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Research Article

Mangiferin enhances human umbilical vein relaxation associated with no signaling, without exhibiting cytotoxicity on human endothelial cells.

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ABSTRACT

Mangiferin, a xanthone isolated from mango, has been shown to effectively induce vasodilation in the rat mesenteric artery without exhibiting toxicity on rat vascular smooth muscle cells (VSMCs). The mechanism of mangiferin was demonstrated through the upregulation of endothelial nitric oxide synthase (eNOS) expression and enhancement of nitric oxide (NO) production in rats. However, the effect of mangiferin on human blood vessels has not been clarified. We aimed to investigate whether mangiferin induces vasodilation in human umbilical vein (HUV) and its toxicity on human umbilical vein endothelial cells (HUVECs). A mangiferin-induced HUV relaxation was measured by using organ bath technique. The cytotoxicity of mangiferin-treated HUVECs were tested using cell viability assay. Mangiferin effectively induced vasodilation in 5-HT-induced HUV contractions, with an EC_{50} of approximately 2 µM and a maximum effect of around 30%. This vasodilatory response was partially mediated through a NO-dependent pathway, as evidenced by its inhibition by eNOS inhibitors. Furthermore, prolonged exposure to mangiferin (72 hours) in HUVECs showed no cytotoxic effects, underscoring its potential as a safe and effective vasodilating agent for vascular health applications.

Keywords:
Mangiferin; Vascular tension; Human umbilical vein; Human umbilical vein endothelial cell.

1. INTRODUCTION

Blood vessels are crucial for regulating blood flow by controlling vascular tension, which is essential for transporting nutrients and oxygen to maintain overall body homeostasis[1]. They are lined with an endothelium that actively secretes vasodilators, such as nitric oxide (NO), promoting healthy blood flow and circulation[1-3]. Malfunctioning endothelium leads to vascular hypercontraction, which in turn causes organ dysfunction due to inadequate oxygen and nutrient supply[3,4]. Currently, therapeutic drugs effectively reduce endothelial dysfunction, decrease vasoconstriction, and ultimately improve blood flow, despite being associated with side effects on the body[5,6]. Thus, natural substances with low side effects offer an alternative for preventing vasoconstriction caused by endothelial cell dysfunction.

Mangiferin, a polyphenol compound classified under the xanthone group (Figure 1), is naturally occurring in the pulp, fruit peel, leaves, and stems of the mango *(Mangifera indica L)*.[7] It has been found to have anti-inflammatory, antioxidant, anti-dyslipidemia, anti-diabetic, and anti-cancer effects[8-11]. According to previous studies, mangiferin displays antioxidant properties in

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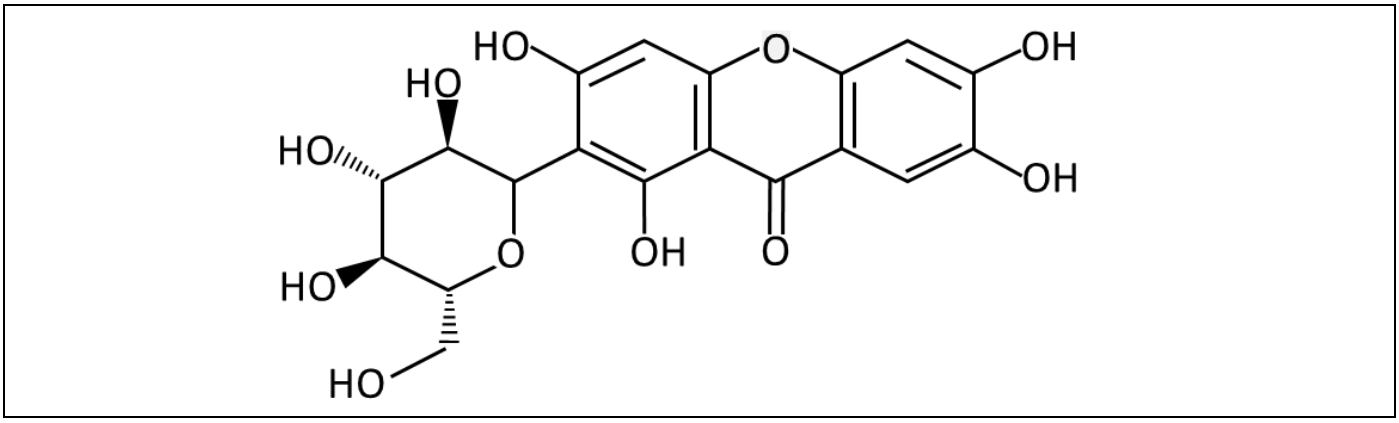

Figure 1 Chemical structure of Mangiferin. A xanthone glycoside commonly found in mango leaves, bark, and fruit (*Mangifera indica L.*).

human umbilical vein endothelial cell (HUVEC) by downregulating mRNA and protein expression involved in inflammation processes while concurrently upregulating eNOS and consequently increasing NO production[9,12]. Furthermore, mangiferin also increased the relaxation of mesenteric arteries in rats without cytotoxic effects[13]. However, there is limited direct evidence supporting the relaxation of human blood vessels and its toxicity on human vascular endothelial cells. Based on evidences indicating the potential role of mangiferin in inducing relaxation and its associated mechanism involving eNOS activation, the objective of this study is to examine the impact of mangiferin on isolated human umbilical veins (HUV) through NO signaling pathway and its toxicity on cultured HUVEC. This introduces a new herbal compound for supporting blood circulation, while also aiding in the prevention and treatment of cardiovascular diseases in humans.

