

# Histopathological change of pancreas in hyperglycaemic wistar rats with nano extract of *Coriandrum sativum* L (ketumbar seeds) consumption



Sri Wahjuni<sup>1\*</sup>, Ida Ayu Raka Astitiasih<sup>1</sup>,  
Ni Made Puspawati<sup>1</sup>, Mustika Lahaya<sup>1</sup>

## ABSTRACT

**Introduction:** *Coriandrum sativum* L (ketumbar seeds) nano extract was prepared using chitosan as a nano extract framework and tripolyphosphate as a stabilizer by ionic gelatin method. This study aimed to reduce free radicals in streptozotocin-induced hyperglycaemic rats by administering *Coriandrum sativum* L nano extract as nano herbal

**Methods:** The surface topography of nano extract and characterization of zeta potential particle size was carried out using PSA (Particle Size Analyser). The ability of nano extract as anti-hyperglycaemic on streptozotocin-induced rats was tested using the randomized post-test only control group design.

**Results:** The result of the antihyperglycemic test on streptozotocin-induced rats showed that oral administration of the nano extract at a dose of 50 mg/Kg BW/day gave the best result for decreasing glucose blood, and MDA and increasing SOD levels in hyperglycaemic rats. The characterization of nano extract using PSA showed change here had been an encapsulation of bioactive substances from *Coriandrum sativum* L extract on the chitosan-tripolyphosphate absorption of NH, PO groups, and change histopathology pancreas of hyperglycaemic wistar rats. Characterization with PSA strongly supports nano extract as a delivery system for bioactive substances with a zeta potential of -25.80 mV and a particle size of 455.20 nm.

**Conclusion:** *Coriandrum sativum* L (ketumbar seeds) nano extract was prepared using chitosan had potential to reduce free radicals in streptozotocin-induced hyperglycaemic rats.

**Keywords:** *Coriandrum sativum* L, hyperglycaemic, nano extract, histopathology

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<sup>1</sup>Faculty of Mathematics and Natural Sciences, Udayana University, Bali, Indonesia

\*Corresponding to:  
Sri Wahjuni; Faculty of Mathematics and Natural Sciences, Udayana University, Bali, Indonesia; Email: sriwahjunimanuaba@unud.ac.id

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## INTRODUCTION

The times have influenced people's lifestyles and eating patterns gradually. Today's society tends to have a habit of consuming foods that are high in fat which can lead to a higher prevalence of degenerative diseases, one of which is diabetes mellitus.<sup>1</sup> Type 2 diabetes accounts for 96% of all cases of diabetes, and is characterized by insulin resistance and damage to the insulin-secreting cells of the pancreas. Hyperglycaemic is a chronic disorder of carbohydrate (glucose) metabolism in the body with characteristics of hyperglycaemic characterized by increased blood sugar level continuously and varies due to abnormalities in insulin secretion, insulin action, or both. Increased blood sugar

levels cause oxidative stress, this occurs due to as imbalance in the number of free radicals with the number of endogenous antioxidants produced by the body.<sup>2</sup> There are many types of free radicals most abundant in the body biological systems are reactive oxygen species (ROS). These free radical are result of the homolytic breakdown of the covalent bond of a molecular or the lone pair of electrons of an atom.<sup>3</sup>

Indonesia very rich in biodiversity containing antioxidant compounds and has been used to be consumed from generation to generation, both in the form of vegetable and fruits, which contain lots of phenolic and flavonoid compounds and have high antioxidant activity. Flavonoid compounds can capture ROS, Inhibit the

work of enzymes that produce ROS and form chelate with metals that stimulate the formation of ROS so that ROS reaction with normal cells such as lipid peroxidation and deoxyribonucleic acid (DNA) damage can be prevented or oxidative stress does not occur.<sup>4</sup> It is suspected that oxidative stress has an impact on the damage to acinar cells, thereby triggering autodigestive to the pancreas and continuing to pancreatic cell- $\beta$  necrosis.<sup>5</sup> Identification of the ethanolic extract of coriander seeds was carried out using Liquid Chromatography Mass Spectrometry (LC-MS/MS). The results of identification using LC-MS/MS produced several peaks of the chromatographic spectrum with different retention times. Coriander seed ethanol extract sample that had

been prepared by the SPE method using methanol eluent was injected into the LC-MS/MS instrument as much as 5 L using a micro syringe. The results obtained are in the form of a chromatogram which is then analyzed using the MassLynx application to interpret the chromatogram in order to determine the mass of the compound and predict the compounds contained in the spectra and similarities with the database. The molecular formula obtained was then checked for the structure and name of the compound on the website [www.chemspider.com](http://www.chemspider.com), so that it could predict the compounds contained in the ethanol extract of coriander seeds. The chromatogram of the ethanolic extract of coriander seeds was thought to contain three active compounds, namely apigenin, 2-flouren-9-ylidenemethyl-pyridine, and 5-Pentyl-1,3-benzenediol as antidiabetic.<sup>6</sup>

