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Table of Contents

Proceedings of 2022 6th International Conference on Medical and Health Informatics (ICMHI 2022)

Preface	viii
Conference Committees.....	ix

• ***Session 1 – Biomedical Image Processing and Data Analysis***

Exploring a Universal Training Method for Medical Image Classification	1
<i>Han Ding, Kun Yan, Zheyang Tu, Ping Wang</i>	
Using a Saliency-Driven Convolutional Neural Network Framework for Brain Tumor Detection	9
<i>Paulo Henrique de C. Oliveira, Mylène C.Q. Farias, Daniel S. Ferreira, Andrey S. Krylov, Yong Ding</i>	
Using Machine Learning for Precision Prognostics in Head and Neck Cancer Images	14
<i>Divya Rao, Prakashini K, Rohit Singh, Vijayananda J</i>	
Facial Attractiveness: Are there Features Recognized as a Standard?	18
<i>Raoul D’Alessio, RDA, D’Alessio, Teresa Angela Trunfio, TAT, Trunfio, Maria Leonetti, ML, Leonetti, Alberto Laino, AL, Laino, Roberto Deli, RD, Deli, Luigi Maria Galantucci, LMG, Galantucci</i>	
A New Poisoning Attacks on Deep Neural Networks	24
<i>Jung-Shian Li, Yen-Chu Peng, I-Hsien Liu, Chuan-Gang Liu</i>	

• ***Session 2 – Telemedicine and Healthcare Information System***

Applying FHIR in Remote Consultation in Dermatology: Interoperability of Information for Digital Dermatoscope	28
<i>Tzu-Fang, Peng, Hung-Wen Chiu</i>	
A Mobile Application for Chronic Kidney Disease (CKD) Diagnosis	32
<i>Kasilingam, Periyasamy, Athira, D, Kaivelikkal, Venkateshwaran, Iyer</i>	
Mobile Applications for Music Recommendation System Combined with Brainwave	37
<i>Rung-Ching Chen, Cheng-Yun Lin, Ming-Jheng Liou, Christine Dewi</i>	
Gauging the Gaps for Decision Support – Data Integration in the Hospital Information Systems with Machine Learning	43
<i>William Y C Wang, Philip H W Jiang, Tiong T Goh, Hsieh, C.C</i>	
Evaluating the Effectiveness of Research Electronic Data Capture System on Home Pharmaceutical Care in Taiwan	48
<i>Yu-Chiung Hsu, Ya-Ming Shiue, Chuan-Gang Liu, Zu-Chueh Wang</i>	
Developing a GraphQL SOAP Conversational Micro Frontends for the Problem Oriented Medical Record (QL4POMR)	52
<i>Sabah Mohammed, Jinan Fiaidhi, Darien Sawyer, Mehdi Lamouchie</i>	

• ***Session 3 – Electronic Medical Record and Medical Data Processing***

Develop a Natural Language Processing Pipeline to Automate Extraction of Periodontal Disease Information from Electronic Dental Clinical Notes	61
<i>Jay S. Patel, Rishi Rao, Ryan Brandon, Vishnu Iyer, Jasim M. Albandar, Marisol Tellez, Joachim Krois, Huanmei Wu</i>	
Doplor Sleep: Monitoring Hospital Soundscapes for Better Sleep Hygiene	69
<i>Elif Özcan, Yiling Liu, Jered Vroon, Daan Kamphuis, Simone Spagnol</i>	
Using Classification and Visualization to Support Clinical Texts Review in Electronic Clinical Documentation	78
<i>Jonah, K Kenei, Elisha, O, Opiyo</i>	
Towards Medical Ontology Construction Using Data Mining: An Approach for Creating a Diabetic Ontology Using Clustering	85
<i>Wejdan, A, Radhwan, Amany, K, Alnahdi</i>	
Digital Public Health Surveillance with Online Health Consultation Data: An Example of HIV Monitoring	89
<i>Chen Liu, William Y. C. Wang, Gohar Khan</i>	
Choice Variation on Electronic Health Database: A Case Study of Medical Decision Mapping from Healthcare Scheme of Thailand	94
<i>Praowpan Tansitpong</i>	
Characteristics of the Information Needs of Hypertension Patients on Online Healthcare Service Platforms	102
<i>Tingting Zhang, Sunjing Zheng, Yundi Zhang</i>	

