Effectiveness of Nano Curcumin and Curcumin as Heart Cell Protectors towards Oxidative Stress through Malondialdehyde (MDA) and Superoxide Dismutase (SOD) Level Analysis in Rats (Rattus norvegicus): A Systematic Review

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Abstract

Background: Oxidative stress is a disturbance which is caused by imbalance of reactive oxygen species (ROS) and antioxidants. Heart is one of the main target organs because it is the highest ROS producer. Malondialdehyde (MDA) and superoxide dismutase (SOD) are two biomarkers often used to evaluate oxidative stress. Due to their antioxidant properties, curcumin and nano curcumin are expected to protect heart from cardiotoxicity caused by oxidative stress. Methods: This is a systematic review of experimental studies available in the literature that reported the curcumin and/or nano curcumin and oxidative stress analyzed through the levels of MDA and SOD in heart of rats. Results: There are 8 out of 8 articles that prove a decrease in cardiac MDA levels after curcumin administration. Seven of them gave significant results with p-value <0.05. Meanwhile, one article stated there is no significant p-value, which is 0.187. A significant increase in SOD levels was shown to occur after curcumin administration in 6 of the 6 articles obtained. Not only curcumin, but nano curcumin can also reduce MDA levels and increase SOD levels of heart significantly. In 4 articles that directly compared the two antioxidants, nano curcumin was able to provide more significant results even at lower doses. Conclusion: Both curcumin and nano curcumin are capable to decrease the level of cardiac MDA and increase the level of cardiac SOD. Nano curcumin is a more effective cardioprotector compared to curcumin through MDA and SOD level analysis in rats.

Keywords: Curcumin; Cardioprotection; Malondialdehyde (MDA); Nano Curcumin; Superoxide Dismutase (SOD)

1. Introduction

Oxidative stress is involved in the pathophysiology of various chronic diseases including cardiovascular disease (Diaconu, 2019). Compared to other organs, the heart has lower levels and total activity of antioxidant enzymes. Due to its high metabolic rate, this organ is one of the main target organs for oxidative stress because it is the producer of the highest reactive oxygen species (ROS) (Costa *et al.*, 2013).

At normal concentrations, ROS has an important role in cell homeostasis, physiological signalling pathways, and other biological processes. However, excessive ROS will damage cells and cause tissue death. Moreover, the accumulation of ROS will result in cardiac remodelling by inducing the proliferation of cardiac fibroblasts (D'Oria *et al*., 2020). Various results of studies in experimental animals have resulted in the hypothesis that

oxidative stress can be a therapeutic target in heart failure patients (Diaconu, 2019).

According to Yin *et al.* (2019), superoxide dismutase (SOD) and malondialdehyde (MDA) are two indices commonly used to evaluate oxidative stress. In cells, including heart cells, SOD is the first and strongest line of antioxidant enzymes to detoxify ROS. In contrast to MDA, this molecule naturally occurs when oxidative stress causes lipid peroxidation. The free radical damage can be inhibited by consuming exogenous antioxidants. These antioxidants can delay, prevent, or eliminate oxidative damage. Curcumin and nano curcumin act as exogenous antioxidants and are targeted to inhibit oxidative stress. The activity of free radical scavenging by curcumin is influenced by its phenolic hydroxyl groups (Syarifah *et al.*, 2021).

Curcumin, the content of turmeric (*Curcuma longa l.*), is one of the herbal antioxidants that has been widely researched and selected as an alternative antioxidant (Djaelani, 2010). However, curcumin has low bioavailability and solubility and is easily degraded, making it difficult for clinical applications. Nano curcumin or curcumin which is formed in nanoparticle size requires a concentration 15 times lower than ordinary curcumin to enter the blood brain barrier (Dende *et al.*, 2017). These nanoparticles are able to penetrate the spaces between cells, increase solubility and bioavailability, thus increasing the effectiveness of treatment (Khasanah and Husni, 2016).

Until now, there have been many studies that have given mixed results regarding the effectiveness of nano curcumin and curcumin as heart cell protectors but none has concluded these studies. This study aims to provide conclusions from actual and relevant studies.

