



## Effectiveness of Curry Leaf Extract Gel on Fibroblast Cell Count in Periodontitis-Induced Wistar Rats

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### ARTICLE INFO

#### Keywords:

*Curry leaves extract;  
Fibroblasts;  
Periodontitis*

#### Article History:

Received : 23/07/2025

Revision : 28/12/2025

Accepted : 10/01/2026

Published : 01/02/2026

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ISSN: 2775-0159



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### ABSTRACT

**Background:** Periodontitis is an inflammatory condition affecting the tissues that support the teeth, triggered by bacterial plaque, which leads to the ongoing and gradual destruction of the periodontal ligament and alveolar bone. Gingival recession and periodontal pockets are characteristics of clinical features. The disparity in the interaction between bacteria and the host's immune response can inhibit fibroblast proliferation, resulting in periodontal tissue damage. Important phytochemical components found in curry leaves (*Murraya koenigii*) include flavonoids, tannins, alkaloids, and saponins. Flavonoids and saponins effectively inhibit the growth of bacterial colonies in periodontal pockets.

**Objective:** The research aims to assess the effect of curry leaf extract gel on the level of fibroblast cells in periodontitis.

**Methods:** A posttest-only control group design was used in the experimental laboratory. Subjects were categorized into 3 categories: a treatment group (10% curry leaf extract), a positive control (metronidazole), and a negative control (aquades). The number of fibroblast cells was statistically assessed with the one-way ANOVA method and the LSD post-hoc test.

**Outcome:** The results showed a significant difference in the number of fibroblast cells stimulated by periodontitis in each group.

**Conclusion:** There was significant variance in fibroblast count between the groups.

### Citation (Vancouver style):

Ismi N, Saputri D, Sunnati, Alibasyah ZM, Arsika DY. Effectiveness of curry leaf extract gel on fibroblast cell count in periodontitis-induced Wistar rats. *Indones J Dent.* 2026;6(1): 1-14.

## INTRODUCTION

Periodontal disease is an inflammatory disorder that develops in the gingiva and may impact other periodontal tissues, including the ligaments and alveolar bone, affecting up to 90% of the world.<sup>1</sup> Periodontal disease is caused by bacterial plaque on the surface of the teeth.<sup>2</sup> *Porphyromonas gingivalis* is a frequently occurring pathogen of periodontal disease with numerous potential virulence factors, including lipopolysaccharide and gingipain. Gingipain contributes to weakening the host immune response by modulating the complement system, interfering with T cell activity, and affecting vascular permeability, while lipopolysaccharide has the selective ability to reduce the immune response by synthesizing heterogeneous lipid A molecules and aggravating periodontal tissue conditions. Long-term imbalances in interactions between bacteria and the host's immune response may disturb the process of fibroblast cell proliferation, resulting in periodontal tissue damage that causes periodontitis.<sup>3,4</sup>

The periodontal tissue wound healing process occurs sequentially, starting from the stages of inflammation, proliferation, and remodeling.<sup>5</sup> Fibroblasts are one of the cell types that play an essential part in the proliferation stage. Fibroblasts can produce collagen, so that the wound will be well covered and the resulting pink granulation tissue will form. After that, the proliferation phase will end and continue with the maturation process that continues in the remodeling stage.<sup>4,5</sup> The main process that occurs in the remodeling phase is the remodeling of the extracellular matrix into a normal tissue structure.<sup>6,7</sup>

Periodontal disease treatment aims to repair the gingival inflammatory tissue, reduce the number of pathogenic bacteria, and reduce the depth of pockets. Periodontal disease management can be mechanical, along with systemic and topical administration of antibiotics. The use of antibiotics must be considered because incorrect use can cause antibiotic resistance and provide side effects in the long term. Innovations are currently being developed to provide herbal ingredients as an alternative to drugs combined in dental treatment actions. Curry leaf extract (*Murraya koenigii*) is a case study of an herbal ingredient with active compounds like alkaloids, flavonoids, and saponins that have antibacterial and anti-inflammatory effects.<sup>8</sup>