• ***Session 4 – Machine Learning in Biomedicine and Computer Aided Diagnosis***

Hypertension Disease Predictions with Various Models Using Data Science Framework	107
<i>Azadeh Alizargar, Tan-Hsu Tan, Yang-Lang Chang, Mohammad Alkhaleefah</i>	
The Development and Implementation of Deep Learning Assisted Interoperable Retinal Image Structured Report Module in PACS	113
<i>Jin Li, Jiahui Shao, Junyi Wu, Jinxia Fang, Tongtong Zhou, Huiqun Wu</i>	
Explainable Machine Learning Models for Suicidal Behavior Prediction	118
<i>Noratikah Nordin, Zurinahni Zainol, Mohd Halim Mohd Noor, Lai Fong Chan</i>	
Human Fall Detection Based on Unidirectional Multi-Scale Spatial Encoder and Bidirectional Temporal Decoder Neural Network	124
<i>C. E., Yeoh, J. G., Wang</i>	
Regression and Classification Methods for Predicting the Length of Hospital Stay After Cesarean Section: A Bicentric Study	135
<i>Emma Montella, EM, Montella, Marta Rosaria Marino, MRM, Marino, Massimo Majolo, MM, Majolo, Eliana Raiola, ER, Raiola, Giuseppe Russo, GR, Russo, Giuseppe Longo, GL, Longo, Andrea Lombardi, AL, Lombardi, Anna Borrelli, AB, Borrelli, Maria Triassi, MT, Triassi</i>	
A Deep Learning Model for Wound Size Measurement Using Fingernails	141
<i>Duc-Khanh Nguyen, Dun-Hao Chang, Thi-Ngoc Nguyen, Trinh-Trung-Duong Nguyen, Chien-Lung Chan</i>	

• **Session 5 – Biomedical Electronics and Biological Signal Analysis**

Vibrotactile Motion Guidance for Stroke Rehabilitation: A Comparative Study	147
<i>Tim Moesgen, Antti Salovaara, Emmi Pouta, Rebecka Pyykko, Yu Xiao</i>	
Design of Plantar Pressure Measurement to Diagnose the Flat Feet Patients Plantar Pressure	153
<i>Warunya, Chaichanyut, Montree, Chaichanyut</i>	
EEG-Based Drivers Mental Fatigue Detection Using ERD/ERS and Hurst Exponent	159
<i>Diana G. González-Rodríguez, Dulce Martínez-Peon, Xochitl A. Ortiz-Jiménez, J. Fernando Góngora-Rivera, Francisco G. Benavides-Bravo, Brayan Soria-Rodríguez, Mariana Ruiz Velazquez</i>	
Design and Kinematics Analysis of 3-URS Ankle Rehabilitation Parallel Robot	163
<i>Thanh, Trung, Trang, Yue, Ming, Hu, Thanh, Long, Pham, Quoc, Khanh, Duong</i>	
Analysis on Mechanisms of Idea Generation: Evidences from fNIRS Hyperscanning	176
<i>Kecheng Lai, Yuqi Liu, Takehiro Iino, Tsutomu Fujinami</i>	