2. Methods

2.1 Sources

A systematic search was performed from 20th May until 18th June 2020 through Science Direct, Pubmed, Semantic Scholar, and Google Scholar databases. The search strategy combined the Medical Subjects Headings (MeSH) terms and keywords with the help of Boolean operator, such as: curcumin *OR* nanocurcumin *OR* curcumin nanoparticle *AND* heart *OR* cardiac *AND* malondialdehyde *OR* superoxide dismutase *AND* rat.

2.2 Study Selection

Studies that met the following inclusion criteria were included in the qualitative synthesis to focus on the effectiveness of nano curcumin and curcumin as heart cell protectors towards oxidative stress:

1. Design: animal research
2. Sample criteria: rats (*Rattus norvegicus*) *in vivo*
3. Intervention: administration of curcumin or nano curcumin as antioxidants of the oxidative stress given.
4. Study outcome: analysis of MDA and SOD levels.
5. Issued in the last 10 years.

3. Results and Discussion

Using the aforementioned search strategy, 107088 articles were retrieved. They were then reduced to 12648 using the filter services provided on each databases. Of these, only 16 were considered relevant with inclusion criteria after reading their abstract. Out of 16, there were 3 that did not pass through the quality assessment. The remaining 13 articles were carefully read. Then, after excluding duplicate records, there were only 9 studies met our criteria (Figure 1). Related data in those studies is then extracted and rearranged in the form of

tables (Table 1 and 2).

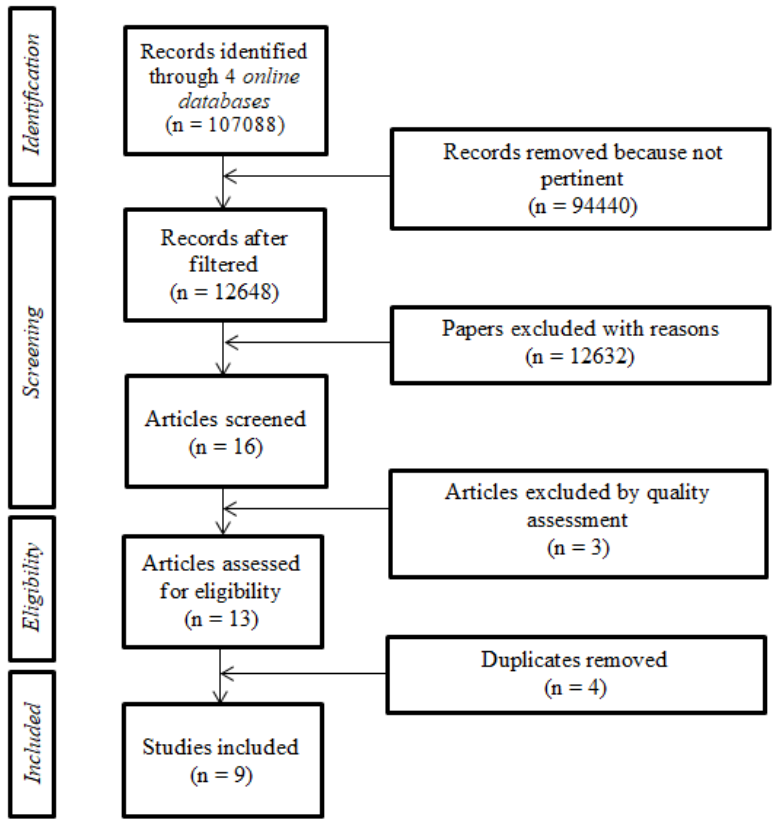

Fig. 1. Flowchart of the studies included in the systematic review.

