FORMULATION AND EVALUATION OF QUERCETIN NANOPARTICLE GEL FOR OSTEOARTHRITIS

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ABSTRACT

Objective: To analyze the effects of the topical gel that consists of quercetin nanoparticles on the mono iodoacetate-induced osteoarthritis.

Methods: Injection of lecitin-quercetin into chitosan-tocopheryl polyethylene glycol succinate (TPGS) was used to prepared quercetin nanoparticle. Evaluation parameter for the quercetin nanoparticle including polydispersity index, zeta potential, particle size using particle size analyzer and morphology were executed using a transmission electron microscope. The evaluation of quercetin nanoparticle gel includes organoleptic and also a homogeneity of quercetin nanoparticle gel includes pH and viscosity. Quercetin nanoparticle gel was given for osteoarthritis (OA) animal model. The amount dosage of quercetin nanoparticle used in this study was 0.84, 1.68, and 3.37 mg/g gel. Measurement of the edema volume was conducted on day 7, 14, 21, 28, 35, 42, 49, 56, 63, and 70.

Results: The quercetin nanoparticle gel dosage 1, 2, and 3 could reduce inflammation on two osteoarthritis animal models. On DMM group, 14 d after the treatment, there were significant differences between negative group and dosage 3 (P=0.028) and A. conyzoides extract gel (P=0.015). It has shown that injection of mono iodoacetate intraarticularly significantly increased the volume of edema in all groups that had been given by mono iodoacetate on day 7 to day 28. On the 42 d after administration of quercetin nanoparticle gel, there were significant differences between the normal and dosage 3 group (P= 0.000).

Conclusion: Quercetin nanoparticle gel could reduce inflammation and prevent cartilage damage on histological evaluation.

Keywords: Quercetin, Osteoarthritis, Nanoparticle, Formulation

INTRODUCTION

Osteoarthritis (OA) is a disease with several characteristics, including joint pain, definite motion, and also inflammation without systemic effect. Inflammation also the key modulator on the pathology of osteoarthritis, therefore inflammation could be the targeted therapy for osteoarthritis [1, 2]. Chondrocytes of knee osteoarthritis can increase the activity and production of inflammatory cytokines, which are also made by other joint tissues [3]. The purpose of osteoarthritis therapy is to improve joint caused by inflammation and reduce patient, particularly pain from daily activity. Pain affecting joint can become worst because of joint motion. OA symptoms such as stiffness of joints, chronic pain, and muscle weakness, are the serious risk factor for patients with osteoarthritis with outcomes of impaired quality and also mobility limitation [4].

Nowadays, osteoarthritis therapy includes non-pharmacology therapy and surgery. The first therapy for osteoarthritis is Nonsteroidal Anti-Inflammatory Drugs (NSAID). However, NSAID has several side effect, including gastrointestinal [5] and cardiovascular risk [6]. It is recommended by Osteoarthritis Research Society International (OARSI) that NSAID should be avoided for prolonged use as much as possible [7]. Topical antiinflammation could be the solution to reduce the severity of OA.

Quercetin is one of flavonoid compound that has been isolated and used for the compliment on therapy of disease [8]. In in vitro studies, it showed anti-inflammatory activity because of its ability to inhibited cyclooxygenase (COX) and lipooxygenase (LOX) [9]. Quercetin could also suppress proinflammatory cytokines in cultured fibroblasts on in vivo experiments [10]. However, research about the anti-inflammation effect of quercetin in the topical application has not been discovered yet.

Nanoparticle becomes a potential option for topical drug delivery because of its unique characteristics. Since the increase of surface area, the nanoparticle has higher efficiency to increase drug permeation into the skin. Lecithin-Chitosan Nanoparticle is a promising vehicle in topical drug delivery because of the negative charge in lecithin and positive charge in chitosan bind firmly on human skin, and generate an effective drug delivery system [11].

In this study, the effects of the topical gel that consists of quercetin nanoparticles on the mono iodoacetate induced OA rats were analyzed to evaluate the pharmacodynamic effects.

