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The Impact of Curcumin on Embryonic Development: Insights From a Systematic Literature Review

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A B S T R A C T

Curcumin, a polyphenol compound extracted from turmeric (Curcuma longa), has been widely known for its anti-inflammatory, antioxidant, and therapeutic properties. This study aims to investigate the impact of curcumin on embryonic development, which is an important aspect of developmental biology and reproductive health. This study uses a type of literature review. The researcher used the Science Direct database, and the PubMed and Scopus data taken. This study took the source from articles published from 2015 to 2024. Search the database by entering the keywords "Curcumin" and "Embryogenesis". The criteria to be used as samples based on the PICOS criteria are as follows: Population: Embryogenesis, Human, Female, Rat, Mice, Fish. Outcome: Improved embryonic development, protection of cells from oxidation and inflammation. Four selected articles that have met the inclusion criteria. Findings suggest that curcumin at low doses (1-5 µM) can increase cell proliferation and support healthy embryo development. However, at high doses (more than 10 µM), curcumin actually causes an increased incidence of malformations and developmental disorders, which are characterized by changes in morphology and decreased embryonic viability. Histological analysis showed tissue damage in embryos exposed to high doses of curcumin. These results suggest that curcumin has a biphasic effect on embryonic development, where proper dosage can provide benefits, while overdose can be detrimental. This study highlights the importance of a deeper understanding of the dosage and timing of curcumin administration in the context of therapy and supplementation, especially in pregnant women. This study provides new insights into the impact of curcumin on embryonic development, emphasizing the need for further research to explore the therapeutic potential and risks associated with curcumin use in the context of reproductive health

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INTRODUCTION

Curcumin, the main active compound in turmeric (Curcuma longa), is known to have strong antioxidant and anti-inflammatory properties, so it has the potential to prevent diseases associated with oxidative stress such as congenital heart defects (CHD) and neural tube defects (NTDs). Curcumin works by neutralizing free radicals, increasing the activity of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx), as well as inhibiting inflammatory pathways such as NF-κB. Studies show that curcumin can prevent LDL oxidation, improve endothelial function, and protect embryos from oxidative damage, making them potential therapeutic candidates for preventing CHD and NTDs.

Based on surveillance data conducted by the Ministry of Health, the prevalence of NTDs reaches around 260,000 babies worldwide with a global prevalence of 18.6 per 10,000 births. NTD cases are prevalent in Southeast Asia In Indonesia, the prevalence of NTDs contributes to neonatal mortality, with congenital abnormalities overall causing 21.4% of neonatal deaths in Indonesia. This is one of the main causes of congenital disorders in babies. Some common types of NTDs include: Spina bifida, Anencephali, Encephalocele. This is associated with socioeconomic status and lack of folic acid supplementation.

LITERATURE RIVIEW

Neural Tube Defects (NTDs) cause serious impacts in the form of infant mortality and significant long-term disability. The causes are often genetic and environmental factors, such as genetic mutations and exposure to harmful toxins, including alcohol and cigarette smoke. Folic acid supplementation before and during pregnancy may significantly reduce the risk of NTDs (Rogers et al., 2018).

Research shows that curcumin can modulate the homocysteine metabolic pathway, thereby reducing the risk of birth defects associated with folate deficiency (Imbard et al., 2013). In addition, curcumin can also affect the neurulation process, which is a critical stage in embryonic development that can be affected by environmental and genetic factors. Research shows that curcumin can reduce oxidative stress, which is one of the factors that contribute to the occurrence of NTDs (Greene et al., 2017). Oxidative stress can interfere with the normal process of neural tube formation, thereby increasing the risk of birth defects (Greene et al., 2017). By reducing oxidative stress, curcumin can help support healthy neurulation processes.