• **Session 6 – Medical Statistics and Modeling in Epidemic Forecasting**

Thyroid Dland Disorders Associated with Combination of Antiangiogenic Agents and Immune Checkpoint Inhibitors: A Pharmacovigilance Study	183
<i>Lujie Zhuge</i>	
Mechanism of Necrotizing Enterocolitis in Preterm Infants Through the Hypoxia Signaling Pathway, Neuronal-Glial Signaling Pathway, and Intestinal Fatty Acid Signaling Pathway	189
<i>Dina Angelika, Risa Etika, I Dewa Gede Ugrasena</i>	
Prevalence of Sociodemographic Factors in a Cohort of Diabetes Mellitus: A Retrospective Study	193
<i>Madurapperumage, A, Erandathi, William Y.C. Wang, Michael Mayo, Ibrahim Shafiu</i>	
Mechanism of Action of Cognitive Behavioral Therapy on Pain in Adult Women with Major TMJ Disorders	198
<i>Shujun Dong, Yuqing Zhang, Xiao Cen, Xiaojing Li, Lixia Yu, Zhongjie Li, Xiaoqin Zhu</i>	
A Multiple Regression Model for Modelling the Hospital Patients LOS' of Laparoscopic Cholecystectomy: A Bicentric Study	205
<i>Ida Santalucia, IS, Santalucia, Marta Rosaria Marino, MRM, Marino, Eliana Raiola, ER, Raiola, Massimo Majolo, MM, Majolo, Giuseppe Russo, GR, Russo, Giuseppe Longo, GL, Longo, Giuseppe Ferrucci, GF, Ferrucci, Anna Borrelli, AB, Borrelli, Maria Triassi, MT, Triassi</i>	
Type II Diabetes as the Main Risk Factor of Arterial Stiffness in Chronic Kidney Disease Patients	210
<i>Hendri Susilo, HEN, Susilo, Mochamad Yusuf Alsagaff, SUF, Alsagaff, Budi Susetyo Pikir, BUD, Pikir, Mochammad Thaha, THA, Thaha, Citrawati Dyah Kencono Wungu, CIT, Wungu</i>	
Predicting Crimean-Congo Hemorrhagic Fever Outbreaks via Multivariate Time-Series Classification of Climate Data	215
<i>Jonathan Harris, Thilanka Munasinghe, Heidi Tubbs, Assaf Anyamba</i>	
New Approach to Policy Effectiveness for Covid-19 and Factors Influence Policy Effectiveness	219
<i>Yile He</i>	

- **Session 7 – Bioinformatics and Biomedical Technology**

The Comparison of Non-Invasive ICP _{snapshot} and Non-Invasive ICP _{monitoring} Methods on Healthy Volunteer: A Pilot Study	225
<i>Vilma Putnynaite, Laimonas Bartusis, Solventa Krakauskaitė, Rolandas Zakelis, Yasin Hamarat</i>	
Rejuvenation through Collagen Induced with a Novel Picosecond Laser	229
<i>Putri Hendria Wardhani, Cita Rosita Sigit Prakoeswa, M. Yulianto Listiawan</i>	
Effects of <i>Nigella Sativa</i> on Female Infertility: A Systematic Review	234
<i>Amirul, Amalia, Hendy, Hendarto, Arifa, Mustika, Inta, Susanti</i>	
The Analysis of Phage rz/rz1 Gene in Shigatoxin Bacteria	238
<i>Tessa Sjahriani, Debi Arivo, Eddy Bagus Wasito, Wiwiek Tyasningsih</i>	
Strategy Arrangement of Road Cycling Individual Time Trial Based on Topology Optimization Algorithm	242
<i>Yuelin Xu, Yue Dai, Haonan Zhang</i>	

- **Session 8 – Applied Computing in Hospital Management and Medical Resource Allocation**

Lean Six Sigma Approach to the Study of the LOS of Patients who Undergo Laparoscopic Cholecystectomy: A Bicentric Study	247
<i>Emma Montella, EM, Montella, Marta Rosaria Marino, MRM, Marino, Massimo Majolo, MM, Majolo, Eliana Raiola, ER, Raiola, Giuseppe Russo, GR, Russo, Giuseppe Longo, GL, Longo, Michele Sparano, MS, Sparano, Anna Borrelli, AB, Borrelli, Maria Triassi, MT, Triassi</i>	
CBRN Weapons as a Threat to Critical Infrastructure Elements	253
<i>Katerina Vichova, Martin Hromada, Frantisek Paulus, Jarmil Valasek</i>	
Mode of Discharge in CoViD-19 Era: The Case of the C.O.U. Oncology of “San Giovanni di Dio e Ruggi d’Aragona” University Hospital	258
<i>Rossella Alfano, RA, Alfano, Ilaria Loperto, IL, Loperto, Arianna Scala, AS, Scala, Teresa Angela Trunfio, TAT, Trunfio, Andrea Lombardi, AL, Lombardi, Anna Borrelli, AB, Borrelli, Maria Triassi, MT, Triassi, Giovanni Improta, GI, Improta</i>	
Spatial Equity and Healthcare Access in the COVID-19 Pandemic	262
<i>Hiranya Sritart, Somchat Taertulakarn, Sakiko Kanbara, Hiroyuki Miyazaki</i>	
The Impact of CoViD-19 on the Hospital Activities: The Case of the Neurosurgery Department of “San Giovanni di Dio e Ruggi d’Aragona” University Hospital	267
<i>Arianna Scala, AS, Scala, Teresa Angela Trunfio, TAT, Trunfio, Ilaria Loperto IL, Loperto, Rossella Alfano, RA, Alfano, Andrea Lombardi, AL, Lombardi, Anna Borrelli, AB, Borrelli, Maria Triassi, MT, Triassi, Giovanni Improta, GI, Improta</i>	
Security Analysis of Authentication and Key Agreement for Internet of Drones	271
<i>Tian-Fu Lee, Wei-Jie Huang</i>	