MATERIALS AND METHODS

Methods

Soybean lecitin Phospholipon 90G (Lipoid GmbH, Germany) and quercetin (Sigma Aldrich, USA) were dissolved in ethanol 96%. Chitosan-TPGS solution achieved by dissolving chitosan (Sigma Aldrich, USA) and TPGS (Sigma Aldrich, USA) with 0.1% acetic acid [12]. The lecithin-quercetin solution was added into chitosan-TPGS solution using plastic needle tubing with 1000 rpm agitator for 30 min. The pH of nanoparticle was arranged until 4.5 using 0.5 M NaOH. The suspension then filtered through a membrane filter to eliminate unfused compound.

Table 1: Quercetin nanoparticle formula

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Formula 1</th>
<th>Formula 2</th>
<th>Formula 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lecithin (g/ml)</td>
<td>0.4%</td>
<td>0.4%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Quercetin (g/ml)</td>
<td>0.06%</td>
<td>0.12%</td>
<td>0.24%</td>
</tr>
<tr>
<td>Chitosan (g/ml)</td>
<td>0.02%</td>
<td>0.02%</td>
<td>0.02%</td>
</tr>
<tr>
<td>TPGS (g/ml)</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Ethanol 96% (ml/ml)</td>
<td>8%</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>0.1% Acetic acid (ml/ml)</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>
The entrapment efficiency of quercetin nanoparticle was measured using High-Performance Liquid Chromatography (HPLC). The nanoparticle was centrifuged at 4500 rpm for 60 min. The collected precipitate calculated with a formula:

Entrapment Efficiency \[ \frac{Q_e}{Q_t} \times 100\% \]

Qe: quercetin concentration on the precipitate
Qt: theoretical quercetin concentration

The concentration of quercetin was analyzed using HPLC with 370 nm wavelength.

Table 2: Formulation of quercetin nanoparticle gel

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Quercetin nanoparticle gel dosage 1</th>
<th>Quercetin nanoparticle gel dosage 2</th>
<th>Quercetin nanoparticle gel dosage 3</th>
<th>A. conyzoides gel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quercetin Nanoparticle</td>
<td>Equivalent to quercetin 0.84 mg/g</td>
<td>Equivalent to quercetin 1.68 mg/g</td>
<td>Equivalent to quercetin 3.36 mg/g</td>
<td>-</td>
</tr>
<tr>
<td>A. conyzoides Extract</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>A. conyzoides Extract 160 mg/g</td>
</tr>
<tr>
<td>Carboplo940</td>
<td>1.5%</td>
<td>1.5%</td>
<td>1.5%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Methylparaben</td>
<td>0.1%</td>
<td>0.1%</td>
<td>0.1%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Butil Hidroxy Toluene (BHT)</td>
<td>0.02%</td>
<td>0.02%</td>
<td>0.02%</td>
<td>0.02%</td>
</tr>
<tr>
<td>Trietanolamin (TEA)</td>
<td>1.5%</td>
<td>1.5%</td>
<td>1.5%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Aquadest</td>
<td>Add 100%</td>
<td>Add 100%</td>
<td>Add 100%</td>
<td>Add 100%</td>
</tr>
</tbody>
</table>

The dosage used was referring to the previous study of A. conyzoides extract with peroral treatment for osteoarthritis animal model [14]. The dosage which gives effect to the OA animal model was 160 mg of A. conyzoides leaves extract, which contains 0.84 mg quercetin. The amount of dosage used in this study was 0.84, 1.68, and 3.37 mg/g gel. A. conyzoides leaves extract was also used in this study. Carbopol 940 (Sumitomo Selka Chemical, Japan) and TEA were added into water. Methylparaben and BHT (Sterlitanak Petrochemical, Russia) were dissolved into propylene glycol (Dow Chemical, Singapore), and was added into the carbopol. HCl 2 M was added to adjusted pH until it suited for skin (4.5-6.5). After the gel was formed, quercetin nanoparticle was mixed into the gel. The formulation of quercetin nanoparticle gel was evaluated, including visual organoleptic, smell, and color. Also, the homogeneity of quercetin nanoparticle gel, including pH and viscosity.