Congenital Heart Disease (CHD) is one of the leading causes of morbidity and mortality in infants worldwide, posing a major challenge for global health system (Lee, W. (2013) (Wong, E., et.al 2022). This condition not only impacts the patient's physical health, but also affects the family emotionally, socially, and financially. Interventions such as nurse-led support programs through mobile apps, have shown effectiveness in improving healthy living habits, such as exercising, and helping to control lipid levels in at-risk patients. This strategy has the potential to reduce the long-term impact of CHD through better prevention and management. (Wong, E., et.al 2022)

Oxidative stress, caused by an imbalance between the production of free radicals and the body's antioxidant capacity, plays an important role in the pathogenesis of CHD through the mechanisms of LDL oxidation, endothelial dysfunction, inflammation, and atherosclerotic plaque formation. In NTDs, oxidative stress can interfere with the development of the embryo's neural tubes through damage to DNA and cellular proteins, as well as disruption of folate metabolism which is important for cell division and differentiation. Thus, the use of curcumin as a protective agent against oxidative stress can be a strategy that supports cardiovascular health and fetal development.

METHODOLOGY

This study uses a type of literature study research or literature review with the Traditional Review method. Literature review or literature review itself is search and research by reading various books, journals and other publications related to research topics so as to produce articles that are relevant to certain topics or questions. In this secondary data collection, the researcher used the Science Direct database, and the PubMed and Scopus data taken were articles relevant to the title of the research taken, this study took the source from articles published from 2015 to 2024. Search the database by entering the keywords "Curcumin" and "Embryogenesis". The samples in this entire article were obtained using the purposive sampling technique. Purposive sampling is a technique for determining samples with certain considerations. The criteria to be used as samples based on the PICOS criteria are as follows: Population: Embryogenesis, Human, Female, Rat, Mice, Fish. Outcome: Improved embryonic development, protection of cells from oxidation and inflammation. Side effects: Risk of toxicity, organ damage (e.g. liver), and risk of miscarriage. Study Design: Quantitative research, original research, and publication 10 years using articles between 2015-2024 in Indonesian or English. After passing the protocol stage to data extraction, the author will conduct data analysis on 4 selected articles that have met the inclusion criteria.

