterone secretion is fundamental for spermatogenesis, maintaining a mature

male reproductive tract, and influencing fertility (Sherwood, 2010). Biosynthesize testosterone as a steroid hormone-regulated by the mitochondria inside the Leydig cells. The abnormal condition can change its function and damage the cells (Ye et al., 2017).

Reactive oxygen species

Free radicals are a state of an unstable number of cell electrons so that it disrupts the balance of other electrons and takes place in a chain. Reactive oxygen species (ROS) have the destructive properties of free radicals. Some examples of ROS such as superoxide anion (O₂⁻), hydrogen peroxide (H₂O₂), and hydroxyl radicals (HO[•]), all of which contain oxygen radical and non-radical species formed by the reduction of some oxygen (Phaniendra, Jestadi



and Periyasamy, 2015). Endogenous cellular production of ROS results from oxidative phosphorylation in mitochondria, or the compound is produced from the interaction between exogenous factors and xenobiotic components (Sisein, 2014).

Antioxidant

Antioxidants are compounds that can eliminate, cleanse, and resist the formation of ROS effects. Antioxidants as compounds that can inhibit the process of auto-oxidation of all ingredients that contain lipids (Rajendran and Devi, 2018). The antioxidant process inhibits the formation of free radicals by acting as an H donor against free radicals, transforming into a more stable form. Antioxidants by source are classified in two groups, namely endogenous antioxidants and exogenous antioxidants. Endogenous antioxidants are antioxidants naturally present in body cells, namely SOD, catalase (CAT), and glutathione peroxidase (GPx) (Ighodaro and Akinloye, 2019). Exogenous antioxidants are antioxidants that come from outside the body, can come from everyday foods that contain vitamins (vitamin C, vitamin E beta-carotene) and phytochemical compounds (carotenoids, isoflavones, saponins, flavonoids, polyphenols) (Asih *et al.*, 2018). Exogenous antioxidants also consist of two major groups: the natural antioxidant group obtained from natural ingredients and synthetic antioxidants obtained from chemically synthesized ingredients.

Antioxidant protective effect on Leydig cells induced by ROS

Leydig cells secreted androgen, which plays a pivotal role in male sexual differentiation and sexual behavior, and it is crucial for initiating, maintaining, and regulating the process of spermatogenesis (Zhou *et al.*, 2019). The various study has been reported that Leydig cells as the main source of androgens. The Leydig cells help to regulate spermatogenesis through its function in steroidogenesis. Testosterone as

the primary androgen synthesized by Leydig cells is required for meiosis and sperm formation, mediating normal spermatogenesis. Significantly, Leydig cells have the important role in maintaining male fertility. Leydig cells are vulnerable to toxicants especially induced by reactive oxygen species (ROS).

Endogenous ROS production mainly occurs in mitochondria as the electron transport processes; other sources are in the endoplasmic reticulum, cytoplasm, peroxisomes, lysosomes, and plasma membrane (Kurutas, 2016). Exogenous sources of ROS are inappropriate diet, lifestyle, and environmental factors. Despite ROS's function in cell signaling mediation, increasing ROS level can trigger an imbalance endogenous antioxidant capacity. The effect of imbalance ROS and antioxidant level become oxidative stress. Oxidative stress as the mediator of damage to cell structures and an inductor for apoptotic cells. A previous study stated that Leydig cell dysfunction and lipid peroxidation of Leydig cell membrane stimulated by oxidative stress (Asadi *et al.*, 2017). Associated with testicular toxicity, it has been noted that ROS elevation induces Leydig cell damage and influence abnormal spermatogenesis.

The germ cells in the testes undergo complex proliferation and maturation processes, from diploid spermatogonia through meiosis to mature haploid spermatozoa, which are highly dependent on oxygen metabolism (Oliveira and Alves, 2015). Cells that are oxidized in the testes become a source of ROS for the testicular organs themselves, thus causing an increase in oxidative stress. If oxidative stress is excessive, communication between cells in the testes, such as Sertoli cells, Leydig cells, and other spermatogenic cells can be damaged (Hai *et al.*, 2014). Oxidative damage occurs in many types of molecules such as lipids, proteins, nucleic acids, and sugars. Every cell, nucleus, and mitochondrial membrane, structural and

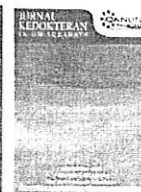


cytoplasmic protein, complex carbohydrates, ribonucleic acid (RNA) and DNA, all have the potential to cause oxidative stress. Tissues such as testes with high metabolic rates and cell replication make oxidative stress increase and surpass the endogenous antioxidant level (Guerrero et al., 2014). Oxidative stress due to increased ROS can cause damage to cells, tissues, to organs. This results in disruption of the process of sperm formation in the seminiferous tubules due to damage to cells that play a role in spermatogenesis so that the number of spermatogenic cells decreases and ultimately leads to male factor infertility.