Table 1. Data extraction result of Curcumin studies

No	Author(s)	Title	Study Design	Sample	Antioxidant	Oxidative Stress	MDA Analysis	SOD Analysis
1	Sheibani *et al.*, 2020	*The protective effects of Curcumin and Curcumin Nanomicelle against cirrhotic cardiomyopathy in bile duct-ligated rats*	Experimental	56 male Wistar rats weighing 250-300 g	Curcumin	Bile-duct ligation	In the animals receiving curcumin 300 and 600 mg/kgBW, a significant reduction was observed in the MDA levels compared to the controls ($p<0.05$).	The SOD levels of the group given curcumin 600 mg/kgBW increased significantly ($p<0.05$).
2	Fakhraei *et al.*, 2019	*On the Benefit of Nanocurcumin on Aluminium Phosphide-induced Cardiotoxicity in a Rat Mode*	Experimental	60 male Wistar rats weighing 200-250 g	Curcumin	Aluminium phosphide (ALP)	Curcumin at dose 50 mg/kg could markedly lower MDA level in ALP-intoxicated rats compared to saline treated intoxicated rats ($p<0.01$)	Curcumin at dose of 50 mg/kg could markedly lower
3	Estakhri *et al.*, 2019	*Organ toxicity attenuation by Nanomicelles containing curcuminoids: Comparing the protective effects on tissues oxidative damage induced by diazinon*	Experimental	48 male Wistar rats weighing 150-200 g	Curcumin	Diazinon (DZ)	A significant decrease of MDA was observed in the groups treated with curcumin 25 mg/kg ($p<0.05$) and 60 mg/kg ($p<0.001$).	Not evaluated
4	Bahadır *et al.*, 2018	*Protective effects of curcumin and beta-carotene on cisplatin-induced cardiotoxicity: An experimental rat model*	Experimental	49 female Wistar rats weighing 190-250 g	Curcumin	Cisplatin (CDDP)	Compared to group control, MDA level were found to be much lower in the group that was given curcumin,	The SOD activity in group that were treated with curcumin was significantly lower than control

							but it was not statistically significant (p=0.187)	(p=0.004).
5	Namdari and Eatemadi, 2017	*Cardioprotective effects of curcumin-loaded magnetic hydrogel nanocomposite against doxorubicin-induced cardiac toxicity in rat cardiomyocyte cell lines*	Experimental	10 male Albino rats weighing 150-200g	Curcumin	Doxorubicin (DOX)	MDA level in rats that were treated with curcumin showed significant increase (p<0.05).	SOD activity in rats that were treated with curcumin was significantly decreased (p<0.05).
6	Imbaby *et al.*, 2014	*Cardioprotective Effects Of Curcumin And Nebivolol Against Doxorubicin-Induced Cardiac Toxicity In Rats*	Experimental	84 male Wistar rats weighing 180-200 g	Curcumin	Doxorubicin (DOX)	MDA level was significantly diminished (p<0.05).	Depleted SOD activity was restored significantly (p<0.05).
7	Correa *et al.*, 2013	*Curcumin maintains cardiac and mitochondrial function in chronic kidney disease*	Experimental	60 rats	Curcumin	Chronic kidney disease	Level of MDA was drastically diminished in the heart of curcumin treated group (p<0.05) compared to the untreated.	Not evaluated
8	Naik *et al.*, 2011	*Protective effect of curcumin on experimentally induced inflammation, hepatotoxicity, and cardiotoxicity in rats: Evidence of its antioxidant property*	Experimental	40 Wistar rats	Curcumin	Isoproterenol (ISO)	Curcumin treatment significantly reduced the elevated MDA levels, p<0.05 for dosage of 200 mg/kg BW, and p<0.01 for dosage of 400 mg/kg BW. However, elevated MDA levels	Curcumin treatment (200 and 400 mg/kg BW, p.o.) significantly restored the decline in SOD level in cardiac tissue (p<0.001).

							in target tissues were not completely restored to normal level.	

Table 2. Data extraction result of Nano curcumin studies

No	Author(s)	Title	Study Design	Sample	Antioxidant	Oxidative Stress	MDA Analysis	SOD Analysis
1	Mohammed *et al.*, 2020	*Protective effect of curcumin nanoparticles against cardiotoxicity induced by doxorubicin in rat*	Experimental	36 male albino Wistar rats weighing 160-180 g	Nano curcumin	Doxorubicin (DOX)	Protection of doxorubicin-treated rats with curcumin nanoparticles succeeded in normalizing the myocardial levels of MDA ($p=0.001$).	Not evaluated
2	Sheibani *et al.*, 2020	*The protective effects of Curcumin and Curcumin Nanomicelle against cirrhotic cardiomyopathy in bile duct-ligated rats*	Experimental	56 male Wistar rats weighing 250-300 g	Nano curcumin	Bile-duct ligation	• In the animals receiving 300 and 600 mg/kg of curcumin, a significant reduction of MDA level was observed compared to control ($p<0.05$). • A more significant difference was observed between the treatment	• The SOD level significantly increased in the animals administered with 100 and 200 mg/kg of nano curcumin compared to controls ($p<0.05$ and $p<0.01$, respectively). • There was also a significant difference

