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CURCUMIN BIOACTIVE SUBSTANCE TO PREVENT DIABETIC RETINOPATHY DUE TO DIABETES MELLITUS COMPLICATIONS: A LITERATURE REVIEW

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ABSTRACT

Diabetes Mellitus is characterized by hyperglycemia, and if it continues, the patients are at risk of having a macrovascular or microvascular complication. One of the most frequent microvascular complications is Diabetic Retinopathy, with a prevalence of 42.6%. Most of the blindness due to Diabetic Retinopathy is a permanent condition and cannot be treated, so prevention is vital in reducing this disease. This literature aimed at providing the recent information related to the effect of curcumin in preventing Diabetic Retinopathy from occurring in patients with Diabetes Mellitus and becoming a source of the latest product innovation in preventing this disease. The writing began by electronic database searching via Google Scholar, Science Direct, Medline, and Research Gate. Only articles in English were taken as a literature review with the following research variables, namely the decrease in ROS *(Reactive Oxygen Species)*, the decline in inflammation, morphological changes in the retina, and reduction in levels of VEGF (Vascular Endothelial Growth Factor) which is an angiogenic factor. Twelve studies showed the following measurement results, namely five studies showed a significant result for giving curcumin extract to decrease ROS; ten studies showed that curcumin extract could significantly improve the morphology of the retina; four studies showed that curcumin extract could significantly help the anti-inflammation process, and four studies showed a significant reduction in VEGF levels. Based on twelve articles reviewed, curcumin can act as a bioactive substance in preventing Diabetic Retinopathy in Patients with Diabetes Mellitus.

Keywords: Curcumin, Diabetic Retinopathy, Diabetes Mellitus, High Glucose Levels, Antioxidant

INTRODUCTION

Diabetes Mellitus is a severe and chronic disease because the pancreas does not produce an adequate amount of insulin (a hormone that regulates blood glucose or glucose) or the body cannot effectively use the insulin produced (WHO, 2016). The most significant number of people with Diabetes Mellitus is estimated at 96 million from Southeast Asia and 131 million from the West Pacific considering around half of the global diabetes cases. The number of patients with Diabetes Mellitus over the world has increased four times, namely 108 million to 422 million from 1980 to 2014 (WHO, 2016). Indonesia Society for Endocrinology (Perkeni) (2015), state that Diabetes Mellitus in Indonesia increased by 4%, from 6.9% (2013) and 10.9% (2018) (Riskesdas, 2018).

Diabetes Mellitus causes the body to have an increase in blood glucose levels or hyperglycemia. Prolonged hyperglycemia in patients with Diabetes Mellitus leads to several complications, both macrovascular and microvascular. One of the frequently occurring microvascular complications is Diabetic Retinopathy that can cause injury in the retinal blood vessels, especially the sunlight-sensitive tissues. This condition causes visual impairment that potentially leads to blindness (Kemenkes RI, 2018).

Diabetic Retinopathy has a pretty high prevalence and it is at the fourth rank as the global cause of blindness after cataract, glaucoma, and macular degeneration (Soewondo et al., 2010). In 2010, of around 285 million people with Diabetes Mellitus globally, more than one-third have Diabetic Retinopathy symptoms, and one-third of them had vision-threatening Diabetic Retinopathy (Lee et al., 2015).

Based on the research data, the prevalence of patients with Diabetes Mellitus who suffered from Diabetic Retinopathy in Indonesia was 42.6%, indicating that around 24,600 people would be found suffering from Diabetic Retinopathy,

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and around 10% of that number suffered from blindness (Kemenkes RI, 2018). The majority of age groups who suffered from this complication were 20–64 years (Suyono & Pandelaki, 2014). Most of the blindness due to Diabetic Retinopathy is a permanent condition, and it cannot be treated. Therefore, preventive action is a vital effort to reduce the occurrence of this disease.