•	<i>Session 9 – Public Health and Applied Statistics in Public Hygienics</i>	
	Study on the Care Burden and Influencing Factors of the Family Caregivers of Disabled Elders in Dalian	276
	<i>Chen Xu</i>	
	Analysis on the Influencing Factors of Adolescent Mental Health	280
	<i>Zibo Wang</i>	
	The Relationship between the Characteristics of Citizens and Healthcare with the Utilization of Health Services in Indonesia	287
	<i>Putri Permatasari, Pps, Cahya Arbitera, Dwi Mutia Wenny, Dmw</i>	
	Prevalence, Risk Factors and Outcomes of Labor Induction Among Women Delivered at Maternity Hospitals of Mongolia	295
	<i>Narantungalag Lkhagvasuren, Batjargal Enkh-Amgalan, Khaliun Bayaraa, Myagmartseren Bandi, Jargalsaikhan Badarch</i>	
	Anxiety, Depression, Insomnia and Stress during the COVID-19 Pandemic: Prevalence and Risk According to Associated Experiences in the General Population	300
	<i>Llerme Nuñez Zarazu, Nalda S. Nuñez Zarazu, Rosario M. Yslado Mendez, Edwin J. Asnate Salazar</i>	
	Are Africa on the Right Track to Prevent COVID-19? Reflections from African Business Magazine’s Coverage of the COVID-19 Pandemic	305
	<i>Huang, Kuo-Kuang</i>	
	Exploration Study on the Effects of Health Education and Public Awareness of COVID-19 Prevention- A Case Study to a Church-Affiliated Primary School in the Kampala, Uganda	309
	<i>Lee, Mu-Chen</i>	
	A Qualitative Approach for the Health Technology Assessment of IT Supported Type 2 Diabetes Management Tools	315
	<i>Giovanni Improta, GI, Improta, Maddalena Illario, MI, Illario, Vincenzo De Luca, VDL, De Luca, Giovanni Annuzzi, GA, Annuzzi, Guido Iaccarino, GI, Iaccarino, Maria Triassi, MI, Triassi</i>	
	Effects of Alcohol and Tobacco Abuse on Multi-Drug Resistant Tuberculosis Treatment Outcome, Mongolia	320
	<i>Dorjmaa Dashdavaa, Naranzul Dambaa, Baatarkhuu Oidov, Zuunnast Khishigsuren</i>	
	The Relationship Among Health and Wellbeing Program Attributes, Personal Lifestyle, and Purchase Intention on Podcast	325
	<i>Chi-Feng Lo, Hsu-Ju Teng, Lin Huang</i>	
	Author Index	330

Preface

We were so glad to announce that 2022 6th International Conference on Medical and Health Informatics (ICMHI 2022) was held successfully through the ZOOM Platform facilitating interactions among conference participants. It aims to provide a scientific platform and promote research in the field of Medical and Health Informatics, and to facilitate the exchange of new ideas and the establishment of research clusters in these fields among academicians, engineers, scientists and practitioners.

In addition to the contributed papers, internationally known experts from several countries are also invited to deliver speech at ICMHI 2022. The conference was highlighted by Keynote Speaker: Prof. Yu-Chuan Jack Li, Taipei Medical University, President of the International Medical Informatics Association. The speech title is 'AI for the Future of Healthcare'. Every participant learned and benefited a lot from the speech.