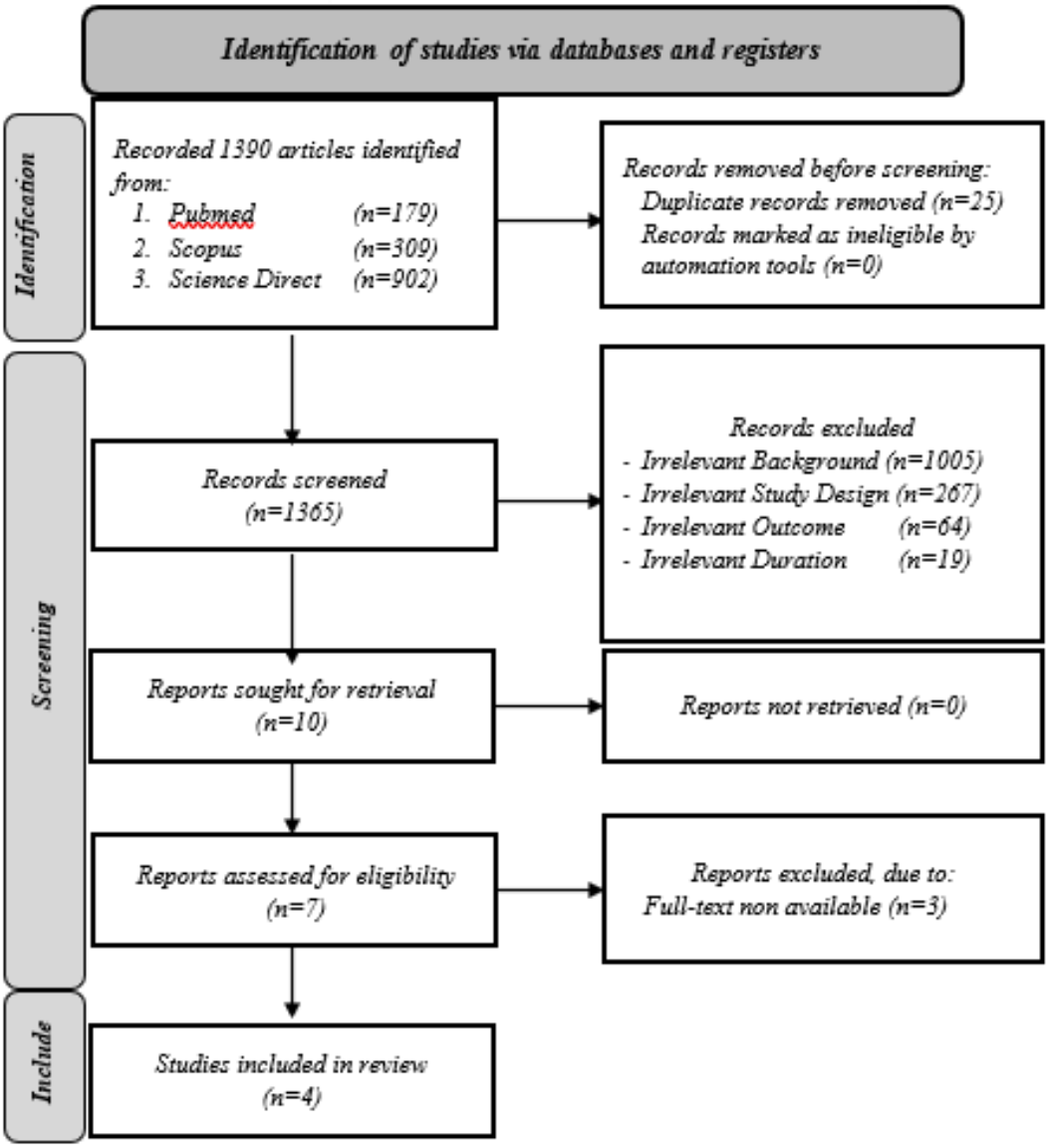

Figure 1. Prism Diagram

Literature searches were conducted through four electronic research databases, namely: Pubmed, SCOPUS, and Science Direct. From the search results through the e-database, 1390 keyword searches were obtained. The researcher screened for the removal of duplicates for 25 articles. Furthermore, the researcher conducted a screening based on titles and abstracts, and 1365 excluded articles consisted of 1005 inappropriate article backgrounds, 267 articles using irrelevant study design, 64 articles that did not describe outcomes in the form of increased embryonic development, cell protection from oxidation and inflammation, 19 articles that were outside the time duration of the inclusion criteria. A total of 10 articles that were thoroughly reviewed (full text screening) were obtained, 3 articles could not be accessed in full text, so that the total results of 4 articles were in accordance with the inclusion and exclusion criteria for the literature study in this study.

RESULT

Table 1.Research Results

Yes	Researcher, Year of Publication	Article Title	Source of the article (name of the journal)	Research Objectives	Research Methods (Design, Population, Sample, Research Site, Variables, Instruments, Analysis)
1	**Researcher** Abdullah, S.N.S., Subramaniam, K.A., Muhamad Zamani, Z.H., Sarchio, S.N.E.,Md Yasin, F., and Shamsi, S. **Year** 2022	Biocompatibility Study or Curcumin-Loaded Pluronic F127 Nanoformulation (NanoCUR) against the Embryonic Development of Zebrafish (Danio rerio)	**Name Journal** MDPI (Multidisciplinary Digital Publishing Institute), Basel, Switzerland, Volume 27 and 14 **Number p-ISSN**: 1420- 3049 **e-ISSN**:1420-3049	Investigating the effects toxicity of NanoCUR (curcumin nanoformulation that Loaded deep Pluronic F127) on the embryonic development of zebrafish (Danio rerio).	**Research Design** Experimental Research quantitative approach **Population** Zebrafish embryo (Danio rerio) **Sample** Zebrafish embryos exposed at various concentrations of NanoCUR, native NUR, and Pluronic F127 **Sampling Techniques** *Purposive Sampling* **Place & Time of Research** Laboratory of Animal Biochemistry and Biotechnology, Department of Biochemistry, Faculty of Biotechnology and Biomolecular Sciences, Universiti Putra Malaysia **Research Variables** Concentrations of NanoCUR, native TUR, and Pluronic F127, Survival rate, hatching rate, heart rate, morphological abnormalities, and ROS generation in zebrafish embryos **Data Collection Instruments** Observations using DLS (Dynamic Light Scattering), UV-Vis Spectrophotometer, FTIR (Fourier Transform Infrared), FESEM (Field Emission Scanning Electron Microscopy), XRD (X-Ray