Nano material are solid colloidal particles containing macromolecular material and can be used a drug delivery agent whose active compounds have been dissolved, entangled and encapsulated.<sup>7</sup> Effort to deliver drugs using nano system cause drugs to spread more easily in the blood and give effect quickly.<sup>8</sup> The nanomaterial that is often used as a drug delivery agent is harmless to the human body is chitosan polymer.<sup>9</sup> Ionic crosslinked chitosan with tripolyphosphate showed a low degree of swelling. The cross-linked chitosan is also easy to adjust according to the desired function. Such as hydrophilicity, density, and crystallinity.<sup>10</sup> The ionic gelation method was also successfully used in the manufacture of the chloroform nano fraction of *Kaempferia rotunda* with chitosan and sodium tripolyphosphate. The result of the analysis of the particle size are between 172 to 877 nm with a zeta potential value between +28,06 mV to 38,03 mV.<sup>9</sup>

Based on the description above, the researcher conducted an analysis/testing of nano chitosan-tripolyphosphate-*Coriandrum sativum L* extract in lowering blood sugar levels.

## METHODS

### Tools and Materials

*Coriandrum sativum L* taken from Kumbasari market, Denpasar, Bali,

Indonesia. They were determined at the LIPI UPT Plant Conservation Centre of The Eka Karya Botanical Gardens, Bali. The following chemical were used 96% ethanol, distilled water, streptozotocin (Sigma Aldirch), chitosan-tripolyphosphate. Filter paper was also utilized. Male wistar rats 2-3 month-old and body weight averaging 150-200 gr were the experimental animals examined in this study.

The following instruments were used in this study, beaker, measuring cup, spatula, blender, glass jar, dropper, filter, measuring flask, funnel, porcelain cup, analytical balance, aluminium foil, water bath, sonde tool, gloves mask, desiccator, liquid chromatography with tandem mass spectrometry (LC-MS/MS) Xevo type G2TOF, rotary evaporator, particle size analyzer (PSA) and glucometer stick, MDA, SOD, and histopathology kit were used for microscopy with  $\times 100$  magnification micro technical method.

The sample of ethanol extract *Coriandrum sativum L* prepared through the SPE method with ethanol eluent was injected into the LCMS/MS instrument with a stationary phase/C18 column (Octadecyl silane) of as much as 5  $\mu$ L using a micro syringe. The results were presented in the form of a chromatogram, which was then analyzed using MassLynx v 4.1 to determine the mass of the compound obtained from each retention time. The structure and name of the compounds were checked on the website [www.chemspider.com](http://www.chemspider.com). One H atom was subtracted because it is separated by firing one proton ( $H^+$  during the separation in MS.

The results of the chromatogram in the figure show 11 peaks at different retention times, so there may be 11 types of compounds contained in the ethanol extract of coriander seeds. After analysis, only 7 peaks were identified. The results of the identification of *Coriandrum sativum L* extract ethanol using LC-MS/MS obtained a chromatogram with 7 peaks in retention time (3.991; 3.991; 7.703; 8.603; 8.664; 9.883; 10.815 minutes). Based on the results of the analysis on the applications <http://www.massbank.ip/> and <http://chemspider.com> the compounds were identified with high agreement with the data available on massbank and chemspider. The results

of LC-MS/MS identification of coriander seed ethanol extract based on the database showed the presence of phenylalanine, indole, 4-methoxybenzaldehyde, 2,5-dimethoxybenzaldehydde, apigenin, 2-floren-9-litemethylpyridine, and 5-pentyl-1,3-benzenediol.