The proceeding tends to present to the readers the newest researches results and findings in the field of Medical and Health Informatics. The proceedings are organized in nine chapters under the topics of: Biomedical Image Processing and Data Analysis; Telemedicine and Healthcare Information System; Electronic Medical Record and Medical Data Processing; Machine Learning in Biomedicine and Computer Aided Diagnosis; Biomedical Electronics and Biological Signal Analysis; Medical Statistics and Modeling in Epidemic Forecasting; Bioinformatics and Biomedical Technology; Applied Computing in Hospital Management and Medical Resource Allocation; Public Health and Applied Statistics in Public Hygienics.

All papers were subjected to peer-review by conference committee members and international reviewers. The papers were selected based on high quality and relevance to the conference theme.

We would like to express our sincere appreciation to the organizing committee and the volunteers who had dedicated their time, effort and help in planning, promoting, and organizing the conference.



Prof. Chi-Chang Chang

Chung-Shan Medical University, Taiwan

ICMHI 2022 Conference Chair

September, 2022

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EFFECTS OF NIGELLA SATIVA ON FEMALE INFERTILITY: a SYSTEMATIC REVIEW

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ABSTRACT

Objective. Nigella sativa is a plant that contains a lot of antioxidants. Nigella sativa is an important medicinal herb that has been utilized for centuries. Given Nigella sativa efficacy in treating a variety of disorders, this systematic study attempts to assess Nigella sativa effect on the female reproductive system. **Materials and methods.** This systematic review was conducted on the Randomize Control Trial (RCT) through electronic databases such as Google Scholar, Science Direct, Pubmed, Scopus and Proquest from January 2012 to January 2022. The keywords or phrases used were Nigella sativa, Black Seeds, Black Cumin, Thymoquinone, Infertility, Women dan Female. **Results.** 14 articles were selected for analysis. The results showed that Nigella sativa and its constituent, Thymoquinone can reduce MDA levels, increase SOD, increase TAS, increase the number of ovarian follicles, and increase body weight. **Conclusion.** Nigella sativa can improve reproductive parameters in women.

CCS CONCEPTS

• General and reference; • Document types; • General conference proceedings;

KEYWORDS

Nigella sativa, Infertility, Female, Systematic Review

ACM Reference Format:

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1 INTRODUCTION

Infertility is defined as the failure to conceive between partners after 1 year of active sexual intercourse without contraception. Infertility is a health problem that affects about 10-15% of couples trying to achieve pregnancy worldwide [1], [2]. It is estimated that there are 48 million couples and 186 million people living with infertility globally. The World Health Organization (WHO)

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presented data that female infertility was the cause of infertility by 35% and men only contributed 8% as the cause of infertility in couples diagnosed as infertile [3]. Some of the causes of infertility are hormonal disorders, genetic disorders, nutritional problems and lifestyle.

Female infertility develops after lack of ovulation, obstruction of the fallopian tubes in low-quality mice, endometriosis and polycystic ovary syndrome (PCOS) [4]. There are many types of drugs for infertility, namely by consuming anti oxidants, nutritional supplements and herbal medicines. One of the herbal plants that are rich in natural antioxidants is Nigella sativa. Visually, Nigella sativa has flowers with 5-10 petals that are white, yellow, pink, pale blue or pale purple. The fruit is a large capsule consisting of 3-7 follicles and contains several seeds. The seeds of black cumin are small dicotyledonous, trigonous, angular, tubercular, black outside and white inside, aromatic smell with bitter taste [5, 6]. Nigella sativa and its derivative component, thymoquinone (TQ) have radical scavenging potential and the capacity to inhibit oxidative stress by increasing antioxidant production [7]. Nigella sativa is also known to have medicinal properties as an antidote, protecting against toxicity in several organs, including the brain, kidneys, lungs, liver, heart, digestive tract and reproductive system [8].

Previous studies have shown that Nigella sativa includes immunomodulatory, anti-inflammatory, antimicrobial, and anti-oxidant drugs. Nigella sativa has not shown any serious complications in clinical trials and has not shown any toxic effects in animals. Nevertheless, the review is limited to studies on the effects of black cumin on female reproduction. Therefore the aim of this study was to evaluate the role of nigella sativa in female infertility.