The curry leaves are members of the Rutaceae family. This plant thrives in tropical climates in the Asian region. The leaves, roots, and stems of the *Murraya koenigii* plant are useful as medicines because they have anti-inflammatory, antibacterial, and antioxidant activities.<sup>9</sup> Research by Sukma et al (2018) found that the ethanol extract of curry leaves (*Murraya koenigii*) includes saponins and flavonoids that exhibit the most effective control against Gram-negative and positive bacteria.<sup>10</sup> elita J et al (2019) indicate that other benefits of curry leaves (*Murraya koenigii*) are increasing collagen deposition, angiogenesis, and fibroblast

density.<sup>11</sup> Unita et al. (2016) found that curry leaf extract (*Murraya koenigii*) at a concentration of 10% has stronger antibacterial activity compared to concentrations of 2.5%, 5%, and 7.5%.<sup>12</sup> In accordance with the previous description, this study aims to assess the impact of curry leaf extract (*Murraya koenigii*) gel application on the number of fibroblast cells in periodontitis-induced male Wistar rats.

## RESEARCH METHODS

This research used an experimental laboratory design with a post-test-only control group., conducted at the Natural Materials Pharmacy Laboratory and Drug Formulation Laboratory, Pharmacy Department, Faculty of Mathematics and Natural Sciences (FMIPA), Universitas Syiah Kuala, for phytochemical testing and extract preparation. Then continued at the Laboratory of Animal Experiments, Faculty of Veterinary Medicine, Histology Laboratory, Veterinary Medicine Faculty, Universitas Syiah Kuala. The ethics committee approved this research with the number 470/KE/FKG/2023. The samples used were Curry leaves (*Murraya koenigii*) obtained from Darussalam, Gampong Tanjung Selamat, Aceh Besar, and male Wistar rats obtained from the Veterinary Medicine Faculty. Selection of Wistar rats as research subjects is based on inclusion criteria including 2-3 months of age, body weight 175 to 200 grams, and are in general healthy condition.

### **The procedure for preparing Curry Leaf Extract (*Murraya koenigii*)**

A total of 2 kg of Curry leaves (*Murraya koenigii*) were cleansed and dried, then crushed into fine powder. Next, the process of extracting the material is carried out through maceration, with 80% ethanol accompanied by periodic stirring to improve the solvent's contact with the surface of the curry leaves (*Murraya koenigii*). This may facilitate the release of bioactive compounds. After 5 days, the solution was put through filtration to isolate the filtrate from the residue. After the filtration process, the resulting filtrate undergoes an evaporation stage through a vacuum rotary evaporator until a thick extract is produced.<sup>13</sup>

### **Curry Leaf Extract (*Murraya koenigii*) Phytochemical Test**

The phytochemical analysis occurred as an initial process to determine and classify the active compounds in curry leaves extract (*M. koenigii*), mainly flavonoids, tannins, saponins, and steroids.<sup>14</sup>

### **Flavonoid Test**

The dissolution stage was completed by mixing 0.5 g of curry leaf extract with 5 ml of ethanol.<sup>15</sup> The process continued with the addition of two drops of concentrated HCl and magnesium powder; the creation of a red color shows a positive result.<sup>16</sup>

### **Alkaloid Test**

The analysis process began by putting 0.5 grams of curry leaf extract (*M. koenigii*) into a test tube as the preliminary phase of the process of formulation. 1 mL of 2 N HCl solution and 9 mL of water were next added. After heating for 2 minutes and cooling, the mixture was filtered, and the filtrate was allocated into three test tubes, containing three drops each.<sup>17</sup> After adding Bouchardat reagent, the first tube shows a brown deposit as an indicator of a positive reaction. Meanwhile, the second tube given Mayer's reagent shows a positive result when a white or yellow deposit is produced. The third tube uses Dragendorff reagent, which shows a positive result with the appearance of a brick red deposit.<sup>18</sup>

### **Saponin Test**

Curry leaf extract (*Murraya koenigii*) of 0.5 g is mixed with 0.5 g is mixed with ten milliliters of hot water in a test tube. After the cooling process, the mixture was shaken for ten seconds to form a 1-10 cm high foam layer, which should be stable for 10 minutes. Then, apply 1 drop of 2 NHCl; if the froth does not disappear, it can be concluded that there is saponin content.<sup>19</sup>

### **Tanin Test**

The dissolution process is carried out by mixing 0.5 grams of *Murraya koenigii* extract into 5 ml of distilled water until a homogeneous solution is obtained. Then add a few drops of 10% FeCl<sub>3</sub> solution. Seen the positive results with the formation of a dark green color.<sup>20</sup>