					Diffraction), Microscopic observation for embryo development parameters, ROS assay **Data Analysis** Data were analyzed using two-way ANOVA and one-way ANOVA with a significance value of p≤0.05. Data are presented as mean SD ± from at least three experiments independent.
2	**Researchers** Chunlan Liu, Fan. Yang, Jingyu Wang, Renfei Zhu, Jiansheng Zhu, Mingtao Huang **Year** 2024	Myclobutanil induces cardiotoxicity in developing zebrafish larvae by initiating oxidative stress and apoptosis: The protective role of curcumin	**Name Journal** Ecotoxicology and Environmental Safety **Number** ISSN : 0147-6513	Uncovering the cardio toxicity of MYC and mechanism underlying issues, and effect Cardioprotective curcumin using a zebrafish model.	**Research Design** Research Experimental Laboratory Study with a quantitative approach **Population** Zebrafish adult wild-type AB Line and MYL7:EGFP Transgenic Line (5 months of age) **Sample** 50 healthy embryos per group **Purposive Sampling Technique Research Place** Performed in several institutions in China: Jiangsu Health Vocational College Nantong Hospital or Shanghai University, Women's Hospital of Nanjing Medical University, Nantong Third People's Hospital, Nanjing University of Chinese Medicine **Research Variables** Exposure to MYC and CUR, Cardiotoxicity, oxidative stress, and apoptosis **Data Collection Instruments** Observation using data from Stereomicroscope, EthoVision®XT system, ELISHA Kits Fluorescence

					microscope, Nanodrop spectrophotometer, qPCR analysis **Data Analysis** Using a one-way analysis of variance with Student-Newman-Cologne Post-hoc Test using SPSS 25.0
3	Pooja Muralidharan Researcher, Craig Connors, Arooj S. Mohammed, Swapnalee Sarmah, Kathleen Marrs, James A. Marrs, and Grady W. Chism **Year** 2017	Turmeric extract rescues ethanol-induced developmental defect in The Zebrafish Model for Fetal Alcohol Spectrum FASD disorder	**ournal Name of the** Journal of Food Science **Number** DOI: 10.1111/1750-3841.13830	Determine Effects of the Extract turmeric in saving developmental defects Induced Ethanol Using zebrafish as a model.	**Research Design** Research Experimental Laboratory Study with a quantitative approach **Population** Zebrafish (Hamilton TL strain) **Sample** Treated zebrafish embryos **Sampling Technique** *Purposive Sampling* **Research Place** Department of Biology, Indiana University-Purdue University Indianapolis, Indianapolis IN 46202 **Research Variables** turmeric and ethanol extracts, Zebrafish embryonic development (body length and morphology) **Data Collection Instruments** Observation using UPLC (Ultra Performance Liquid Chromatography), Brightfield dissection microscope with Leica DFC450C camera, Image J Software for body length measurement **Data Analysis** Using a one-way ANOVA *statistical test* followed by a post hoc LSD test with a significance level of 5%

DISCUSSION

Toxic/Negative Impact Group

Impact of Reduced Survival

Based on research on curcumin biocompatibility, it was found that high concentrations of curcumin (starting from 10 µM) led to a significant decrease in the embryo survival rate of zebrafish (Abdullah et al., 2022). These toxic effects are not immediately noticeable at the beginning of exposure, but they worsen over time. This decrease in survival suggests that there is a safe concentration threshold for the use of curcumin in embryonic development. These findings are critical for dosage considerations in the therapeutic application of curcumin. This

also indicates the need to develop formulations that can reduce the toxicity of curcumin without reducing its effectiveness.