In the database, the compound is suspected to be apigenin. The structure of the compound is shown in figure It is suspected that there is a compound Apigenin. Apigenin is a flavonoid derivative compound that is abundant in nature and is present in large amounts in various plants and fruits such as celery, onions, chamomile flowers, oranges, and tea leaves, and has potential as anticancer, anti-inflammatory, and antioxidant compounds with intrinsic toxicity.

### Ethanol Extract of *Coriandrum sativum L*

*Coriandrum sativum L* extract with ethanol 96 % once for 48 h (maceration), result maceration the solvent was evaporator at 450°C, Afterward the moisture content was determined (7,55%) This is the requirement for simplisia for herbal medicine that the water content should not be more than 10%. This Extract was used to nano-chitosan-tripolyphosphate to examine the decrease in blood glucose.

### Manufacture of nanoparticles

The thick ethanol extract of *Coriandrum sativum L* was weighed as much as 1 gram, dissolved with 50 mL of 96% ethanol then added with distilled water to a volume of 100 mL. A total of 1 gram of chitosan was dissolved in 1% glacial acetate to a volume of 100 mL and 1 gram of tripolyphosphate was dissolved in 100 mL of distilled water. The three solutions were then mixed and stirred using a magnetic stirrer for  $\pm 2$  hours. Chitosan-tripolyphosphate-coriander seed extract nanoparticles were separated by centrifugation. The solids obtained were then separated and put into the freezer ( $\pm -4^\circ\text{C}$ ) for  $\pm 2$  days. Storage is transferred to the refrigerator ( $\pm 300^\circ\text{C}$ ) until dry.

### Size of *Coriandrum sativum L* as medicine

Determination of Zeta Potential Value Nanoparticles Ethanol Extract of *Coriandrum sativum L*. Sample was

injected into the cuvette until the cuvette was completely filled and there were no bubbles. Then a cover on the inlet is installed to prevent vibration so as not to affect the results. The cell penetration is mounted in front of the arrow of the cell support. Furthermore, the electrode cell is checked to ensure that the electrode cell is connected to the instrument electrode and the tool cover is installed. Then press the "Measurement start" button. After the measurements were completed, the cells were removed and cleaned.

### Blood glucose level reduction

A real experimental method with the randomized post-test only control group design was performed. A total of 27 male Wistar rats aged  $\pm$  3 months and weighing 150 -200 grams were alkylated for 1 week divided into three groups. K0: Positive control group induced by streptozotocin 40 mg/KgBW. P2: Treatment group 2 which was induced by streptozotocin 40 mg/KgBW and given coriander seed ethanol extract 50 mg/KgBW. P3: Treatment group 3 was induced by streptozotocin 40 mg/KgBW and consumed nano particles of *Coriandrum sativum L* seed extract. The reduction in blood glucose levels is the blood sugar level measured in the tail vein blood of rats by the GLUCO method in unit mg/dL. Measurement of blood sugar levels in Wistar rats using the GLUCO glucose test kit was carried out after streptozotocin induction, after being treated with coriander seed ethanol extract, and after being treated with coriander seed

ethanol extract nanoparticles at a dose of 50 mg/Kg BW/day. Blood glucose levels were measured with a glucometer on the 4th day after streptozotocin induction and 17th after the treatment with one doses of the ethanol of *Coriandrum sativum L* and nano partikel *Coriandrum sativum L* the blood drawn from the tail vein of the rats. The blood glucose level was statistically analyzed through ANOVA in SPSS ver. 23 Windows if the result were significant a post hoc test LSD was performed.

### Data Analysis

Data were analyzed using ANOVA. If the result were significant a post hoc test LSD was performed to analyze the difference of *Coriandrum sativum L* extract effect in each group. Post Hoc analysis was carried out to determined which group have a significant result. Analysis was carried out using SPSS ver. 24.

## RESULTS

### *Coriandrum sativum L* extract

After the maceration of 2000 gram of powdered *Coriandrum sativum L* with ethanol solvent once for 48 h 147.25 g of thick blackish dark yellow ethanol extract with a yield percentage 7.55% was obtained Ethanol was chosen as the solvent because the percentage of water content *Coriandrum sativum L* powder has met the simplisia standard. *Coriandrum sativum L* sample was macerated using 96% ethanol as solvent. They yield of the ethanol extract of *Coriandrum sativum L* was obtained by