### **Steroid Test**

Curry leaf extract (*Murraya koenigii*) as much as 0.5 g was added to 10 drops of CH<sub>3</sub>COOH and 2 drops of concentrated H<sub>2</sub>SO<sub>4</sub>. Positive results show the color changes to green or blue.<sup>21</sup>

### **Preparation of Curry Leaf (*Murraya koenigii*) Extract Gel**

The curry leaf (*Murraya koenigii*) gel formulation process involves the addition of carbopol into distilled water, followed by intensive stirring so as to strengthen the gel base structure. Methyl paraben and glycerin were mixed until homogeneous. Next, curry leaf extract

(*Murraya koenigii*) was mixed with propylene glycol. Triethanolamine was added with constant stirring until the mixture became homogeneous.<sup>22</sup>

### **Evaluation of Formulation and quality of leaf extract gel preparation (*Murraya koenigii*)**

Evaluation of the gel is aimed at assessing the physical stability of the formulation through a series of tests. The pH measurement is carried out by inserting a digital pH meter electrode into the gel preparation. Observing the pH value, which appears to be the most important parameter of the preparation's chemical stability. The ideal pH range for the gel is between 4.5-6.5 so that it remains stable and comfortable to use.<sup>23,24</sup> The adhesion test involved weighing 0.25 g of gel, depositing it on a glass object, and then placing another glass object on top of it and applying a 1 kg load for five minutes. After the first load is lifted, another load of 80 grams is given, and the amount of time required for dividing the two glass items. Gel preparations must adhere for more than one second.<sup>23,25</sup> For the spreadability test, prepare 0.5 g of gel, put it on a glass slide, cover it with another glass slide for up to a minute, and then measure the spread's diameter. Then give each load (multiples of 50 g) for up to 1 minute, then measure how much the diameter of the gel spreads. A good gel has a spreadability of 5-7 cm.<sup>23</sup> Viscosity measurements were made using a rheology spindle no. 5 type viscometer with a speed of 50 rpm. A good gel has a viscosity in the range of 2000-4000 Cpss.<sup>22,26</sup>

### **Manipulation of Chronic Periodontitis in Male Wistar Rats (*Rattus norvegicus*)**

The process of anesthesia in Wistar rats is done intramuscularly using a combination of ketamine hydrochloride and xylazine hydrochloride which will be injected into the leg in the tricep musculus area.<sup>27</sup> Periodontitis was induced with a 0.008 inch wire ligature in the area of the cervical mandibular incisor using a needle holder.<sup>28</sup> The gingival irritation and plaque accumulation were then left for 21 days, resulting in periodontal disease.<sup>29</sup>

### **The Use of Curry Leaf Extract (*Murraya koenigii*) Based Gel**

At the 21st day, periodontitis conditions are clinically estimated to begin to appear in the test animal model (rats). A total of 9 rats were grouped into three groups to be used with 10% Curry (*Murraya koenigii*) leaf extract gel, metronidazole, and distilled water using a syringe on the gingival sulcus that experienced periodontitis. Gel application was done twice a day for 7 days.<sup>30</sup>

### **Histopathology Evaluation**

After 7 days of treatment, rats were euthanized by cervical dislocation method, which had previously been anesthetized using ketamine hydrochloride and xylazine hydrochloride.<sup>31</sup>

Mandibular tissues from rats were separated and fixed in 10% neutral buffered formalin. Decalcification was carried out for 14 days at room temperature using 10% formic acid solution.<sup>32</sup> Furthermore, tissue dehydration was carried out using graded alcohol (70%, 80%, 90%, and 100%).<sup>33</sup> Then the purification was done by soaking the tissue in xylol for 3 hours.