2 MATERIAL AND METHODS

This systematic review was carried out by searching from various database, like Google Scholar, Science Direct, Pubmed, Scopus and Proquest from January 2012 to January 2022. The Search was limited to relevant keywords or phrases, "Nigella sativa" or "Black cumin" or Thymoquinone and Infertility and Women or female. The largest search for articles in English.

The study design was limited to RCTs because it was the gold standard for experimental studies to prove causality. Case reports, review articles, abstract at symposiums and congresses were excluded. All article that met the inclusion criteria were included study. Duplications were also checked and unrelated articles were excluded (Figure 1). For each study, the data taken were the subject,

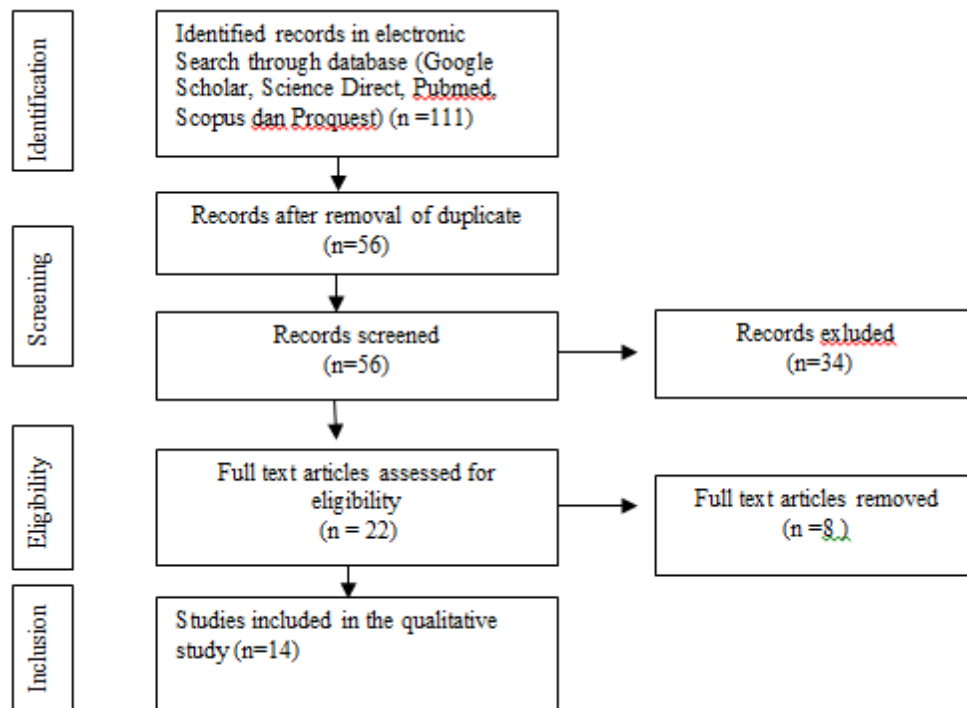


Figure 1: PRISMA Flow Chart

sample size, study design, type of *Nigella sativa*, dose and research results.

The characteristics of include studies are summarized in table 1.

3 RESULT

Our systematic review conducted from 14 RCTs, Article using the same method are categorized in the same group, we use studies relevant to the inclusion criteria in the results and discussion.

Study in human:

From the 14 articles selected, one study evaluated the effects of *Nigella sativa* in women. Islam M. Ammar, et al., showed that administration of a combination of metformin 500 mg and thymoquinone in *Nigella sativa* oil 500 mg three times daily for 6 months in PCOS patients can reduce the number of patients experiencing amenorrhea or oligomenorrhea, significant weight loss, increased SOD activity and decreased MDA levels [9].

Animal studies:

According to a study from Kamarzaman, et al., administration of 0,2 ml, 0,5 ml and 1,0 ml/100g of *Nigella sativa* oil for 5 days to mice injected with cyclophosphamide resulted in normal primary and secondary follicle counts including increased ovarians diameter. In this study, *Nigella sativa* was shown as a prophylactic property in the reproductive system of female mice [4].

The study conducted by Mohammed arif, et al. Thymoquinone treatment 2 mg/200 ml olive oil can suppress NF-k core B translocation, COX2 expression, and ROS in PCO mice. In addition, TQ administration led to significant restoration of molecular normality of the ovaries, such as decreased cysts, increased ovulation rate,

and normalization of key ovarian factors such as TNF- α , matrix metalloproteinase, COX2, during follicular maturation [10].