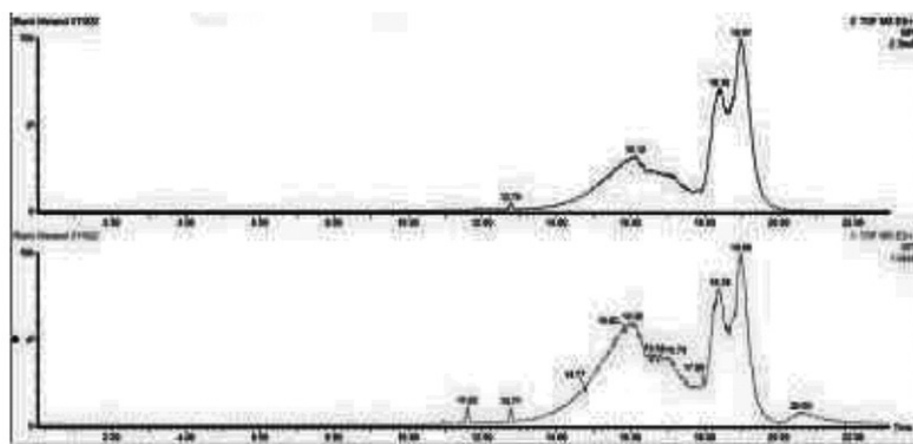
14,74 % (w/w). Results of phytochemical test of *Coriandrum sativum L* extract were positive for containing polyphenol compounds, flavonoid alkaloid with the appearance of colour change from brownish red to black.

### Nano extracts

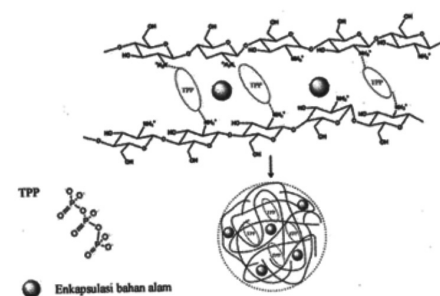
The nano extracts were analyzed by crosslinking method using chitosan and sodium tripolyphosphate as the base material for the nano-extracts. The bioactive substances contained in the flavonoid are trapped in the encapsulated chitosan-polyphosphate crosslink. The process of making nano-chitosan tripolyphosphate-*Coriandrum sativum L* extract is an interaction between the positive charge of the protonated amine group of chitosan in an acidic environment with partially negatively charged atoms of the compounds contained in the flavonoid extract. The partial negative charge of *Coriandrum sativum L* extract ethanol can come from the hydroxyl groups of phenolic and flavonoid compound it has so as to form chitosan-(NH<sup>3+</sup>)-O-phenolic/flavonoid interaction (Desti et al., 2020). **Figure 1.** The ionic interaction produces nano size and this method is called the ionic gelatin method.

### Decrease in blood glucose levels

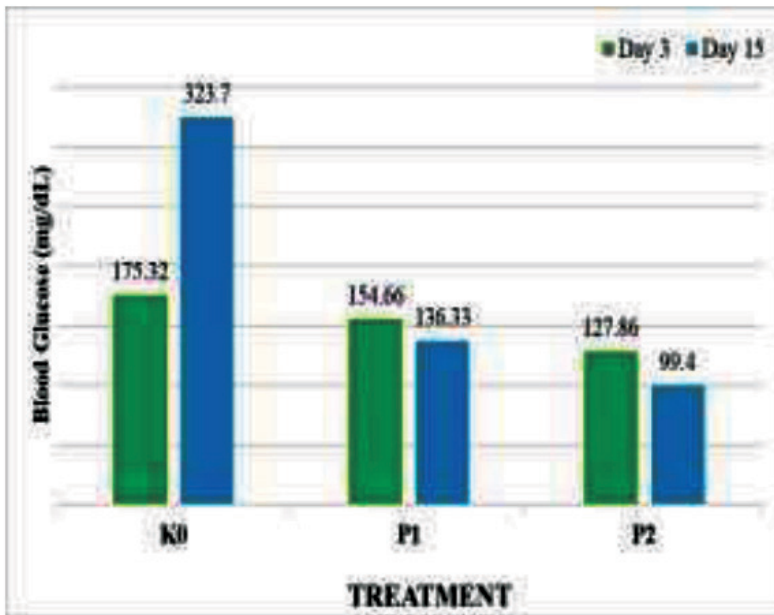
The blood glucose level profile of Wistar rats, particularly the blood glucose levels after streptozotocin induction on day 3 and after the administration (15 day) of