The next step is the process of embedding the tissue by mixing liquid paraffin for 2 hours at 56-60 °C. The paraffin and tissue were frozen into blocks, which were then sliced with a microtome measuring 5-6 µm. The pieces were placed on a water bath to avoid folds in the tissue due to cutting. Then the tissue was transferred to a glass slide for staining.<sup>34,35</sup>

The staining process was carried out with Hematoxylin-Eosin (HE) after paraffin was removed with xylol, followed by dipping the preparation into alcohol 100%, 90%, 80%, 70%, and distilled water, then put into hematoxylin for 15 minutes. Next, the preparation was rinsed with distilled water and dipped in eosin, and then continued in alcohol for 5 minutes. The preparations were then dipped gradually into a series of alcohol solutions with concentrations of 70%, 80%, 90%, and 100%, and then put into xylol for 3 minutes. After that, the preparations were covered with a cover glass. Measuring the number of fibroblast cells histologically in 3 fields of view with a light microscope at 400x magnification.<sup>36</sup>

### Data Analysis

The Statistical Package for Social Science (SPSS) software was used for data analysis, and the one-way ANOVA approach was used for evaluating hypotheses on the variable number of fibroblast cells.

## RESEARCH FINDINGS

The findings from the phytochemical analysis of curry leaf extract (*Murraya koenigii*) are presented in Table 1.

**Table 1.** Data on Phytochemical Analysis Results on Curry Leaf Extract (*Murraya koenigii*)

Metabolite compounds	Reagents	Test Results
Tanin	Gelatin + H <sub>2</sub> SO <sub>4</sub>	+
Flavonoid	HCL dan Logam Mg	+
Alkaloid	Mayer	+
	Wagner	+
	Dragendorff	+
Saponin	Pengcokan	+
Steroid	Liebarmann Banchard Test	-

### Evaluation Results of Curry Leaf Extract Gel (*Murraya koenigii*)

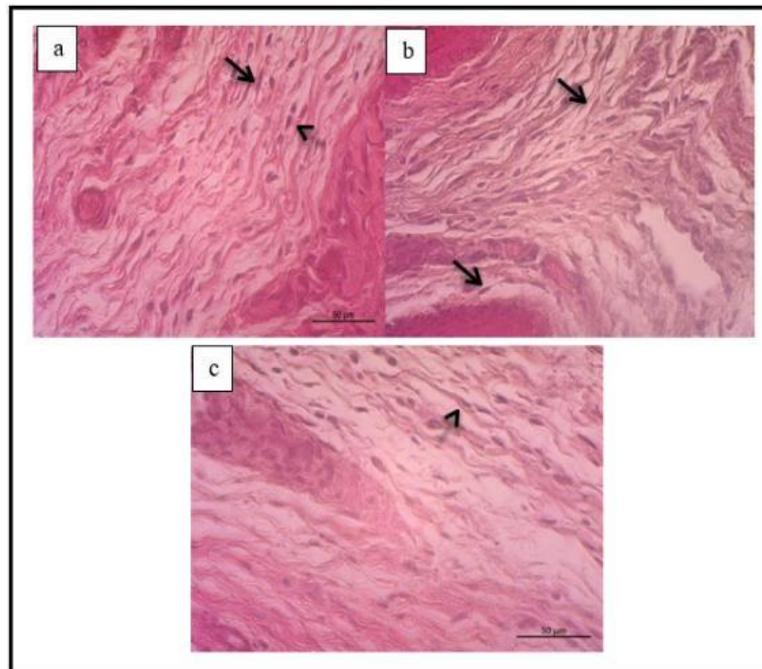
The assessment of the gel made from curry leaf extract (*Murraya koenigii*) is presented in Table 2.

**Table 2.** The Gel Results of Curry Leaf Extract (*Murraya koenigii*) Assessment

Test Parameters				
Homogeneity	pH	Spreadability	Adhesiveness	Viscosity
Homogeneous	5,5	No load = 4 cm 50 gr load = 4,2 cm 100 gr load = 5 cm	1,4 sec	5692 cPoises

### Fibroblast Cell Count and Results of Observation

Histopathological samples from 9 rats were observed using a light microscope with 400x magnification and five fields of view to count fibroblast cells.



**Figure 1.** Histopathological features of fibroblast cells (black arrows) In: Group (a) Treatment, (b) Positive Control, (c) Negative Control.