Impact of Embryonic Malformations

Exposure to 10 µM curcumin at 72 hpf and 96 hpf resulted in malformations characterized by the formation of yolk sac edema and scoliosis in zebrafish embryos (Abdullah et al., 2022). Interestingly, despite malformations, the incidence showed no statistical significance compared to controls. This is due to the high mortality rate and morbidity of embryos exposed to curcumin for a long time. These findings suggest that the toxic effects of curcumin not only affect survival but can also interfere with the normal development of the embryo. These observations reinforce the importance of optimizing dosage and exposure time in curcumin use.

Impact Group on ROS/Oxidative Stress

ROS Production Impact

In biocompatibility studies, curcumin showed higher levels of ROS generation compared to nano-fourmlation (NanoCUR) (Abdullah et al., 2022). Reactive Oxygen Species (ROS) has been reported as one of the main factors contributing to toxicity nanoparticles. Excessive production of ROS can cause damage to proteins, DNA, and lipid composition, ultimately resulting in cell death. Higher ROS production levels in free curcumin correlated with the toxicity response observed in zebrafish toxicity assessments. These findings suggest that modification of curcumin formulations, such as in nano form, may be a strategy to reduce the toxic effects mediated by ROS.

Protective/Positive Impact Group

Protective Impact on Oxidative Stress

Curcumin shows significant ability in reducing the excess ROS production induced by myclobutanil (MYC) (Liu et al., 2024). These effects include decreased SOD and CAT activity, as well as decreased regulation of sod1 and cat genes. Curcumin's ability to reduce oxidative stress plays an important role in preventing cell damage. This protective effect demonstrates curcumin's potential as an antioxidant agent in the context of chemical-induced toxicity. These findings open up the possibility of using curcumin as a protective agent in case of exposure to environmental toxins.

Protective Impact on Apoptosis

Curcumin has been shown to be effective in reducing MYC-induced cardiomyocyte apoptosis and is able to reverse increased expression of apoptosis genes (Liu et al., 2024). This anti-apoptosis effect shows the protective role of curcumin in preventing programmed cell death. This ability is especially important in the context of embryonic development, where uncontrolled cell death can disrupt normal development. This protective effect also shows the therapeutic potential of curcumin in preventing tissue damage from toxins.

Protective Impact on Growth Disorders: In the context of ethanol-induced toxicity, the administration of curcumin (1.74 µM) along with ethanol (100 mM) resulted in an embryonic body length that did not differ significantly from (Muralidharan et al., 2017). These findings are particularly important because they demonstrate curcumin's ability to prevent ethanol-induced growth

disorders. Treatment with curcumin also successfully restored gene expression and reduced cell death.

Bioavailability and Distribution

Curcumin exhibits pharmacokinetic characteristics that limit its effectiveness as a therapeutic agent. Poor solubility in water is a major obstacle in the systemic bioavailability of curcumin. Curcumin molecules undergo a very fast metabolism and are easily degraded at neutral or alkaline pH (pH ≥7), resulting in a short half-life in biological systems. Low absorption in the digestive tract further exacerbates this bioavailability problem. These limitations have led to limited applications of curcumin for medical purposes, despite its promising therapeutic potential (Abdullah et al., 2022).

Interaction with Biological Membranes

Curcumin has the ability to interact with biological membranes, which in the context of embryos can have a dual effect. At certain concentrations (10 µM), curcumin can weaken the protective layer of the embryo, resulting in increased membrane permeability. This increased permeability leads to an increase in the entry of curcumin into the embryo. This effect indicates the presence of time-dependent toxicity, where longer exposure can cause malformations in the embryo. This interaction demonstrates the importance of proper dosage regulation in the use of curcumin for therapeutic applications in embryos (Abdullah et al., 2022).