Preparation of the animal model was conducted using white male Sprague-Dawley rats (2-3 mo old) weighed 200-300 g purchased from Bogor Agricultural Institute, Indonesia. The animals were grouped and housed in acrylic cages and maintained on standard laboratory condition (temperature 25±2 °C) with dark and light cycle (12/12 h). This research had been certified by ethical certification of Faculty of Medicine, the University of Indonesia (UI FK No. 668/UN2. F 1/ETIK/2017) for the use of animals in the experiment. Rats were divided into seven groups, with five rats per group. The groups consisted of 1 negative group, one normal group, one positive group, and four treatment groups.

Table 3: Group and treatment of the animal model

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of rats</th>
<th>Treatment on MIA OA model</th>
<th>Treatment on DMM OA model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal group</td>
<td>5</td>
<td>Day-0 were given 0.05 ml saline solution</td>
<td>Day-0 were given open knee surgery without DMM and at day 29-70 were given 1 g of clear gel</td>
</tr>
<tr>
<td>Negative group</td>
<td>5</td>
<td>Day-0 were given 0.05 ml MIA</td>
<td>Day-0 were given DMM surgery and at day 29-70 were given 1 g of clear gel</td>
</tr>
<tr>
<td>Positive group</td>
<td>5</td>
<td>Day-0 were given 0.05 ml MIA and at day 29-70 were given 1 g sodium diclofenac gel</td>
<td>Day-0 were given DMM surgery and at day 29-70 were given 1 g sodium diclofenac gel</td>
</tr>
<tr>
<td>Nanoparticle gel dosage 1</td>
<td>5</td>
<td>Day-0 were given 0.05 ml MIA and at day 29-70 were given 1 g quercetin nanoparticle gel dosage 1</td>
<td>Day-0 were given DMM surgery and at day 29-70 were given 1 g quercetin nanoparticle gel dosage 1</td>
</tr>
<tr>
<td>Nanoparticle gel dosage 2</td>
<td>5</td>
<td>Day-0 were given 0.05 ml MIA and at day 29-70 were given 1 g quercetin nanoparticle gel dosage 2</td>
<td>Day-0 were given DMM surgery and at day 29-70 were given 1 g quercetin nanoparticle gel dosage 2</td>
</tr>
<tr>
<td>Nanoparticle Gel dosage 3</td>
<td>5</td>
<td>Day-0 were given 0.05 ml MIA and at day 29-70 were given 1 g A. conyzoides gel</td>
<td>Day-0 were given DMM surgery and at day 29-70 were given 1 g A. conyzoides gel</td>
</tr>
<tr>
<td>A. conyzoides gel</td>
<td>5</td>
<td>Day-0 were given 0.05 ml MIA and at day 29-70 were given 1 g A. conyzoides gel</td>
<td>Day-0 were given DMM surgery and at day 29-70 were given 1 g A. conyzoides gel</td>
</tr>
</tbody>
</table>

All the group of treatment, positive and negative of MIA OA model were induced intraarticularly with three mg/0.05 ml mono iodacetate on 0.9% saline. The normal group was given 0.9% saline. In treatment with DMM OA model, rats were given DMM surgery. The normal group of DMM OA model was only given open knee surgery without DMM.

The normal group was given clear gel without nanoparticle quercetin, the positive group was given sodium diclofenac gel (Voltaren®), three doses variation of quercetin nanoparticle gel, and A. conyzoides group was given A. conyzoides gel with 160 mg/g gel on day 29 until 70 as seen on table 3. Measurement of edema volume in day 7,14,21,28,35,42,49,56,63 and 70 using plethysmometer.
Statistical calculation was analyzed by One-way ANOVA, followed by multiple comparison tests. P value<0.05 were considered to be significant (P denoted probability). Statistics software (SPSS version 24) was used for statistical analysis. The data represented mean±standard error of the mean.

RESULTS
The visual observation of quercetin nanoparticles formula 1, 2, and 3, respectively shown in fig 1. The yellow color of nanoparticle was achieved from the color of quercetin powder. Quercetin nanoparticle had a translucent yellow with slightly more yellow color on the higher dose of quercetin. It had a specific aroma of quercetin.