							groups receiving 200 mg/kg nano curcumin ($p<0.001$). • The most positive response to the reduction of the MDA level was obtained from the animals treated with 200 mg/kg nano curcumin.	between the treatment groups receiving 200 mg/kg of nano curcumin and 600 mg/kg of curcumin ($p<0.05$).
3	Fakhraei *et al.*, 2019	*On the Benefit of Nanocurcumin on Aluminium Phosphide-induced Cardiotoxicity in a Rat Mode*	Experimental	60 male Wistar rats weighing 200-250 g	Nano curcumin	Aluminium phosphide (ALP)	• Nano curcumin at doses 10, 20, and 50 mg/kg decreased MDA level in a significant manner ($p<0.001$). • Although nano curcumin at doses 20 and 50 mg/kg could lower MDA to levels similar to normal	• Nano curcumin at doses 10, 20, and 50 mg/kg decreased SOD activity in a significant manner ($p<0.001$). • Although nano curcumin at doses 20 and 50 mg/kg could lower SOD activities to levels

								vehicle-treated group, at dose of 10 mg/kg was still markedly different from it ($p<0.01$).	similar to normal vehicle-treated group, at dose of 10 mg/kg was still markedly different from it ($p<0.05$).
4	Estakhri *et al.*, 2019	*Organ toxicity attenuation by Nanomicelles containing curcuminoids: Comparing the protective effects on tissues oxidative damage induced by diazinon*	Experimental	48 male Wistar rats weighing 150-200 g	Nano curcumin	Diazinon (DZ)	• MDA levels were decreased significantly in curcumin and nano curcumin groups at all dose (25 and 60 mg/kgBW). • Nano curcumin at 25 and 60 mg/kg could significantly decrease MDA levels ($p<0.01$) compared to different doses of curcumin ($p<0.5$).	Not evaluated	

5	Namdari and Eatemadi, 2017	*Cardioprotective effects of curcumin-loaded magnetic hydrogel nanocomposite against doxorubicin-induced cardiac toxicity in rat cardiomyocyte cell lines*	Experimental	10 male Albino rats weighing 150-200g	Curcumin	Doxorubicin (DOX)	Compared with the nano curcumin, the myocardial MDA level in rats treated with curcumin was significantly higher ($p<0.05$).	Compared with the nano curcumin, SOD activity of the control group (free curcumin) was significantly decreased ($p<0.05$).

3.1 Effect of curcumin on cardiac MDA levels

There are 8 articles examining the effect of curcumin on cardiac MDA levels. Of the 8 articles, all stated that there was a decrease in MDA levels in the curcumin-treated group when compared to the positive control group or those treated with oxidative stress. However, 1 in 7 gave insignificant results even though the results showed a decrease in MDA levels.

In the research of Sheibani *et al.* (2020), a significant reduction in MDA levels ($p < 0.05$) was found in the experimental animal group that received 300 and 600 mg / kg BW curcumin. This result is in line with other studies conducted in previous years, namely research by Estakhri *et al.* (2019), Namdari and Eatemadi (2017), research by Imbaby *et al.* (2014), research by Correa *et al*. (2013), and research by Naik *et al.* (2011) with a p-value <0.05. In another study, namely the research of Fakhraei *et al.* (2019), found a decrease in MDA levels with a p value <0.01 in the curcumin treatment group at a dose of 50 mg/kgBW.

Unlike the case with research conducted by Bahadır *et al.* (2018), the increase in MDA levels due to CDDP induction was proven to be reduced by administering curcumin, but did not provide statistically significant results ($p = 0.187$).

3.2 Effect of curcumin on SOD levels

Of the 8 articles examining curcumin, 6 articles analyzed cardiac SOD levels. In the latest articles, namely, the study conducted by Sheibani *et al*. (2020), the SOD levels of the group given curcumin 600 mg/kgBW increased significantly ($p<0.05$). This significance value ($p<0.05$) was also obtained from research in the previous year by Fakhraei *et al.* (2019).

A very significant increase in SOD levels resulted from a study conducted by Bahadır *et al.* (2018). A significance value of $p = 0.000$ was obtained from the experimental animal group that received cisplatin induction and 50 mg / kg BW curcumin treatment. In the research of Imbaby *et al.* (2014), the administration of curcumin 100 and 200 mg/kgBW significantly ($p<0.05$) increased levels of SOD. Curcumin administration also significantly ($p<0.001$) restored cardiac SOD levels that fell due to isoproterenol administration in Naik *et al.* (2011).