The effort to prevent Diabetic Retinopathy is by controlling the oxidative stress due to an increase in blood glucose that happens for quite a long time (Kumawat et al., 2012). One of the ways to control oxidative stress in the body is by utilizing bioactive substances in certain food ingredients, such as curcumin (Panasea, 2014).

Curcumin is a polyphenol substance in the flavonoids group containing phenolic compounds. Hence, it functions as an antioxidant, anti-inflammatory agent, anti-mutagenic agent, anti-cancer, and anti-microbe (Hewlings & Douglas, 2017). Curcumin can prevent Diabetic Retinopathy by several mechanisms with the molecular target in the body (Zhang et al., 2013). The body needs antioxidant property to prevent cell damage by completing lacking electron tied by free radicals and inhibit the chain reactions that can cause oxidative stress.

This paper aimed at investigating some literature reviews using narrative synthesis in interpreting some recent empirical literature related to the effectiveness of curcumin against the prevention of Diabetic Retinopathy.

METHODS

This literature study searched for articles via electronic databases, such as *Google Scholar, Science Direct, Medline,* and *Research Gate*. The inclusion criteria of this literature review comprised the selected articles that were published, at least, in the last ten years, from 2011 to 2021,

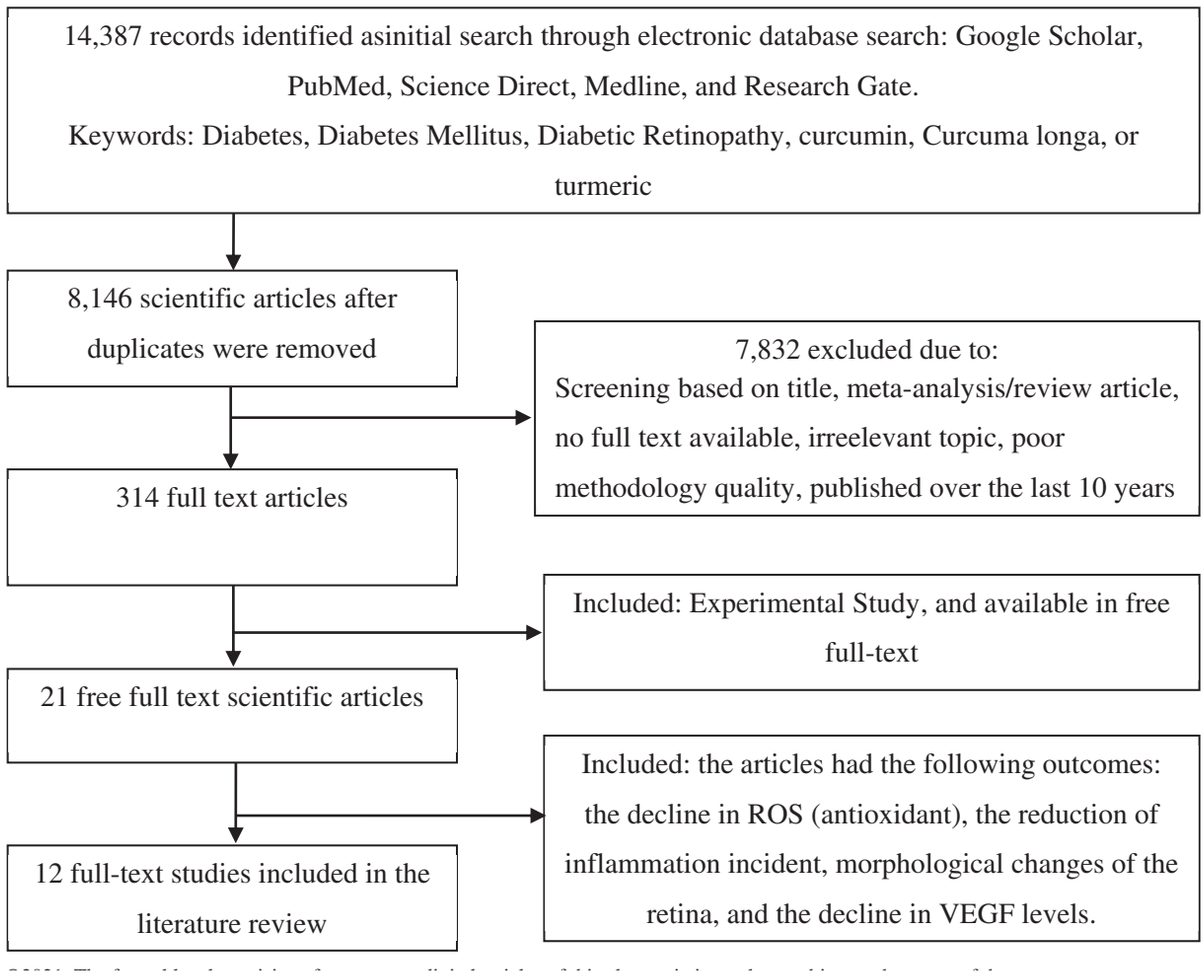


Figure 1. Diagram Flow of Excluded and Included Criteria for This Article

available in *free full-text*, and were experimental studies. The selected articles had the following measurement variables: the decline in ROS (Reactive Oxygen Species), the reduction of inflammation incident, morphological changes in the retina, and the decline in VEGF (Vascular Endothelial Growth Factor) levels. The search keywords were the variation and the combination of these following words: "Diabetes", "Diabetes Mellitus", "*Diabetic Retinopathy*", "curcumin", "*Curcuma longa*", or "*turmeric*".

Based on the search result, the writer found twenty-one scientific articles. After completing the identification process using the full-text method, twelve articles fulfilling the inclusion criteria for this literature review had been collected, the other nine articles did not meet the inclusion criteria. All articles were independently reviewed and coded by the writer. The extracted data consisted of research year, country of research site, research method, research duration, and the collected results.

Table 1. Review of Curcumin against the Prevention of Diabetic Retinopathy