One of the main physique characteristics of a nanoparticle is the particle size. In this research, particle size was measured by Particle Size Analyzer. Z-average size of formula 1, 2, and 3 respectively were 242.2 nm, 215.6 nm, and 212.2 nm. Polydispersity index of formula 1, 2 and 3 respectively were 0.474, 0.460, and 0.405. It showed that nanoparticle quercetin formula 3 had the smallest Z-average size and polydispersity index (0.405) compared with formula 1 and 2.

![Fig. 1: Visual observation of quercetin nanoparticle suspension, A: quercetin nanoparticle formula 1; B: quercetin nanoparticle formula 2; C: quercetin nanoparticle formula 3](image)

Table 4: Zeta potential result of quercetin nanoparticle

<table>
<thead>
<tr>
<th>Quercetin nanoparticle dosage</th>
<th>Zeta potential (m/V)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula 1</td>
<td>+19.5±0.45</td>
</tr>
<tr>
<td>Formula 2</td>
<td>+24.0±1.55</td>
</tr>
<tr>
<td>Formula 3</td>
<td>+26.5±0.30</td>
</tr>
</tbody>
</table>

*Data given in mean±SD

Zeta potential more than (+/-) 30 m/V proven to be more stable in colloid and could resist aggregation between the particles because the higher the value of zeta potential the bigger the production of electrostatic deduction [15]. All of the quercetin nanoparticles had zeta potential under±30 m/V. This may occur as a result of electrostatic attraction between acidic phenolic OH group of quercetin and a positive load of the particle, and produce load distribution, making the low zeta potential value on the system. Based on the measurement of zeta potential in this study, formula 3 had the most significant zeta potential (+26.5±0.30 m/V) which indicated that formula 3 was the most stable formula besides formula 1 and 2.

Table 5: Entrapment efficiency of quercetin nanoparticle

<table>
<thead>
<tr>
<th>Quercetin nanoparticle</th>
<th>Entrapment efficiency (%)*</th>
<th>Amount of quercetin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula 1</td>
<td>60.28±0.48</td>
<td>0.36 mg/ml</td>
</tr>
<tr>
<td>Formula 2</td>
<td>62.83±0.25</td>
<td>0.75 mg/ml</td>
</tr>
<tr>
<td>Formula 3</td>
<td>41.41±0.33</td>
<td>0.994 mg/ml</td>
</tr>
</tbody>
</table>

*Data given in mean±SD

Morphology of quercetin nanoparticles was observed under a transmission electron microscope. The results of the observation showed that the nanoparticle was spherical. The nanoparticle size from the photograph showed that the nanoparticle was around 200 nm and it matched with the result of Z-average size of the quercetin nanoparticle formula 3.

![Fig. 2: Vesicle morphology of nanoparticle quercetin formula 3](image)

The entrapment of efficiency in this study was performed using the direct method calculated by compared quercetin concentration on the precipitate and theoretical concentration on formula. The amount of quercetin had been used on formula 1, 2, and 3 respectively were 0.06%, 0.12%, and 0.24% (w/v). The entrapment of efficiency gel was shown in table 5. The higher entrapment efficiency of quercetin nanoparticle was on formula 2, but the highest amount of nanoparticle entrapped on suspension was formula 3, and it showed the best result on Z-average size, index polydispersity, and zeta potential among the others. Therefore, quercetin nanoparticle formula 3 was the chosen formula for quercetin nanoparticle gel.

![Fig. 3: Visual observation of gel, A: clear gel; B: quercetin nanoparticle gel dosage 1; C: quercetin nanoparticle gel dosage 2; D: quercetin nanoparticle gel dosage 3](image)
Quercetin nanoparticle gel had a bright yellow color on every dose. There was a slight difference of yellow color between dosage 1, 2, and 3 with the densest yellow color in nanoparticle gel dosage 3. The yellow color was achieved from the quercetin nanoparticle.