**Table 3.** The mean value of fibroblast cells obtained through histological evaluation in five fields of view

Sample	The Mean Number of Fibroblast Cells Viewed from 5 Microscopically Seen Fields		
	Treatment	Positive Control	Negative Control
1	40,6	51	31,8
2	32,6	55	40,4
3	35,8	49,2	33
Mean	36,33	51,733	35,06

The results of observations and the calculated quantity of fibroblast cells in each of five fields of view the average is obtained by summing all cells per field of view and dividing by 5. The mean number of fibroblast cells in the subject group treated with curry leaf extract gel (*Murraya koenigii*) was 36.3 cells /5 field of view. The positive control group received treatment with metronidazole obtained an average of 51.7 cells/5 visual fields, while the average number of fibroblast cells in the negative control group treated with distilled water gel was 35.06 cells/5 visual fields.

### Analysis of Data Results

The one-way ANOVA statistical test was used to examine fibroblast cell counts for the purpose of determining whether treatment groups differed significantly. The assumptions of normality and homogeneity in the data must be met first, with the Shapiro-Wilk test for normality and a homogeneity test for uniformity of variance. Data were considered qualified if the p-value > 0.05.

**Table 4.** ANOVA Test One-Way Results of Fibroblast Cell Counts

<b>Fibroblast Cell Count Results</b>	
p	0,000

One-way ANOVA statistical test resulted in a p-value = 0.000 ( $p < 0.05$ ). This demonstrates a significant variation in the overall number of fibroblast cells between treatment groups. The study shows that the administration of curry leaf extract gel (*Murraya koenigii*) has the effect of increasing the number of fibroblast cells in the periodontitis-induced gingiva of male Wistar rats. A post hoc LSD test was then used to compare the treatment groups.

**Table 5.** Results of Post Hoc LSD Test on the Number of Fibroblast Cells in Each Group

<b>Comparison Groups</b>	<b>Mean±SD (group 1)</b>	<b>Mean±SD (group 2)</b>	<b>p-value</b>
Gel Extract vs Positive Control (metronidazole)	36,33±7,65	51,73±6,78	0,000*
Gel Extract vs Negative Control (aquades)	36,33±7,65	38,00±9,79	0,580
Positive Control vs Negative Control	51,73±6,78	38,00±9,79	0,000*

\*Statistically significant difference ( $p < 0.05$ )

The post hoc LSD test results demonstrated a statistically significant difference between the groups given Curry leaf extract gel and metronidazole ( $p=0.000$ ), as well as distilled water and metronidazole ( $p=0.000$ ). A comparison between the use of curry leaf extract gel (*Murraya koenigii*) and aquades  $p=0.58$ , stated that there was no statistically significant difference.

## DISCUSSION

In this study, researchers used curry leaves (*Murraya koenigii*), which are widely known to have potential health benefits. Several studies have proven the existence of various bioactive compounds contained in curry leaves that have medicinal properties. The choice of maceration technique in the extraction process is based on its advantages, that do not require high-intensity heating. This effort is made to minimize the degradation of thermolabile compounds contained in curry leaves (*Murraya koenigii*).<sup>37</sup> The solution used is 80% ethanol because it has low toxicity and can extract flavonoid, phenolic, tannin, alkaloid, and terpenoid compounds.<sup>38</sup>

The finding of the phytochemical test (Table 1) show that the composition of curry leaf extract (*Murraya koenigii*) contains alkaloids, flavonoids, saponins, and tannins, but no steroid compounds were detected. The results of this study differ from those of studies carried out by Mustanir et al (2018), which show that curry leaf extract (*Murraya koenigii*) is found to comprise a range of active components, including alkaloids, flavonoids, terpenoids, saponins, and steroids.<sup>39</sup> A study by Friska F et al stated that the phytochemical content in plants is influenced by various environmental factors, including climatic conditions, soil nutrient composition, and light intensity, which can modulate the concentration of bioactive compounds contained.<sup>40</sup> Secondary metabolite compounds of curry leaf extract (*Murraya koenigii*) have various benefits, such as the presence of flavonoids and saponins, which are most often associated with anti-inflammatory and antibacterial activities. Kusumawardhani's research (2015) shows that betel leaf extract ointment (*Piper betel linn*) containing saponins can increase the number of fibroblasts.<sup>41</sup> Flavonoids function as anti-inflammatory agents and have an impact on the growth of fibroblast cells. Flavonoids are also known to inhibit arachidonic acid activity via the cyclooxygenase and lipoxygenase pathways. Restriction of prostaglandin, thromboxane, and leukotriene production leads to reduced leukocyte movement towards the inflammatory area. With a reduced inflammatory response, the inflammatory process can more quickly transition to the proliferation phase, ultimately accelerating the tissue healing process.<sup>41</sup> Saponins are known to affect and enhance Transforming Growth Factor-beta synthesis (TGF- $\beta$ ). Platelets, macrophages, and T lymphocytes release TGF- $\beta$ , which acts as a major signal in the control of fibroblast function. This increase in TGF- $\beta$  activity will stimulate fibroblast proliferation so that their numbers increase in the process of tissue healing.<sup>43</sup>