No	Study	Method	Dosage	Duration (week/s)	Result	Reference
1	An experimental study using Wistar albino rats	Wistar albino rats were divided into three groups: the control, diabetic with normal diet, and diabetic treated with curcumin with a 1g/kg bodyweight dosage.	1 g/kg BW/day	16 weeks	Rats that were treated using curcumin had significantly lower blood glucose levels than the diabetic group (P<0.05), yet higher than normal (P<0.001). The HbA1C level in the rats treated using curcumin is significantly lower (P<0.05) than that of the diabetic group. The diameter of retinal blood vessels in the control group is lower than that of diabetic rats (p<0.05). The antioxidant parameter in the form of Retinal GSH, SOD, and CAT activity in the control group is similar to that of the normal rat group (p<0.05). The inflammation parameter showing the TNF-a level of the retina of the rats that are treated using curcumin is 2.5 times lower than the retina of diabetic rats that are not treated (P <0.05). The mean score of VEGF-treated rats is significantly lower than untreated ones (P <0.05). Curcumin prevents the thickening of Basement Membrane (BM) in the control group (p<0.05).	Gupta et al. (2011)

No	Study	Method	Dosage	Duration (week/s)	Result	Reference
2	An experimental study using male Sprague-Dawley (SD) rats	Rats are divided into four groups randomly: control group (rats are injected with citrate buffer), diabetic group (diabetic rats are induced with streptozotocin or STZ), DMSO group (STZ diabetic rats are given the mixture of DMSO (dimethyl sulfoxide) and normal saline intraperitoneally, once a day), and curcumin group (curcumin is given to diabetic-STZ rats intraperitoneally with a dosage of 80mg/kg, once a day).	80mg/kg BW/day	15 weeks	The MDA (malondialdehyde, indication of oxidative stress level) level of the retina compared to the control group significantly increases. In contrast, the GSH (glutathione) in the diabetic group and DMSO (dimethyl sulfoxide) group decreases (0.05 of each). No difference in GFAP (glial fibrillary acidic protein) or GS can be detected between the control groups and the curcumin groups (＞0.05).	Zuo et al. (2013)
3	An experimental study using male Sprague–Dawley (SD) rats	This experimental study was conducted using in vivo curcumin effects in the retina of rats streptozotocin (STZ)-induced diabetes and *in vitro* effects in muller cells stimulated by high glucose levels.	100 mg/kg BW/day	12 weeks	Curcumin reduces bleeding in the retinal vascular. Inflammation parameter in the form of VEGF, iNOS, ICAM_1 significantly decreases in the rats treated using curcumin	Li et al. (2016)