According to ROS's deleterious effect oxidative stress-induced, it has been reported to administer exogenous antioxidants. Antioxidant sources are varied and can be a natural or synthetic antioxidants. Recently, natural antioxidants have been chosen for ameliorating cell damaged caused by ROS. As we have known, Leydig cells need to be protected, and numerous studies have been reported that ROS elimination through antioxidant supplementation. Many experimental studies showed that medicinal plants rich in vitamin C and vitamin E have a strong antioxidant capacity to eliminate ROS. Moreover, some minerals like Zinc also have the antioxidant capacity to encounter cell damage by ROS (Ko et al., 2014). The mechanism of action of antioxidant to protect cells are complex and need better understanding. Studies show that antioxidant plays a key role in achieving balance or cellular redox homeostasis (He et al., 2017). Supplementation of antioxidants is needed to protect Leydig cells damage from testicular toxicity induced by ROS. However, a misleading dose of administration of antioxidants can cause severe cell damage (Shahidi and Zhong, 2015). The antioxidant dose variation can give different effects, which can be an inverse relationship

between antioxidant activity and antioxidant concentration. The greater concentration of antioxidants results in smaller antioxidant activity. Antioxidants are chemical compounds that can contribute one or more electrons to free radicals, so that free radicals can be suppressed. The higher the concentration of antioxidants the more dense the molecules so that the electrons of the antioxidant become unable to react with free radicals (Apak et al., 2016). The rate of oxidation can be affected by increasing antioxidant concentration. Another previous study also mentioned that giving concentrations of antioxidants with high concentrations can be a pro-oxidant. Essentially, the importance is balanced the ROS and antioxidants level to protect Leydig cells.

Antioxidants' protective effect on the Leydig cells has been reported to raise male fertility. The exposure of ROS increased Leydig cells damage and decline its function. Administration of antioxidants as pretreatment increased Leydig cells viability and regenerated its function on steroidogenesis and spermatogenesis (Darbandi et al., 2018). Antioxidants' activities to protect Leydig cells regarding to its administration, dosage, and duration (Haw et al., 2012). The administration of antioxidants through oral or injection can give slightly different effects. Various dosage of antioxidant supplementation has been studied to find the best-chosen dosage that does not harm the cells. Moreover, antioxidant supplementation duration is crucial to prevent the accumulation of exogenous antioxidants that can inverse into pro-oxidant and damage the cells. Long term of ROS exposure will decrease anti-oxidative defense system of the Leydig cells. Therefore, antioxidant supplementation is needed to be a protective agent of the Leydig cells within rational recommendation, so that can maintain and enhance male fertility.

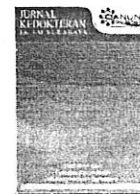


CONCLUSION

This literature review has been shown that antioxidants as a potential agent to protect Leydig cells induced by ROS. The importance is to maintain the cellular redox state of ROS and antioxidant level. Several studies have proven that supplementation of antioxidants within the correct dosage and duration can enhance Leydig cells viability and generate its function to influence normal spermatogenesis. Genetic factors originate in Leydig cells, and the mechanism of survival with an antioxidant defense system need to get a better understanding to identify innovation for treating male infertility.