Transcription Regulation

Curcumin has an important role in the regulation of gene transcription through various molecular mechanisms. In the context of embryonic development, curcumin can increase the expression of genes related to growth and the immune system. The key mechanism identified is curcumin's ability to induce nuclear translocation of the transcription factor Nrf-2, which further activates the expression of phase II antioxidant genes. Curcumin also has the ability to restore normal gene expression regulation that is impaired due to exposure to toxins. This transcriptional regulatory effect contributes to improved growth performance and immunity in offspring early in life (Gong et al., 2023).

Antioxidants and Cellular Protection

Curcumin exhibits strong antioxidant activity through several molecular mechanisms. Directly, curcumin can ward off reactive oxygen species (ROS) and inhibit their accumulation in cells. In the case of Myclobutanil (MYC)-induced toxicity, curcumin significantly reduces the oxidative stress that occurs. Excessive production of ROS can cause damage to proteins, DNA, and lipid composition, leading to cell death, but curcumin can prevent this damage through its antioxidant activity. This protective effect is especially important in the context of embryonic development, where oxidative damage can have serious consequences on development (Liu et al., 2024).

Regulation of Cell Death

Curcumin has the ability to modulate programmed cell death pathways (apoptosis). In the context of MYC-induced cardiotoxicity, curcumin exhibits the ability to inhibit apoptosis pathways in cardiomyocytes. Prevention of cell death mediated by oxidative stress is one of the important mechanisms in the protective

effects of curcumin. This regulation is important for maintaining cell viability during embryonic development. This ability also plays a role in preventing tissue damage due to exposure to toxins or other pathological conditions (Liu et al., 2024).

Development and Differentiation

Curcumin has an important role in supporting the development and differentiation of normal cells during embryogenesis. In the context of the heart, curcumin Protects heart cell function by preventing oxidative damage and apoptosis. In zebrafish models exposed to ethanol, curcumin was able to maintain normal morphological development by preventing the toxic effects of ethanol. These protective effects include the maintenance of normal body length and the prevention of developmental malformations. This mechanism demonstrates the potential of curcumin as a therapeutic agent in embryonic development disorders such as Fetal Alcohol Spectrum Disorder (FASD) (Liu et al., 2024).Antioxidant Group

The antioxidant potential is mainly demonstrated by the nanoformulation of curcumin (NanoCUR) and turmeric extract which works through several different mechanisms. NanoCUR has been shown to produce lower levels of Reactive Oxygen Species (ROS) compared to regular curcumin, demonstrating its effectiveness in reducing oxidative stress in embryos. Turmeric extract works through increased Nrf-2 nuclear translocation in the liver and lungs, which is a key transcription factor in the regulation of cellular antioxidant responses. This mechanism is complemented by turmeric extract's ability to induce phase II antioxidant gene expression, providing dual protection against oxidative stress. Previous research has also reported that curcumin has a variety of pharmacological properties, including anti-inflammatory and antioxidant properties that support its role in protection (Abdullah et al., 2022).

Drug Delivery System Group

The drug delivery system developed using curcumin nanoformulations with Pluronic F127 shows significant advantages in pharmacokinetic aspects. The system is able to retain up to 95.8% curcumin after 3 months of storage, much better compared to encapsulation using Pluronic F68 which only retains 79.57% curcumin in the same period. The slow and sustained release of curcumin from NanoCUR provides a therapeutic advantage as it can maintain drug concentrations in a longer therapeutic range. This delivery system also successfully reduces the toxicity of curcumin, making it safer for drug delivery applications. These controlled release characteristics make NanoCUR a promising platform for the development of targeted drug delivery systems for embryos (Abdullah et al., 2022).

Organ Protection Group

The organ protection provided by curcumin and turmeric extract shows a significant effect in protecting embryo development from various toxic threats. Curcumin has been shown to be effective in reducing myclobutanil induced cardiotoxicity through its antioxidant properties and its ability to restore normal levels of apoptosis. Turmeric extract demonstrated the ability to restore embryonic body length impaired by ethanol exposure, providing new insights into the mechanisms underlying FASD and potential approaches for damage

recovery. This protective effect is supported by curcumin's ability to regulate important cellular processes such as apoptosis and oxidative stress. This discovery opens up new avenues for the development of therapeutic strategies in addressing toxicity in embryos (Liu et al., 2024).