No	Study	Method	Dosage	Duration (week/s)	Result	Reference
4	An experimental study using male Wistar rats	Diabetic rats (blood glucose level ≥11.6 mmol/L) were randomly classified into three groups: diabetic rats without any treatment, diabetic rats treated using 100 mg/kg of curcumin, and diabetic rats treated using 200 mg/kg of curcumin. Curcumin was given orally every day for 16 weeks.	100 mg/kg BW of curcumin, and 200 mg/kg BW of curcumin	16 weeks	Giving curcumin keeps the thickness of the retina equal to that of normal rats ($p<0.01$). Giving curcumin with both dosages keeps the INL (Inner Nuclear Layer) in normal condition and decreases the thickness of BM (Basement Membrane). Giving curcumin decreases the SOD and T-AOC levels ($p<0.01$).	Yang et al. (2017)
5	An experimental study using mice	Mice are divided into four groups: diabetic group, diabetic treated using 25 µM curcumin, nondiabetic controls, and nondiabetic treated using 25 µM curcumin. Rats made to have Diabetes Mellitus using some methods: (1) Curcumin Treatment, (2) Determination of Reactive Oxygen Species (ROS), (3) DNMT Activity Quantification, and (4) Statistical Analysis using ANOVA, Student's t-test, and GraphPad version 6.0.	25 µM curcumin	8 weeks	Rats treated using curcumin can keep that stability of normal glucose level or acute/chronic condition using the treatment of 25 µM for 6 hours and trigger the decline in ROS in both acute and chronic conditions with a high blood glucose levels.	Maugery et al. (2018)

No	Study	Method	Dosage	Duration (week/s)	Result	Reference
6	An experimental study using retinal epithelial cells	The experimental study was conducted by treating the Retinal Pigment Epithelial Cell (RPEC) using 30 mmol/L of glucose considered a high-glucose group, the cell that was treated using 24.4 mmol/L of mannitol was determined as an equivalent osmolarity group.	10 µmol/L	-	Giving curcumin before the diabetic condition reaches a high blood glucose levels increases the viability (ability to survive) of RPECs. Giving curcumin decreases the inflammation indicators, such as TNF-α, IL-6, and IL1 B in RPECs. Giving curcumin decreases the ROS level in RPECs.	Ran et al. (2018)
7	An experimental study using male Sparague Dawley (SD) rats	The experimental study was conducted by giving curcumin or saline vehicle to the animal model every day for 12 weeks. Rats were randomly divided into three groups. The first group of rats were administered a 40mg dose of Alloxan/kg, then divided into Diabetic rats and Diabetic rats with curcumin at a dosage of 100mg/kg/day. At the same time, the third group of rats were administered only citrate buffer (0.1 mol/L,pH 4.5).	100mg/kg BW/day	12 weeks	Giving curcumin can keep the BM *(Basement Membrane)* in normal condition, Curcumin can keep the retinal vascular normality from bleeding and keep the thickness of blood vessels, Curcumin can decrease the VEGF level and iNOS-1 cytokine.	Pradhan et al. (2018)