Noreen Anwar, et al. conducted an experiment to investigate *Nigella sativa* at doses of 1 and 4 mg/Kg BW in PCOS mice showed that there was a decrease in the number of cystic follicles [11].

According to Melahat and Zeyneb's study, administration of *Nigella sativa* 2 ml/Kg before laparotomy and 2 ml/Kg 1 hour after laparotomy showed an increased antioxidant status in the group 1 hour after laparotomy [12].

Pakdel, et al. showed that the administration of *Nigella sativa* at doses of 100 mg/kg, 200 mg/kg, 400 mg/kg in hypothyroidism rats could increase prolactin levels in the 400 mg/kg group [13]. According to research by Sima T, et al., Treatment with thymoquinone 8 and 16 mg/kg for 30 days in PCOS model mice showed an increase in body weight, ovarian morphology, and ovulation. In addition, this study showed improvements in serum biochemical parameters such as glucose, triglycerides, total cholesterol, lipoprotein, LH and FSH [14].

Fatemeh, et al. concluded that the administration of NSE at doses of 0,1; 50 and 100 g/ml in culture media showed higher rates of maturation, fertilization and blastocyst formation in the 50 g/ml treatment. Furthermore, oocytes at 50 g/ml treatment showed up-regulation of mRNA expression in epigenetic-related genes, and down regulation of cyclooxygenase mRNA expression [15].

Based on the results obtained in the study of Khani, et al. administration of NS doses of 50, 100, 200 mg/kg for 30 days in PCOS model rats showed a decrease in LH, testosterone, glucose, insulin resistance, and MDA levels in the 200 mg/kg treatment. In addition,

Table 1: Characteristics of include studies

Author /Year	Sampel	Intervention	Dose	Results
Human				
Islam M Ammar, et al. (2021) (9)	207 PCOS patient	NSO	1500 mg/day + metformin for 6 month	Decreased amenorrhea, decreased body weight, increased SOD, and decreased MDA
Animal's				
Kamarzaman, et al. (2014) (4)	48 Mice cyclophosphamide	NSO intraperitoneal	0.2, 0.5 and 1ml/100g	Increase in primary, secondary follicles and ovarian diameter
Mohammed Arif, et al. (2016) (10)	Rats Wistar PCOS	TQ sub cutan	2mg / 200ml olive oil	TQ suppresses NF-k, COX2, and ROS
Noreen Anwar, et al. (2016)(11)	40 Mice BALB/c PCOS	NS	1 mg and 4 mg/ KgBW	Decreased number of cystic follicles
Melahat dan Zeynab (2017) (12)	48 Rats Wistar iskemia reperfusi	NSO	2 ml/kg before laparotomy and 2 ml/kg 1 hour after laparotomy	Antioxidant status in the 2 ml/kg 1 hour after laparotomy group increased
Roghayeh Pakdel, et al.(2017) (13)	70 Rats hipotiroidesme	NS	100 mg/kg, 200 mg/kg, 400 mg/kg	The results of T4 increased, the weight of the mice increased,
Sima T, et al. (2018) (14)	30 Rats PCOS	TQ	8 and 16 mg/kg for 30 days	TQ improves ovarian function and ovulation in mice
Seflek, et al. (2019) (2)	21 Rats DM	NSO	0,2 mg/Kg/hari for 4 weeks	NS reduces hyperglycemia, lowers TOS and MDA, increases TAS and SOD
Fatemeh Eini, et al. (2020) (15)	40 Rats PCOS	NSE	0, 1, 50 dan 100 µg/ml	Doses of 50 g/ml increase oocyte maturation, GSH concentration, GPx and epigenetic modification
Kaabi A, et al. (2020) (16)	Sheep	NSO	5%, 10%, dan 20% cultured for 24 hours	Sheep oocyte maturation rate was better at 5% NSO
Seiyedah N Naseran, et al. (2020)(17)	40 Rats PCOS	NS	300 mg/kg + honey 1200 mg/kg and 600 mg/kg + honey 2400 mg/kg for 28 days	Decrease in LH, estrogen and testosterone. Increased progesterone at the combined dose of NS and honey
Samira Khani, et al. (2021)(18)	36 Rats Wistar PCOS	NS	50, 100, 200 mg/kg for 30 days	LH, testosterone, glucose, insulin, and MDA decreased at a dose of 200 mg/kg, NS improved the structure of ovarian tissue
Khairani Sukatendel, et al. (2021)(19)	32 Rats Cisplatin chemoterapy	NS	500 mg/KgBW and 1000 mg/KgBW for 2 weeks	The highest number of primary, secondary and tertiary follicles was in the 500 and 1000 mg/KgBW .
Afrina Mustari, et al. (2022)(20)	80 male and female mice	NSO	0.5 ml/kg for 16 weeks	Males: increased testosterone Females: increased number of follicles