As a result of observing and measuring the fibroblast cell count (Table 3), we found variations in the average number of fibroblast cells between the groups. The average number of fibroblast cells recorded in the group treated with gel made from curry leaf extract (*Murraya*

*koenigii*) was 36.33, less than the control group (Metrodinazole), with an average of 51.733. This is due to the extract gel's low amount of compounds contained in the curry leaves.

The quantity of fibroblast cells varied significantly between the treatment groups, according to the one-way ANOVA test results shown in Table 4. This effect is thought to be related to the presence of bioactive compounds in curry leaves, such as flavonoids and saponins, which have biological activities in inhibiting the inflammatory process, antioxidants, contributing to the growth and migration of fibroblast cells to the wound area. The findings of this study show a relationship that is in line with the results of previous research conducted by Prestiyanti et al (2021), which also showed significant results with a p-value = 0.001 in the one-way ANOVA test. This indicates a significant difference ( $p < 0.05$ ) in the average number of fibroblast cells following treatment. The increase in the number of fibroblast cells and the reepithelialization process in the study is thought to occur due to the administration of gotu kola leaf extract, which is known to include active ingredients like tannins and flavonoids. Both of these compounds are crucial to the healing of wounds, including the stimulation of fibroblast cell proliferation and new tissue formation.<sup>44</sup>

Based on the Post Hoc LSD test shown in Table 5, It is known that there are considerable differences in the curry leaf extract gel and metronidazole test groups ( $p=0.000$ ), as well as distilled water and metronidazole ( $p=0.000$ ). The group with no significant difference was the curry leaf extract gel and distilled water group ( $p=0.580$ ). This is due to the mechanism of metronidazole gel, which is effective in killing bacteria by disrupting the DNA synthesis process in the nucleus of bacterial cells and inhibiting the formation of proteins against microbes. Then, metronidazole gel is bactericidal against anaerobic microorganisms, which are the main pathogens of periodontitis, while curry leaf extract contains metabolite compounds that can affect the number of fibroblasts.<sup>45</sup>

The evidence in this study reinforces the results of earlier studies provided by Atiqah et al. (2021), which discovered no discernible difference between the metronidazole gel group (25%) and the mangosteen peel extract gel group (75%) ( $p = 1.000$ ). This is because metronidazole gel is the most effective anti-inflammatory and antibacterial in triggering fibroblast proliferation.<sup>46</sup> The anti-inflammatory effect will activate macrophages to release cytokines and growth factors, which in turn can induce fibroblast cells to proliferate as a part of the tissue healing process.<sup>47</sup> Anti-inflammation is induced by blocking the cyclooxygenase enzyme process that contributes to the production of inflammatory mediators. As a result, the inflammatory process can stop immediately, and the proliferation process begins in new tissues. Mangosteen peel extract is known to contain active substances such flavonoids, alkaloids,

saponins, tannins, and xanthones that are antibacterial and anti-inflammatory, components that are also found in curry leaf extract gel.<sup>46</sup> These findings of this study show that the use of curry leaf extract gel (*Murraya koenigii*) has the capacity to increase the number of fibroblast cells in the periodontitis-induced gingival tissue of Wistar rats, although not comparable to the effectiveness of metronidazole gel.

## **CONCLUSION**

There was significant variation in fibroblast count between the groups. The post hoc LSD analysis demonstrated that the positive control group (metronidazole) was the group that received treatment that increased the quantity of fibroblasts the most. The curry leaf extract gel had no significant difference from the negative control (aquades); hence, it cannot be regarded as effective in increasing the number of fibroblast cells in periodontitis-induced Wistar rats.

## **ACKNOWLEDGMENTS**

The author's thanks go to all those who have provided support and contributions during the research process until the publication of this article.

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