REFERENCES

- Agustina, D., Budihastuti, U. R. and Murti, B. (2018). Biopsychosocial Factors of Infertility among Men in Surakarta , Central Java, *Indonesian Journal of Medicine*, 3(1), pp. 14–21. doi: 10.26911/theijmed.2018.03.01.02.
- Ali, R. I. and Ibrahim, M. A. (2018). Malathion induced testicular toxicity and oxidative damage in male mice : the protective effect of curcumin, *Egyptian Journal of Forensic Sciences*. Egyptian Journal of Forensic Sciences, 8(70), pp. 1–13.
- Apak, R. et al. (2016). Antioxidant activity / capacity measurement: I . Classification, physico- chemical principles, mechanisms and electron transfer (ET) based assays, 64(5), pp. 997–1027. doi: 10.1021/acs.jafc.5b04739.
- Asadi, N. et al. (2017). The Impact of Oxidative Stress on Testicular Function and the Role of Antioxidants in Improving it : A Review, *Journal of Clinical and Diagnostic Research*, 11(5), pp. 1–5. doi: 10.7860/JCDR/2017/23927.9886.
- Asih, I. A. R. A. et al. (2018). The Flavonoid Glycosides Antioxidant From Terong Belanda (Solanum betaceum), *Biomedical and Pharmacology Journal*, 11(4), pp. 2135–2141.
- Basalamah, M. A., Abdelghany, A. H. and El-boshy, M. (2018). Vitamin D alleviates lead induced renal and testicular injuries by immunomodulatory and antioxidant mechanisms in rats. *Scientific Reports*. Springer US, 8(March), pp. 1–13. doi: 10.1038/s41598-018-23258-w.
- Bisht, S. et al. (2017). Oxidative stress and male infertility. *Nature Reviews Urology*. Nature Publishing Group, 14(8), pp. 470–485. doi: 10.1038/nrurol.2017.69.
- Darbandi, M. et al. (2018). Reactive oxygen species and male reproductive hormones. *Reproductive Biology and Endocrinology*. pp. 1–14.
- El-Maddawy, Z. K. and El-Sayed, Y. S. (2018). Comparative analysis of the protective effects of curcumin and N -acetyl cysteine against paracetamol-induced hepatic , renal , and testicular toxicity in Wistar rats, *Environmental Science and Pollution Research*. Environmental Science and Pollution Research, 25, pp. 3468–3479.
- Eleiwa, N. Z. H. et al. (2018). Antioxidant activity of Spirulina platensis alleviates doxorubicin - induced oxidative stress and reprotoxicity in male rats, *Oriental Pharmacy and Experimental Medicine*. Springer Singapore, 18(2), pp. 87–95. doi: 10.1007/s13596-018-0314-1.
- Erboga, M. et al. (2016). Anti-Apoptotic and Anti-Oxidant Effects of Caffeic Acid Phenethyl Ester on Cadmium-Induced Testicular Toxicity in Rats. *Biological Trace Element Research*. Biological Trace Element Research, 171, pp. 176–184. doi: 10.1007/s12011-015-0509-y.



- Guerriero, G. et al. (2014). Roles of reactive oxygen species in the spermatogenesis regulation, 5(April), pp. 10–13. doi: 10.3389/fendo.2014.00056.
- Hai, Y. et al. (2014). The roles and regulation of Sertoli cells in fate determinations of spermatogonial stem cells and spermatogenesis, *Seminars in Cell and Developmental Biology*. Elsevier Ltd. doi: 10.1016/j.semdb.2014.04.007.
- Hamzeh, M. et al. (2019). Cerium Oxide Nanoparticles Protect Cyclophosphamide - induced Testicular Toxicity in Mice, *International Journal of Preventive Medicine*, 10(5), pp. 1–9. doi: 10.4103/ijpvm.IJPVM.
- Haw, K. Y. E. N. et al. (2012). Effects of *Etlingera elatior* extracts on lead acetate-induced testicular damage: A morphological and biochemical study, *Experimental and Therapeutic Medicine*, 2012(3), pp. 99–104. doi: 10.3892/etm.2011.355.
- He, L. et al. (2017). Antioxidants Maintain Cellular Redox Homeostasis by Elimination of Reactive Oxygen Species, *Cellular Physiology and Biochemistry*, 2017(44), pp. 532–553. doi: 10.1159/000485089.
- Hu, W. et al. (2017). Adrenomedullin protects Leydig cells against lipopolysaccharide-induced oxidative stress and inflammatory reaction via MAPK / NF- κ B signalling pathways, *Scientific Reports*. Springer US, 7(2), pp. 1–15. doi: 10.1038/s41598-017-16008-x.
- Ighodaro, O. M. and Akinloye, O. A. (2019). First line defence antioxidants-superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX): Their fundamental role in the entire antioxidant defence grid, *Alexandria Journal of Medicine*. Alexandria University Faculty of Medicine, 54(4), pp. 287–293. doi: 10.1016/j.ajme.2017.09.001.
- Ji, X. et al. (2015). Cytotoxic mechanism related to dihydrolipoamide dehydrogenase in Leydig cells exposed to heavy metals, *Toxicology*. Elsevier Ireland Ltd, 334, pp. 22–32. doi: 10.1016/j.tox.2015.05.003.
- Khushboo, M. et al. (2018). Testicular toxicity and sperm quality following copper exposure in Wistar albino rats: ameliorative potentials of L-carnitine, *Environmental Science and Pollution Research*. Environmental Science and Pollution Research, 25, pp. 1837–1862.
- Ko, E. Y. et al. (2014). Male infertility testing: reactive oxygen species and antioxidant capacity, *Fertility and Sterility*. Elsevier Inc., 102(6), pp. 1518–1527. doi: 10.1016/j.fertnstert.2014.10.020.
- Kong, Z.-L. et al. (2018). Effect of Cistanche Tubulosa Extracts on Male Reproductive Function in Streptozotocin–Nicotinamide-Induced Diabetic Rats, *Nutrients*, 10(1562), pp. 1–22. doi: 10.3390/nu10101562.
- Kumar, T. S. and Neeraja, P. (2019). Factors Associated With Oxidative Stress in the Testes and the Mitigating Role of Antioxidants: A Review, *International Journal of Recent Innovations in Medicine and Clinical Research*, 1(1), pp. 6–12.
- Kurutas, E. B. (2016). The importance of antioxidants which play the role in cellular response against oxidative / nitrosative stress: current state, *Nutrition Journal*. Nutrition Journal, pp. 1–22. doi: 10.1186/s12937-016-0186-5.
- Moneim, A. E. A. (2016). Prevention of carbon tetrachloride (CCl₄)-induced toxicity in testes of rats treated with *Physalis peruviana*, *Toxicology and Industrial*