No	Study	Method	Dosage	Duration (week/s)	Result	Reference
8	An experimental study using male New Zealand white rabbits	White rabbits were divided into 6 groups: the control group, untreated diabetes group, diabetes group with 1, 10, 20, and 100 μM concentrations of curcumin. This study was developed in the eyes of rabbits with high glucose levels.	1, 10, 20, and 100μM	-	Curcumin (10 mM) significantly decreases ($p < 0.01$) the ROS concentration and TNF- α discharge (inflammation indicators) in the retinal pigment epithelium and endothelial cells. The exact concentration of curcumin significantly ($p < 0.01$) protects retinal pericytes from the impact of high glucose. The highest concentration of curcumin(100μM) reached a statistically significant effect to decrease the ROS concentration.	Platania et al. (2018)
9	An experimental study using male Sprague-Dawley (SD) rats.	The experimental study was conducted in 60 mice by forming 4 groups: normal control group, osmolarity control group, high glucose group, curcumin-treated group (high glucose + curcumin). The curcumin-treated group was exposed to glucose with a concentration of 25 mmol/L for 72 hours, then, it was treated with 30 μmol/L of curcumin for 48 hours.	30 μmol/L	1 week	The ROS levels in the retinal vascular endothelial cells in the control group, osmotic control group, high glucose group, and curcumin-treated group are significantly different ($p \leq 0.001$). Compared to the high glucose group, the ROS content in the retinal vascular endothelial cells of the curcumin-treated group significantly decreases ($P < 0.001$). The NF-κB expression decreases significantly in the curcumin-treated group compared to the high glucose group ($p < 0.05$).	Huang et al. (2020)
10	An experimental study using male Sprague-Dawley (SD) albino rats	The experimental study was conducted in 48 albino Sprague-Dawley mice. There were three groups, namely the control group, diabetic group, and diabetic and curcumin-treated group. The treatment received diet powder completed with curcumin 0.5g/kg.	0.5g/kg BW/day	4 and 8 weeks	There was no significant improvement of the eye's retina in the treated diabetic group with curcumin duration treatment of four weeks ($p < 0.101$). The thickness of the eye's retina is improved in the treated diabetic mice with the curcumin treatment duration of weeks ($p < 0.046$). A significant decline in the retinal ganglion cells occurs in the diabetic mice compared to the control group. The improvement of the retinal ganglion cells significantly happens in the treated diabetic mice group with a duration of 8 weeks ($p < 0.033$).	Salem et al. (2012)

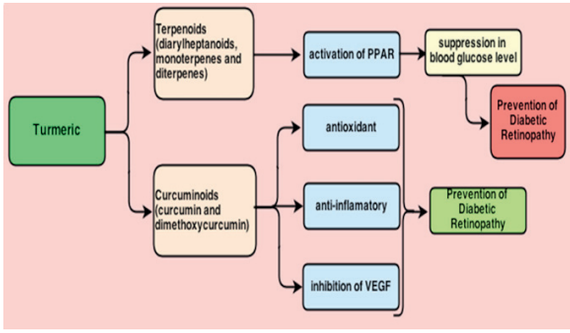
No	Study	Method	Dosage	Duration (week/s)	Result	Reference
11	An experimental study using male Wistar Strain (Wistar/NIN) rats	The experimental study was conducted on 29 mice classified into 4 groups: control group, diabetic group, SC diet-treated group, and RC diet-treated group. SC (Soluble Curcumin) diet contains 20% of curcumin from 20%-28% of turmeric extract. The RC (Regular Curcumin) diet contains 95% of curcumin.	SC (Soluble Curcumin) contains 20% of curcumin (0,01%). RC (Regular Curcumin) contains 95% of curcumin (0,01%).	12 weeks	Giving curcumin prevents morphological changes in the retina significantly. The SC (Soluble Curcumin) diet or curcumin solution is proven more effective than RC (Regular Curcumin) or curcumin powder. Giving RC formula did not effect VEGF expression Giving SC formula decreases the VEGF expression in the retina	Deshpande et al. (2015)
12	An experimental study using male Sprague-Dawley (SD) rats	The experimental study was conducted on 36 mice divided into three groups, the control group, diabetic mice group, and diabetic mice group treated with a curcumin diet. The dosage of the given curcumin was 100 mg/kg/ day orally.	100 mg/kg BW/day	12 weeks	The thinning of the retina can be significantly prevented in diabetic mice that are treated with a curcumin diet ($P < 0.01$) Curcumin significantly prevents the retinal nerves from losing in the diabetic mice group Compared to the diabetic mice group, the apoptosis in GCL (ganglion cell layer), INL (inner nuclear layer), and ONL (outer nuclear layer) are significantly inhibited in the diabetic mice that are treated using curcumin ($P <0.05$ for GCL, $P <0.01$ for INL and ONL).	Li et al. (2015)