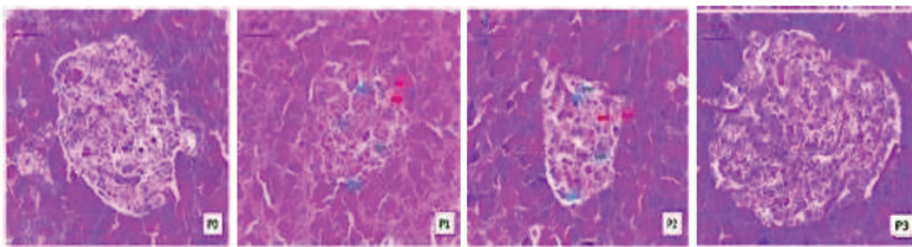
**Figure 1.** Chromatogram of liquid chromatography with tandem mass spectrometry ethanol extract of *Coriandrum sativum L*.



**Figure 2.** Formation of nano-chitosan-tripolyphosphate which encapsulate bioactive substances from *Coriandrum sativum L* extract ethanol to form nano-chitosan-tripolyphosphate-*Coriandrum sativum L* extract ethanol



**Figure 3.** Decrease in blood glucose levels



**Figure 4.** Changes of Pancreas in Hyperglycemic Wistar Rats.

one doses of ethanol extract is presented in **Figure 3**.

On the 15<sup>th</sup> day, the administration of nano chitosan-tripolyphosphate-*Coriandrum sativum L* the group K0 without treatment (only streptozotocin induced) had an average blood glucose level of 323.7 mg/dL, the group of rats given the *Coriandrum sativum L* ethanol extract at a dose of 50 mg/KgBW. P1 group had an average blood glucose level of 136.33 mg/dL, and a group of rats given coriander seed ethanol extract nanoparticles at a dose of 50 mg/KgBW. P2 group had an average blood glucose level of 99.4 mg/Dl. If the decrease in blood glucose levels of rats is compared, the administration of *Coriandrum sativum L* ethanol extract nanoparticles at a dose of 50 mg/KgBW is more effective in reducing blood glucose levels.

Histopathological observations of hyperglycaemic Wistar rats were carried out by observing the micro anatomical

structure of the islets of Langerhans in normal rats (P0), hyperglycaemic Wistar rats in extract (P1), ethanol extract of *Coriandrum sativum L* (P1), chitosan-tripolyphosphate-ethanol extract of *Coriandrum sativum L* (P3). Histopathological changes in the pancreas of Wistar rats hyperglycaemic. *Coriandrum sativum L* has excellent medicinal value.

**Figure 4** histopathology of the pancreas of normal mice (Fig. P0) is seen in Langerhans cells composed of healthy cells or not damaged. In figure P1 the pancreas in negative treatment induced by streptozotocin will be identified as diabetes by the occurrence of blue, green and red colours in the middle of the islets of Langerhans, this is a sign of cell damage. In Figure P2, it can be seen that the blue, green and red colours of the islets of Langerhans docked with the administration of *Coriandrum sativum L* 50.0 mg/KgBW ethanol extract, with streptozotocin induction, the damage

still occurs. In Figure P3 with intake of chitosan-tripolyphosphate-ethanol extract of *Coriandrum sativum L* 50.0 mg/kg BW induced by streptozotocin islets of Langerhans looks like Langerhans shape in P0 treatment (close to normal pancreas state).

## DISCUSSION

In this study, several tests were carried out, started from maceration process to histopathological evaluation of pancreas. The maceration method was used to reduce water excess in extract. Excess water content can cause easy microbial growth in the simplicial and hydrolysis of active compounds occurs and the extraction solvent is less effective due to the influence of water content in the simplicial.<sup>11</sup> The type of extraction solvent effects the mount of bioactive substances that can be extracted from the sample according to the concept of like dissolves like, where polar compounds will dissolve in polar solvents and non-polar compound will dissolve in non-polar solvent.<sup>12</sup>