3.3 Effects of Nano Curcumin on MDA levels

This significant reduction was evidenced by 5 of the 5 articles examining the effect of nanomedicine on MDA levels. In the research of Mohammed *et al.* (2020) MDA levels were significantly reduced ($p=0.001$). Doxorubicin-induced cardiac MDA levels can also be normalized by administering nano curcumin.

Research by Sheibani *et al.* (2020) also showed a significant reduction in MDA levels ($p<0.001$) was found in the experimental animal group receiving nano curcumin 100 and 200 mg/kg. In his study, the most positive response was found in mice that received 200 mg/kg nano-curcumin treatment.

Similar to the 2 previous articles, Fakhraei *et al.* (2019) proved that there was a significant decrease in MDA levels ($p<0.001$) in the group treated with 10, 20, and 50 mg/kg nano-curcumin. Reduction in these levels can be obtained even at the lowest dose.

In the research of Estakhri *et al.* (2019) MDA levels were significantly reduced in the nano curcumin treatment group (25 and 60 mg/kg) after diazinon induction, namely $p<0.01$. Namdari and Eatemadi (2017) who compared nano curcumin with curcumin as a control group also found a significant reduction ($p<0.05$).

3.4 Effect of Nano Curcumin on SOD levels

There was an increase in SOD levels in all groups treated with nano curcumin. In the research of Sheibani *et al.* (2020), SOD significantly increased in the administration of nano curcumin 100 mg/kgBW ($p<0.05$) and 200 mg/kgBW ($p <0.01$) when compared to controls. In fact, in a previous study conducted by Fakhraei et al.

(2019) giving nano curcumin gave more significant results (p<0.001). Likewise, what was obtained from the results of Namdari and Eatemadi's (2017) study, compared to the control group (curcumin), a significant increase (p <0.05) was shown by the group treated with nano curcumin.

3.5 Comparison of the Effects of Curcumin and Nano Curcumin

Four articles compare the nano effects of curcumin and curcumin directly. In the research of Sheibani *et al.* (2020), a significant reduction in MDA levels (p<0.05) was found in the experimental animal group that received curcumin 300 and 600 mg/kgBW. Meanwhile, a more significant reduction (p<0.001) was found in the experimental animal group that received 100 and 200 mg/kgBW of nano curcumin. The 200 mg/kgBW nano curcumin group also gave more significant results (p<0.01) in increasing SOD levels compared to curcumin administration at 600 mg/kgBW (p<0.05).

Estakhri *et al.* (2019) also stated that both curcumin and nano curcumin could significantly reduce MDA levels, but with different significance values. Nano curcumin (25 and 60 mg/kgBW) gave more significant results, namely p<0.01, when compared to the control group. Meanwhile, curcumin 25 and 60 mg/kgBW resulted in p values <0.05.

Research by Fakhraei *et al.* (2019) also compared nano curcumin with curcumin. It was proven that nano curcumin at doses of 10, 20, and 50 mg/kgBW significantly increased MDA levels and decreased SOD levels in the heart (p<0.001). Meanwhile, compared to curcumin 50 mg/kgBW, the lowest dose of nano curcumin given was also able to provide significant results (p<0.05).

Similar results were also obtained in research conducted by Namdari and Eatemadi (2017). Nano curcumin was compared with curcumin as a control group on doxorubicin-induced cardiotoxicity. With the same dose, namely 5 mg/kgBW, a significant difference was seen in decreasing MDA levels and increasing levels of SOD (each p<0.05).

Conclusion and Acknowledgements

Both curcumin and nano curcumin are capable to decrease the level of cardiac MDA and increase the level of cardiac SOD as their antioxidant property. Nano curcumin is a more effective cardio-protector compared to curcumin through MDA and SOD level analysis in rats.

The systematic review still has some limitations: first, the literature we searched is limited to English due to the limitation of language, may cause certain retrieval omissions. Secondly, although we tried to find articles that used rats as the experimental animal, the sample sizes, weight, oxidative stress given, and the dosage of curcumin and nano curcumin were different as it is almost impossible to retrieve very similar projects for experimental studies. Thirdly, the original articles we could found were low at present. We look forward to better and more researches to confirm the cardioprotective effect of curcumin and nano curcumin.

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