A topical gel must be in the pH range that is suitable for the skin, which is 4.5-6.5. The pH of quercetin nanoparticle gel dosage 1, 2, and 3 respectively were 5.54, 5.60, and 5.58. All of the gel were qualified with a skin pH range. The viscosity of the quercetin nanoparticle gel was measured by Brookfield viscometer using spindle 6 with 10 rpm. The viscosity of the quercetin nanoparticle gel dosage 1, 2, and 3 were respectively 54400 cps, 55200 cps, and 55600 cps.

Fig. 4: Edema profile during treatment in MIA Osteoarthritis model, *Significantly different with the normal group (p<0.05), #significantly different from the negative control group (p<0.05)

Fig. 5: Edema profile during treatment in DMM Osteoarthritis model, *Significantly different with normal group (p<0.05), #significantly different from the negative control group (p<0.05)

In this study, there were seven groups of treatment on each model of osteoarthritis. The normal group consisted of no osteoarthritis rats, and also the negative group consisted of osteoarthritis rats were given clear gel without nanoparticle quercetin. Three different doses of nanoparticle were given to osteoarthritis rats to determine the best dosage for the treatment. A. conyzoides gel group which is from the previous study proven to contained quercetin. A. conyzoides gel group reduced edema of osteoarthritis rats orally. The positive group was that the osteoarthritis rats were given sodium diclofenac gel (Voltaren®). Sodium diclofenac is a potent NSAID use for the treatment of degenerative joint diseases such as osteoarthritis and rheumatoid arthritis [16]. On the previous study, sodium diclofenac gel was proven effective for relieving symptom on osteoarthritis [17]. The treatment was given on day 29 until 70.

Edema volume measurement was measured on day 0, 7, 14, 21, 28, 35, 42, 49, 56, 63, and 70. Edema volume was measured to determine changes in the volume of edema in animals with osteoarthritis before and after the treatments. On DMM group, 14 d after treatment, there were significant differences between negative group and dosage 3 (P=0.028) and A. conyzoides extract gel (P=0.015). On MIA group, it showed that injection of mono iodoacetate intraarticularly significantly increased the volume of edema in all groups given by mono iodoacetate on day 7 to day 28. On the 42 d after administration of quercetin nanoparticle gel, there were significant differences between the normal group and dosage 3 (P= 0.000).

DISCUSSION

In this study, a quercetin nanoparticle gel was given for OA animal model. Nanoparticle becomes the preference for a delivery system of topical drugs because of its typical characteristic. Since the increasing for its surface, a nanoparticle has a higher efficiency to increase drug permeation into the skin [18]. The preparation of nanoparticle consisted
of soybean lecithin, chitosan, and TPGS results in good form of the nanoparticle. Lecithin is a natural phospholipid used for the variety of nanoparticles, and classified as a safe and biocompatible excipient [19, 20]. Chitosan is a polycationic polymer with mainly of glucosamine units that could tie the negatively charged substance resulting in a core-shell nanostructure and proven to be a promising carrier for drugs [21]. It has been reported that lecithin and chitosan can be formed a perfect round nanoparticle by the electrostatic interaction of chitosan polycationic and charge negative of lecithin. The molecule of lecithin formed a core and molecule of chitosan formed the hydrophilic shell layer to protect the inner structure [22]. The injection of lecithin into chitosan aqueous solution from the previous studies could exhibit an excellent spherical shape of nanoparticle and has better stability in the 20:1 ratio [lecithin: chitosan] [23].

The hydrophobic group on TPGS and lecithin molecules tied into each other and formed the hydrophobic core of the nanoparticle. Because of the lipophilicity of quercetin, quercetin should disperse on the hydrophobic core, and protected by the outer shell layer. TPGS had a crucial role in quercetin nanoparticle formulation by intruding stratum corneum to reduce the barrier of the skin and facilitating drug diffusion through the barrier layer. TPGS can also add the diffusion coefficient of nanoparticle between skin and vehicle [24, 25]. In the previous study, TPGS was used as a stabilizer for nanoparticles [26-28].