- Health*, 32(6), pp. 1064–1073. doi: 10.1177/0748233714545502.
- Mosbah, R. et al. (2016). Protective role of *Nigella sativa* oil against reproductive toxicity, hormonal alterations, and oxidative damage induced by chlorpyrifos in male rats, *Toxicology and Industrial Health*, 32(7), pp. 1266–1277. doi: 10.1177/0748233714554675.
- Ok, S., Kang, J. S. and Kim, K. M. (2016). Testicular antioxidant mechanism of cultivated wild ginseng extracts, *Molecular Cell Toxicology*, 12, pp. 149–158. doi: 10.1007/s13273-016-0019-9.
- Oliveira, P. F. and Alves, M. G. (2015). *Metabolism and Spermatogenesis*. New York: Springer.
- Phaniendra, A., Jestadi, B. D. and Periyasamy, L. (2015). Free Radicals: Properties, Sources, Targets, and Their Implication in Various Diseases, *Indian Journal of Clinical Biochemistry*, 30(1), pp. 11–26. doi: 10.1007/s12291-014-0446-0.
- Rajendran, S. K. and Devi, S. A. (2018). Lead Toxicity on Male Reproductive System and its Mechanism: A Review Lead Toxicity on Male Reproductive System and its Mechanism: A Review, 11(3), pp. 1228–1232. doi: 10.5958/0974-360X.2018.00228.7.
- Rawi, S. M., Seif, F. M. and Nassr, A. (2015). Zinc sulphate and vitamin E alleviate reproductive toxicity caused by aluminium sulphate in male albino rats, *Toxicology and Industrial Health*, 31(3), pp. 221–234. doi: 10.1177/0748233712469650.
- Redza-dutordoir, M. and Averill-bates, D. A. (2016). Biochimica et Biophysica Acta Activation of apoptosis signalling pathways by reactive oxygen species, *BBA - Molecular Cell Research*. Elsevier B.V., 1863(12), pp. 2977–2992. doi: 10.1016/j.bbamcr.2016.09.012.
- Sadeghzadeh, F., Mehranjani, M. S. and Mahmoodi, M. (2019). Vitamin C ameliorates the adverse effects of dexamethasone on sperm motility, testosterone level, and spermatogenesis indexes in mice, *Human and Experimental Toxicology*, 38(4), pp. 409–418. doi: 10.1177/0960327118816137.
- Schaalan, M. F., Ramadan, B. K. and Elwahab, A. H. A. (2018). Ameliorative effect of taurine-chloramine in azathioprine-induced testicular damage; a deeper insight into the mechanism of protection, *BMC Complementary and Alternative Medicine*. BMC Complementary and Alternative Medicine, 18(255), pp. 1–14.
- Shahidi, F. and Zhong, Y. (2015). Measurement of antioxidant activity, *Journal of Functional Foods*, 18, pp. 757–781. doi: 10.1016/j.jff.2015.01.047.
- Sherwood, L. (2010) *Human Physiology From Cells to Systems*. Seventh. Canada: Cengage Learning.
- Sisein, E. A. (2014). Review Article Biochemistry of Free Radicals and Antioxidants, *Scholars Academic Journal of Biosciences*, 2(2), pp. 110–118.
- Wagner, H., Cheng, J. W. and Kó, E. Y. (2018). Role of reactive oxygen species in male infertility: An updated review of literature, *Arab Journal of Urology*. Arab Association of Urology, 16(1), pp. 35–43. doi: 10.1016/j.aju.2017.11.001.
- Ye, L. et al. (2017). Insights into the Development of the Adult Leydig Cell Lineage from Stem Leydig Cells, *Frontiers in Physiology*, 8(June), pp. 1–18. doi: 10.3389/fphys.2017.00430.
- Yousaf, B. et al. (2016). Bisphenol A exposure and healing effects of *Adiantum capillsveneris* L. plant extract (APE) in bisphenol A-induced reproductive toxicity in albino rats', *Environmental Science*