RESULT AND DISCUSSION

All of the reviewed studies aimed to identify the effect of using curcumin in preventing Diabetic Retinopathy. The sample used rats as the laboratory animal in eleven studies and rabbits in one study using the experimental method. The duration of the studies was approximately one to sixteen weeks reported by the ten studies, while the two other studies did not report the research duration.

The analysis of twelve studies involved several measurement results, namely the decline in ROS level, decline in blood glucose levels, an improved morphology of the retina of the eyes, preventing inflammation, and a decline in VEGF level. Around five studies reported a significant result of giving curcumin extract against preventing Diabetic Retinopathy by decreasing the ROS level. Two studies reported a decrease in blood glucose levels with a significant result. Ten studies reported the measurement result in the retinal morphology improvement with a significant result. Besides, giving curcumin extract helps the anti-inflammation process in the retina of the eyes; four studies reported this with a significant result. Moreover, four studies reported that the bioactive substance of curcumin could decrease the VEGF level with a significant result.

Of twelve publications that had been analyzed, the best time needed for curcumin to give positive effects was sixteen weeks with a dosage of 100 mg/kg BW up to 1 g/kg BW daily. This dosage is in line with a study stating that giving curcumin 500 mg up to 1000 mg daily, as recommended



Source: Aldebashi (et al., 2013)

Figure 2. Curcumin and its constituents play a vital role in the management of Diabetic Retinopathy.

by medical experts, can prevent complications due to Diabetes Mellitus and metabolic disorders (Phillip, 2013). The bioactive substance of curcumin in solutions has a more effective potency than the regular curcumin or curcumin powder in preventing Diabetic Retinopathy (DR) (Deshpande et al., 2015).

The curcumin bioactive substance mainly contained in turmeric plays a role as a molecular target and has proven therapeutic potency in preventing Diabetic Retinopathy. The strength of curcumin involvement in controlling gene actions creates strong positive effects against the new therapeutic strategy of Diabetic Retinopathy with the following characteristics: no side effects, affordable, and easy to be accessed. The bioactive substance of curcumin can be made as a promising substance in controlling Diabetic Retinopathy (Aldebashi et al., 2013).

The Decrease in Blood Glucose Levels

The bioactive substance curcumin is able to lower blood glucose levels. Based on the review, There are two articles that have a significant result on reducing glucose levels. Curcumin acts as a hypoglycemic agent by increasing the activation of peroxisome proliferator-activated receptor (PPAR) (Aldebashi et al., 2013).

PPAR is a transcription factor bound to the nuclear membrane that plays a role in adipogenesis, glucose homeostasis, fat metabolism, and improves insulin sensitivity. PPAR activation on pancreatic β-cells will increase Insulin Receptor Substrate-2 (IRS-2) sensitivity. IRS-2 will activate the expression of pancreatic and duodenal homeobox-1 genes, which are transcription factors in the process of differentiation and maturation of pancreatic β-cells. The final effect obtained is a decrease in blood glucose levels (Jung et al., 2014).

The Decrease in Reactive Oxygen Species (ROS) levels

Based on the review in the table above, five studies showed a significant result ($P<0.05$) of giving curcumin extract towards the Diabetic Retinopathy prevention by decreasing the ROS levels. According to Huang et al. (2020), the mice with high blood glucose levels untreated using curcumin and those with high blood glucose levels treated using curcumin were significantly different ($p\leq0.001$).