Polydispersity Index (PDI) less than 0.5 until approaches 0 indicated a low heterogeneity and a homogenous size particle. Measurement of particle size with PDI less than 0.5 was measured using Z-average. On the other way, if a sample has PDI more than 0.5, it is measured using the diameter by volume (DV) to measure the particle size distribution. The polydispersity index of all nanoparticle formula was less than 0.5. Therefore it was measured using Z-average to measure the particle size distribution. The Z-average of nanoparticle 1, 2, and 3 respectively were 242.2 nm, 215.6 nm, and 212.2 nm.

The particle size of the sample is very affected by zeta potential. Zeta potential is a measure of potential electrostatic or capacity of repulsion between particles on a liquid suspension. Zeta potential is an important parameter that affected the stability of a dispersion system. Zeta potential could predict the aggregation or flocculation on suspension. Zeta potential of the nanoparticle respectively were 19.5 ± 0.45, 24.0 ± 1.55, and 26.5 ± 0.30 mV. Electrostatic attraction among the acidic phenolic OH group of quercetin and the positive charge particle affected the distribution of charges and caused a decrease of zeta potential of the system [29].

The vesicle morphology result of quercetin nanoparticle dosage 3 on Transmission Electron Microscope has shown that the quercetin nanoparticle was spherical. This result had matched with the previous study, which proven that lecithin and chitosan can form a perfect round nanoparticle. The vesicle size of nanoparticle was quite similar to the particle size measured by Particle Size Analyzer.

One of the primary purposes of osteoarthritis therapy is to escalate quality of life, such as relieving pain and reduce inflammation. The inflammation can develop due to the depletion layer of articular cartilage [30]. In this study, two of the osteoarthritis animal model were used. The DMM method is one of the animal model of Post Traumatic Osteoarthritis (PTOA) that causes inflammation. Higher mechanical loading of the medial compartment is the cause of increased incidence of medial compartment knee OA that changes the mechanical environment of the knee, and this has a profound influence on the initiation and progression of knee OA [31]. Intrarticularly injection of MIA inhibits glyceraldehyde-3-phosphate dehydrogenase activity in chondrocytes and causing cell death. It increases cytokines releases into the joint cavities and causing cartilage matrix damages [32]. The result of chondrocytes loss is morphological changes of articular cartilage, firmly in human osteoarthritis [33]. Another result is rapid inflammation and pain on day post-injection, and therefore, inflammation can serve as a measure of disease progression and also treatment outcomes in OA.

Edema volume was measured to observe the changes in the volume of edema in animals with osteoarthritis before and after the treatment. It had shown that injection of mono iodicacetic intraarticularly significantly increased the volume of edema in all groups that had been given mono iodicacetic on day 7 to day 28. On 42 d after administration of quercetin nanoparticle gel, there were significant differences between the negative group and dosage 3. Joint inflammation of inflammatory cells and fluid to the inflamed area. The difference between edema of joint of negative group and quercetin nanoparticle group showed that quercetin had the anti-inflammation effects in OA animal model. In previous in vivo study, quercetin nanoparticle gel could prevent proteoglycan degradation by inhibits matrix metalloproteinase -9 (MMP-9), matrix metalloproteinase-13 (MMP-13), and a diastereis and metalloproteinase with thrombomodulin motifs-5 (ADAMTS-5) expressions on OA rats [34]. In the previous in vitro study showed that quercetin could inhibit lipopolysaccharide (LPS)-induced tumor necrosis factor α (TNFα) production in macrophages [35]. Quercetin also has antiapoptotic and membrane protective effects [36]. Flavonoid has anti-inflammatory effects by inhibits the activity of enzyme cyclooxygenase (COX) and lipoxygenase (LOX) [37]. It also has the inhibition mechanism of leukocyte accumulation, histamine, and neutrophil degranulation [38].

CONCLUSION

In conclusion, the author had designed the quercetin nanoparticle gel for osteoarthritis rats. Nanoparticle lecithin chitosan vehicle could bring quercetin into the target sites and be able to reduce inflammation process by reducing the edema volume. Nanoparticle quercetin gel dosage 3 showed the best efflication on osteoarthritis model of rats.

AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICTS OF INTERESTS

There are no conflicts of interest

REFERENCES


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