- and *Pollution Research*. *Environmental Science and Pollution Research*, 23, pp. 11645–11657. doi: 10.1007/s11356-016-6330-0.
- Yu, Y. *et al.* (2018). Ameliorative Effect of VE, IGF-1, and hCG on the Fluoride-Induced Testosterone Release Suppression in Mice Leydig Cells, *Biological Trace Element Research*. *Biological Trace Element Research*, 181, pp. 95–103. doi: 10.1007/s12011-017-1023-1.
- Zhou, R. *et al.* (2019). The roles and mechanisms of Leydig cells and myoid cells in regulating spermatogenesis. *Cellular and Molecular Life Sciences*. Springer International Publishing, (76), pp. 2681–2695. doi: 10.1007/s00018-019-03101-9.
- Zirkin, B. R. and Papadopoulos, V. (2018). Leydig cells: formation, function, and regulation †, *Biology of Reproduction*, 99(1), pp. 101–111. doi: 10.1093/biolre/i0y059.

The difference in severity and management between children and adult's cases of COVID-19
Muhammad Ihsan¹, Chandra Djalilah², R. A. Kusnanti³, Alifa Amalia Laksana⁴

The role of gut microbiota in health and disease
Roni Nurrobbil¹, Fandiqa Nurrobbil², Gani Saqibani³

Keefektifan: A review of chronic obstructive pulmonary disease (COPD) treatment
Ira Dwiastuti¹, Dwi Denny Sari², Nani Permatasari³, Nandini Ananda⁴, Linda Pratomo⁵, Nurhasanah⁶, Fida Nurrobbil⁷, Fida Nurrobbil⁸, Muhammad Fatah Mubandari⁹, Fanni Nurrobbil¹⁰

Effect of intensive therapy period towards blood sugar level in type 2 diabetes mellitus patients at Lonsajaya subequivalent clinic
Anang Pata Hudaib¹, Dean Satrio²

clinical and functional outcome of cervical degenerative disc disease after operative treatment in 2013-2018 at Dr. Soetomo General Hospital Surabaya
Rizka Rizka¹, Rendi Rizka², Pratiwi³, Anandita⁴, Dharma⁵, Dharma⁶

Association between gestational age and perinatal pulmonary hypertension of the newborn (PPHN) severity in preterm babies at Sidoarjo Regional Hospital
Aryani Fadhilah¹, M. Fauziah², Nurul Hudaib³, Nurul Hudaib⁴, Gita Nurrobbil⁵

Correlation between extract give protective effect on spermatogenesis morphology of mice exposed to lead acetate
Rizka Nurrobbil¹, Rizka Nurrobbil², Rizka Nurrobbil³, Rizka Nurrobbil⁴, Rizka Nurrobbil⁵, Rizka Nurrobbil⁶, Rizka Nurrobbil⁷, Rizka Nurrobbil⁸, Rizka Nurrobbil⁹, Rizka Nurrobbil¹⁰

Identification of the osteoclast marker in a tooth (permanent tooth) of Puskesmas Fortopul Paksiwang comparison of five erythrocyte indices
Muzni Nurrobbil¹, Rizka Nurrobbil²