Nigella sativa has a role in improving the structure of ovarian tissue [18].

Study of Sukatendel, et al., administration of Nigella sativa 500mg/KgBW and 1000 mg/KgBW for 2 weeks to rats exposed to Cisplatin chemotherapy showed the highest number of primary, secondary and tertiary follicles in the 500 and 1000 mg/KgBW groups and the lowest number of atretic follicles in the 1000 mg/KgBW group [19].

4 DISCUSSION

The RCTs on the efficacy of Nigella sativa on female infertility are the focus of our systematic review. Beginning in 2012, we decided to conduct a systematic review. This paper examines 14 studies that looked at the impact of Nigella sativa on female infertility. It should be noted that the most relevant articles are found in the results section. Most studies report no negative effects from giving Nigella sativa.

Nigella sativa's mechanism of action in infertility has been widely reported in various studies, including as a bronchodilator,

gastroprotective, hepatoprotective, anti-tumor, anti-diabetic, anti-hypertensive, antioxidant, antifungal, immunomodulatory, anti-inflammatory, analgesic, antiviral, antipyretic, contraceptive, and anti-inflammatory. antibacterial, anticonvulsant, antitussive, anti-cancer, and antihyperlipidemic [6, 21, 22].

Polycystic ovary syndrome has received a lot of attention recently because it affects women of childbearing age and is a common cause of infertility [23]. The only effective drug for PCOS is metformin [24]. It is an insulin sensitivity drug that reduces weight and has an effect on increasing ovulation and fertility [25]. In the sima study, investigated the therapeutic effect of thymoquinone in rat model PCOS. Similar results to metformin were found in thymoquinone-treated animals. Thymoquinone is a bioactive ingredient in *Nigella sativa* that has potential therapeutic properties. Polycystic ovarian syndrome is characterized by persistent inflammation. As a result, thymoquinone's therapeutic efficacy in PCOS may be attributable to its anti-inflammatory effects [14]

Oxidative stress is a persistent imbalance between ROS and RNS exposure that exceeds antioxidants [26]. Endometriosis, tubal factor infertility, and polycystic ovary syndrome are all caused by oxidative stress [27]. Seflek et al. discovered antioxidant capabilities in a rat model of diabetes mellitus by reducing serum TOS and MDA levels while raising SOD and TAS levels [2]. Furthermore, *Nigella sativa*'s antioxidant properties prevent oxidative stress and ovarian follicle damage [23].

Nigella sativa causes weight gain in hypothyroidism patients. The results of Niki, et al. on the effect of *Nigella sativa* oil on weight gain in hypothyroid rats [23]. More than 100 distinct chemicals have been discovered in *Nigella sativa* and have been reported in several studies to have antioxidant benefits, renal protection, and increased pancreatic insulin secretion. This impact could be responsible for the rise in body weight in *Nigella sativa*-treated hypothyroid rats, specifically the increase in insulin secretion [28].

5 CONCLUSION

Nigella sativa and its constituent, Thymoquinone can decrease MDA levels, increase SOD, increase TAS, increase ovarian follicle count, and increase body weight in animal studies. The antioxidant capabilities of *Nigella sativa* in radical scavenging are the most likely mechanism. Although the findings of this systematic review indicate that *Nigella sativa* is a good candidate for female infertility, there is still insufficient evidence to recommend the use of *Nigella sativa* as adjunctive therapy in infertile women. It is recommended to conduct further RCTs on the positive effects of clinical trials of *Nigella sativa* in the management of infertile women.

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