Hyperglycemic conditions caused the increase in the ROS levels was due to Diabetes Mellitus. Based on several articles reviewed, the bioactive compound of curcumin had a significant result against the decline in the ROS levels. That can help decrease the risk of Diabetic Retinopathy since the increased ROS levels can activate poly-(ADP-ribose)-polymerase (PARP). Hence, it can inhibit glyceraldehyde phosphate dehydrogenase (GADPH). GADPH contributes to catalyzes the sixth step of glycolysis process. This condition can lead to the accumulation of glycolytic metabolism. It activates the Advanced Glycation End Products (AGE), Protein Kinase C (PKC), polyols, and hexosamines; the mechanism are supposed to play a role in microvascular damage and Diabetic Retinopathy. The activation of those mechanisms can worsen the Diabetic Retinopathy condition (Elvira & Ernes, 2019). The bioactive compound of curcumin acts as an antioxidant that can suppress ROS in the body to prevent the Diabetic Retinopathy condition from being worse in patients with diabetes mellitus.

Comparison of Retinal Morphology

According to a study by Salem et al. (2012), there was no significant retinal improvement in the diabetic-treated group by giving curcumin powder for four weeks ($p<0.101$); however, a significant retinal improvement occurred in the group treated using curcumin powder for eight weeks ($p<0.046$). A study by Deshpande et al. (2015) showed that there was a significant improvement in the retinal

morphology ($p<0.05$) with a research duration of twelve weeks. From the twelve studies reviewed, the improvement of retinal morphology showed a significant result with an average research duration of twelve weeks or more. Besides, giving the diet containing curcumin solution had more effective therapeutic potency than the powder curcumin for Diabetic Retinopathy (DR) prevention by preventing the morphological changes in the retina (Deshpande et al., 2015).

Around ten articles had a significant outcome against the morphological improvement of the retina of the eye. Patients with Diabetic Retinopathy will experience thickening or swelling in the retinal capillary basement membrane due to the endothelial cells' sorbitol accumulation. Retinal thickening is related to the characteristics of impermeable sorbitol or the inability to pass through the basement membrane resulting in the accumulation in the cell. Sorbitol accumulation can increase the osmotic stress that can result in morphological abnormalities, and it causes the occurrence of microaneurysms or capillary blockage (Septadina, 2015). The bioactive substance of curcumin can keep the typical morphology of the retina in the eyes by protecting the retinal vascular from bleeding and the thickness of blood vessels.

Besides, Diabetic Retinopathy causes nerve cell damage and loss in the retina or the occurrence of apoptosis (Li et al., 2016). Diabetic Retinopathy can cause an increase in NF-κB (transcription factor playing a role in cellular responses) that can cause apoptosis in the retina's nerve cells. Curcumin can decrease and inhibit the structuring of NF-κB significantly (Kowluru & Mamta, 2007). Hence, the bioactive substance of curcumin can keep the typical morphology of the retina of the eyes and its health.

Anti-inflammation

Based on Table 1, four studies reported that giving curcumin extract significantly ($P<0.05$) helped the anti-inflammation process. Based on the result of a study by Gupta et al. (2011), the inflammation parameter showed that the TNF-a level in the retina of the mice treated using curcumin was significantly different and 2.5 times lower than the diabetic retina that was not treated ($P <0.05$) within sixteen weeks.

Hyperglycemia due to Diabetes Mellitus is a pro-inflammation condition. Several paths of Diabetic Retinopathy structuring, such as polyols, AGE, PKC, and hexosamine, can cause a circulatory disorder, hypoxia, and inflammation in the retina. Hypoxia and inflammation in the retina occur due to microaneurysms or capillary blockage of the retina (Simorangkir, 2020). The bioactive substance of curcumin has an inflammatory agent, such as inhibiting cytokine production through a decline in Protein Kinase C (PKC) activation. Its ability inhibits cytokines because curcumin can inhibit the phosphorylation of phosphatidylserine that is phospholipids playing a role in the PKC activation process (Adrian, 2017).