Depression, anxiety, and stress levels in Denpasar community during the pandemic of Corona Virus Disease 2019 (COVID-19) outbreak
Rizka Nurrobbil¹, Rizka Nurrobbil², Rizka Nurrobbil³, Rizka Nurrobbil⁴, Rizka Nurrobbil⁵, Rizka Nurrobbil⁶, Rizka Nurrobbil⁷, Rizka Nurrobbil⁸, Rizka Nurrobbil⁹, Rizka Nurrobbil¹⁰

The association between demographic and anthropometric factors with the practice of malaria prevention among the rural community in Puriwaja district, Indonesia
Yusuf Nurrobbil¹, Rizka Nurrobbil², Rizka Nurrobbil³, Rizka Nurrobbil⁴, Rizka Nurrobbil⁵, Rizka Nurrobbil⁶, Rizka Nurrobbil⁷, Rizka Nurrobbil⁸, Rizka Nurrobbil⁹, Rizka Nurrobbil¹⁰

In vitro alpha D-glucosidase inhibition in liver-ripped human sperm: the impact of DNA fragmentation index
Rizka Nurrobbil¹, Rizka Nurrobbil², Rizka Nurrobbil³, Rizka Nurrobbil⁴, Rizka Nurrobbil⁵, Rizka Nurrobbil⁶, Rizka Nurrobbil⁷, Rizka Nurrobbil⁸, Rizka Nurrobbil⁹, Rizka Nurrobbil¹⁰

cardio-vascular syndrome as a complication patient with severe mitral regurgitation and moderate aortic regurgitation with Pulmonary Hypertension
Rizka Nurrobbil¹, Rizka Nurrobbil², Rizka Nurrobbil³, Rizka Nurrobbil⁴, Rizka Nurrobbil⁵, Rizka Nurrobbil⁶, Rizka Nurrobbil⁷, Rizka Nurrobbil⁸, Rizka Nurrobbil⁹, Rizka Nurrobbil¹⁰

Characteristics of complaints and functional outcomes of conservatively treated distal radius fractures in Dr. Soetomo general hospital, Ayang series
Rizka Nurrobbil¹, Rizka Nurrobbil², Rizka Nurrobbil³, Rizka Nurrobbil⁴, Rizka Nurrobbil⁵, Rizka Nurrobbil⁶, Rizka Nurrobbil⁷, Rizka Nurrobbil⁸, Rizka Nurrobbil⁹, Rizka Nurrobbil¹⁰

Role of antioxidants in prevent Lysing cell damage induced by reactive oxygen species: a literature review
Rizka Nurrobbil¹, Rizka Nurrobbil², Rizka Nurrobbil³, Rizka Nurrobbil⁴, Rizka Nurrobbil⁵, Rizka Nurrobbil⁶, Rizka Nurrobbil⁷, Rizka Nurrobbil⁸, Rizka Nurrobbil⁹, Rizka Nurrobbil¹⁰

The effectiveness of clinic lecture and workshop as interventions to improve primary health care providers knowledge and skill on the management of pediatric emergencies
Rizka Nurrobbil¹, Rizka Nurrobbil², Rizka Nurrobbil³, Rizka Nurrobbil⁴, Rizka Nurrobbil⁵, Rizka Nurrobbil⁶, Rizka Nurrobbil⁷, Rizka Nurrobbil⁸, Rizka Nurrobbil⁹, Rizka Nurrobbil¹⁰

Keefektifan: A review of chronic obstructive pulmonary disease (COPD) treatment
Ira Dwiastuti¹, Dwi Denny Sari², Nani Permatasari³, Nandini Ananda⁴, Linda Pratomo⁵, Nurhasanah⁶, Fida Nurrobbil⁷, Fida Nurrobbil⁸, Muhammad Fatah Mubandari⁹, Fanni Nurrobbil¹⁰

diterbitkan oleh:
Fakultas Kedokteran
Universitas Muhammadiyah Surabaya **2021**

Journal Profile

Qanun Medika : Jurnal Kedokteran Fakultas Kedokteran Universitas Muhammadiyah Surabaya

eISSN : 25489526 | pISSN : 25412272

Health

Universitas Muhammadiyah Surabaya



S3

Sinta Score



Indexed by GARUDA

4

H-Index

4

H5-Index

96

Citations

95

5 Year Citations