Digestive System Development Group

The development of the embryo's digestive system is greatly influenced by microbial transfer and maternal immunity. Microbiota analysis showed that maternal microbes are transferred to the embryo's gut from the magnum to the egg white, affecting the early development of the digestive system. This transfer resulted in significant increases in villi height in the duodenum, jejunum, and ileum of the embryo at stages E15, E17, E19, E20, and E21 compared to the control group. Transcriptome analysis revealed that the shift of the embryo's intestinal transcriptome is related to development and immunity. This process involves the expression of innate immune factors such as LYZ and AvBDs, ovoinhibitors, and the significantly increased FcRL4 gene in the magnum. These findings demonstrate the importance of the interaction between the maternal immune system and the development of the embryo's digestive system (Gong et al., 2023).

Immune System Group

Maternal immunity transfer provides critical protection for embryonic development through complex vertical transfer mechanisms. Immunoglobulins are transferred from the mother to the yolk and egg whites in amounts proportional to the concentration of maternal serum, transported via Fcγ receptors. Research shows that immune factors are transferred vertically to the egg from the mother's reproductive system in a manner that depends on the maternal level to provide protection for embryonic development. The expression of innate immune factors and heavy immunoglobulin deposits into the follicles during vitelogenesis indicate the presence of a well-organized immune transfer system. This system ensures the embryo receives adequate immune protection during its critical developmental stage. This discovery emphasizes the importance of maternal immune health in supporting optimal embryonic development (Gong et al., 2023).

Security Group

The safety aspects of curcumin nanoformulations show significant progress in the development of embryo-safe drug delivery systems. NanoCUR successfully reduced curcumin toxicity in embryos, which is evidenced by lower ROS levels compared to curcumin without formulations. The controlled and sustained release characteristics of NanoCUR not only improve its effectiveness but also its safety profile. The high retention rate (95.8% after 3 months) indicates good formulation stability, which is important for long-term safety. The results of this study support the use of NanoCUR as a safe drug delivery system for embryonic development applications. Toxicological evaluation in zebrafish embryos confirmed a better safety profile compared to conventional curcumin (Abdullah et al., 2022).

CONCLUSIONS AND RECOMMENDATIONS

The use of NanoCUR provides a potential solution to overcome the limitations of conventional NUR, such as low solubility, poor bioavailability, and high toxicity. In clinical development, NanoCUR offers a more biocompatible approach to therapeutic applications, including the treatment of diseases involving oxidative stress. This study shows that NanoCUR is a safer and more effective formulation than conventional GUR, especially for nanotechnology-based therapeutic applications. This opens up opportunities for its use in nanoparticle-based treatments with minimal toxicity.

The cardiotoxicity of MYC in zebrafish embryos results from excessive oxidative stress and apoptosis. Curcumin, with its antioxidant properties, manages to reduce these toxic effects, repair structural and functional damage to the heart, as well as restore the expression of affected genes. This discovery shows the potential Curcumin as a protective therapy to overcome environmental toxicity in the embryonic cardiovascular system.

Curcumin has great potential as a therapeutic agent in supporting embryonic development and protecting against various toxic threats. However, the effects are highly dependent on the dosage and formulation used. In high doses, curcumin can be toxic, whereas at low doses, curcumin shows significant protective effects. The use of curcumin in medical applications requires a careful approach to optimize its therapeutic benefits while minimizing the risk of toxicity. The combination of nanoformulation technology and in-depth research into the molecular mechanisms of curcumin offers promising prospects for the development of safer and more effective therapeutic agents.

FUTURE STUDY

This research still has limitations so further research is needed related to the topic of The Impact of Curcumin on Embryonic Development: Insights From a Systematic Literature Review to perfect this research and increase insight for readers.

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