Based on this study, phytochemical test of *Coriandrum sativum L* extract were positive for containing polyphenol compounds with the appearance of the colour change from brownish red to black that was caused by the reaction between OH-group on the poly phenol with Fe<sup>3+</sup>-ions in the FeCl<sub>3</sub> reagent to form a complex compound {Fe (Phenol) 6} C<sub>13</sub>.<sup>13</sup> In the flavonoid test with Wilstater reagent where Mg and HCl function to reduce the benzopiron core contained in the flavonoid structure to form a red flavilium salt {C<sub>15</sub>H<sub>11</sub>O<sub>3</sub>} Cl and the formation of air bubbles is the release of H<sub>2</sub> gas.<sup>14</sup> The test using Wegner's reagent showed positive result because Wegner's reagent binds to nitrogen in the alkaloid compound and forms a potassium alkaloid salt complex in the form of a precipitate and red in colour characterized by the formation of I-3.<sup>15</sup>

The scheme for the formation of nano-chitosan-tripolyphosphate which encapsulates bioactive substance from flavonoid extract to form nano-chitosan-tripolyphosphate-cinnamon bark extract to form nano chitosan-tripolyphosphate-*Coriandrum sativum L*, The **Figure 1** for the formation of nano-chitosan-tripolyphosphate which encapsulate

bioactive substances from *Coriandrum sativum* L extract ethanol to form nano-chitosan-tripolyphosphate-*Coriandrum sativum* L extract ethanol through the ionic gelatin method as presented in the report of Desti et al., 2020 as follow bioactive substance from *Coriandrum sativum* L extract ethanol can be attached or dissolved and can also be adsorbed or combined on the surface of the chitosan-tripolyphosphate nano. As a result, nano-chitosan-tripolyphosphate became a reservoir system where the bioactive substance from *Coriandrum sativum* L extract ethanol, namely flavonoids are encapsulated in a core surrounded by polymer walls and a matrix system so that flavonoid molecules are embedded in the polymer.<sup>8</sup>

Based on this study, we found the potential of *Coriandrum sativum* L in decreasing the level of glucose in *in vitro* setting. Similar results were found in several studies, such as study that conducted by Cardoso et al., 2019 found that administration of *Coriandrum sativum* L extract significantly control the blood glucose in alloxan-induced hyperglycaemic rats.<sup>16</sup> The decrease in blood glucose levels in Wistar rats is thought to have come from the presence of secondary metabolites that are antihyperglycemic and as antioxidants. In a state of hyperglycaemia, it will cause an increase in oxidative stress and a decrease in endogenous antioxidants (antioxidants produced in the body). Natural antioxidant intake is one of the protections against the progression of diabetes by inhibiting the reaction of peroxides that damage pancreatic beta cells. According to Yulianty et al., 2015) coriander seeds contain several active compounds that can lower blood glucose levels. The results of phytochemical screening showed the presence of polyphenolic compounds, alkaloids, and flavonoids.<sup>17</sup>

Many biologically active compounds contained in this plant extract, including alkaloids, phenolic compounds such as flavonoids, triterpenoids, carotenoids, steroids, and ketones.<sup>18</sup> Through their research, Detsi et al., 2020 found that nanoparticles of *Coriandrum sativum* L ethanol extract have antidiabetic activity by lowering blood glucose and

repairing islets of Langerhans and cells.<sup>8</sup> For the preparation of impregnation preparation, in the pancreas of Wistar rats hyperglycaemic. Staining used was haematoxylin Ehrlich-Eosin. Histological changes in islets of Langerhans and cells present.

## CONCLUSION

Based on the result of the research and discussion above, it can be concluded that nano chitosan-tripolyphosphate-*Coriandrum sativum* L extract can be used as nano herbal for hyperglycaemia therapy through the free radical pathway by observing glucose level and histopathological of pancreas in streptozotocin-induced Wistar rats. Encapsulation of bioactive substances from *Coriandrum sativum* L extract ethanol into nano chitosan-tripolyphosphate by crosslinking with the ionic gelatin method causes changes in physical chemical properties such as function groups, compounds that carry characteristics of bioactive substance, zeta potential, particle size, FTIR and PSA. Further studies are needed to validate these findings with more comprehensive treatment and strict observation to get more precise results.

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## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

## AUTHOR CONTRIBUTION

All authors similarly contribute to the think about from the investigate concepts, information acquisitions, information investigation, factual investigations, changing the paper, until detailing the consider comes about through publication.

## ETHICAL CONSIDERATION

This study was approved by Research Ethics Committee, Faculty of Medicine, Udayana University, Denpasar, Bali,

Indonesia with the number of approval: 3452/UN14.5.2.VII.14/LT/2022.

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