The Decrease in VEGF Levels

Based on the review in the table above, three studies showed that the bioactive substance of curcumin could ($P<0.05$) significantly decrease the VEGF (Vascular Endothelial Growth Factor) levels. VEGF is a protein that helps the angiogenesis process or new blood vessel formation. According to a study by Pradhan et al. (2018), curcumin could significantly decrease the VEGF levels for twelve weeks. In the twelve studies reviewed, the average duration for giving curcumin with a significant result to decrease the VEGF levels was twelve weeks to sixteen weeks. Besides, the diet containing curcumin solution effectively decreases the VEGF levels than the diet containing curcumin powder (Deshpande et al., 2015).

Vascular Endothelial Growth Factor (VEGF) has a role in the process of structuring Diabetic Retinopathy. VEGF is the inflammation mediator that can be stimulated by the damage of vascular endothelial cells and tissue hypoxia due to microaneurysms or capillary blockage. VEGF can function in the angiogenesis process and stimulate endothelial cell growth to trigger neovascularization in the retinal capillaries (Adrian, 2017). The retinal blood vessels become weak due to the neovascularization process, so it is vulnerable to recurrent bleeding that can form fibrosis tissue. This process has a risk of vision degeneration. The bioactive substance of curcumin

has the anti-inflammatory characteristic that can suppress the VEGF level (Zhou et al., 2015). In the review result against 12 studies, the rats given curcumin intervention had a lower VEGF level than the diabetic rats without curcumin intervention. This condition can prevent the occurrence of Diabetic Retinopathy.

DISCUSSION

The review against twelve studies showed a significant result related to the intervention of curcumin bioactive substance toward the prevention of Diabetic Retinopathy. All articles used experimental study design since it is the best study design to know the effectiveness of a specific intervention. Curcumin has antioxidant activity, anti-inflammation, and inhibits the VEGF cellular signal modulation, and as a result, it can cause phenotype changes in Diabetic Retinopathy (Jeenger et al., 2015). The significant proof from several experimental studies showed the potency of curcumin in preventing the complications of Diabetes Mellitus.

The following study in the future implies that the researcher that uses an experimental study shall measure the research duration in each intervention applied. Besides, the researcher shall explain the primary ingredient of curcumin that is used. It is related to the effectiveness of curcumin on Diabetic Retinopathy. The result of this experimental study can be an alternative for further study; therefore, a clinical assessment of the bioactive substance of curcumin is required (Jeenger et al., 2015). The biological activity of curcumin is perfect for health; hence, further study can lead to the development of curcumin as herbal medicine orally related to the dosage for better effects in preventing Diabetic Retinopathy, a complication of diabetes mellitus.

A study is also required to be conducted on humans to ensure the potency of curcumin in preventing complications due to Diabetes Mellitus and the prevention of increased blood glucose levels. The study in the future shall discuss curcumin with the best effectiveness appropriate to the latest development of formulation, such as nanoparticles, encapsulations, emulsions, or tablets, in preventing complications due to Diabetes Mellitus (Zhang et al., 2013).

The strength of this literature review is that reviewing Scopus-indexed international journals with experimental study design or intervention; consequently, the effects of the treatment can be seen, namely, the effectiveness of curcumin bioactive substance against the prevention of Diabetic Retinopathy. Besides, the reviewed articles had been published, at least, in the last ten years. Meanwhile, the weakness of this paper is the limited references related to the effectiveness of curcumin in preventing Diabetic Retinopathy that fulfills the inclusion criteria.

CONCLUSION AND SUGGESTION

Based on the review result against twelve articles, most of the studies show that the intervention using curcumin bioactive compound is quite effective in preventing Diabetic Retinopathy. Curcumin is able to have a positive effects by controlling the oxidative stress, preventing inflammation, keeping the normal morphology of the retina, decreasing the blood glucose levels, and decreasing the VEGF levels. Curcumin can provide a significant result within 8-16 weeks with a dosage of 100mg-1g/kg/day.

A similar research development, especially in Indonesia, needs to be conducted to identify the benefits of the bioactive substance of curcumin against the prevention of Diabetic Retinopathy in a more specific way.

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