2. MATERIALS AND METHODS

2.1 Chemicals and solutions

All chemicals and reagents were obtained from Sigma Chemicals (St. Louis, MO, USA), stored and prepared following the manufacturer's instructions. The chemicals were prepared as stock solutions. Mangiferin and L-NAME were dissolved in dimethyl sulfoxide (DMSO), while serotonin (5-hydroxytryptamine; 5-HT) was dissolved in 1 N hydrochloric acid (HCl). In all experiments, the maximum final cumulative DMSO and HCl concentrations in the bath were less than 1% and 0.1% v/v, respectively.

2.2 Umbilical cord collection and HUV preparation

Human umbilical cords were randomly obtained from healthy pregnant women without any diseases or abnormal vascular conditions. A total of fourteen umbilical cords were collected following either vaginal delivery or cesarean section. This protocol was approved by the Naresuan University Institutional Review Board (NU-IRB), under certificate of approval (COA) number 521/2020. The umbilical cord was carefully cut approximately 5-10 cm from its attachment to the placenta, preserved in modified Krebs solution (mM): 119 NaCl, 4.7 KCl, 2.5 $CaCl_2$, 1 $MgSO_4$, 25 $NaHCO_3$, 1.2 KH_2PO_4, 0.004 EDTA, 11 D-glucose), and used within an hour of collection. Human umbilical vein (HUV) was isolated from the umbilical cord and stripped of Wharton's jelly. The cleaned HUV was then cut into rings measuring 2 to 3 mm each. The vascular reactivity of these rings was later measured using the organ bath technique.

2.3 Vascular reactivity measurement

HUV rings were utilized for the measurement of isometric tension in an organ bath setup. The rings were mounted in an organ chamber by using stainless-steel hooks, which connected to a force transducer. The transducer was interfaced with an amplifier, which in turn was connected to a personal computer. Ring tensions were graphically displayed using LabChart software (ADInstruments, Dunedin, New Zealand). During the 90-minute equilibrium period, the resting tension of the HUV rings was adjusted to 3 grams. Throughout this process, the organ chambers were continuously filled with Krebs solution at 37°C and continuously aerated with a carbogenic gas mixture (95% O_2, 5% CO_2). Before starting experiments, HUV ring viability was determined twice by 35 mM KCl and then washing it out with Krebs solution.

To assess the effects of mangiferin-induced vasodilation, HUV rings were precontracted with 1 μM serotonin (5-HT) until the contraction stabilized. Mangiferin was then added in cumulative doses ranging from 0.1 to 100 μM to obtain concentration-relaxation curve. All doses were administered after the responses reached a plateau. The effect of DMSO was assessed as a solvent control using the same protocol.

The NO signaling pathway involved in mangiferin-induced relaxation was investigated by pre-incubating the rings with 100 µM N^G-Nitro-L-arginine Methyl Ester (L-NAME), a NOS inhibitor, for 30 minutes, followed by pre-contraction with 1 µM 5-HT. Cumulative concentrations of mangiferin were then added.

After the experiment was completed, all HUV rings were tested with 35 mM KCl to confirm that the vessels still functioned normally. The representative tracings were obtained following the experimental protocols outlined in the timeline shown in Figure 2A and 3A.

2.4 Cell culture and cytotoxicity assay

Human umbilical vein endothelial cells (HUVECs; Lonza Walkersville, MD, USA) were commercially obtained, prepared following the manufacturer's instructions, and cultured with endothelial culture medium M199[14] at 37°C in a humidified 5% CO_2 incubator. A cell viability assay was conducted to investigate the toxicity of mangiferin on HUVECs. Cells at passages 4-5 were counted with hemocytometer using 0.3% trypan blue solution (Gibco™, Thermo Scientific, USA), then equally suspended into a 96-well plate, and incubated until they reached approximately 100% confluence. Plated HUVECs were treated with mangiferin (0.1-100 µM), or 0.1% DMSO, and kept in 37°C incubator for 72 h. The treated-HUVECs were incubated with 0.5 mg/ml of 3-[4, 5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) solution for 4 h at 37°C to allow the formazan crystal formation. The crystals were then dissolved with DMSO and absorbance was read at 595 nm using a spectrophotometer (Bio-Rad Laboratories, Hercules, CA, USA). HUVEC viability was calculated as percentage of control (DMSO) absorbance.

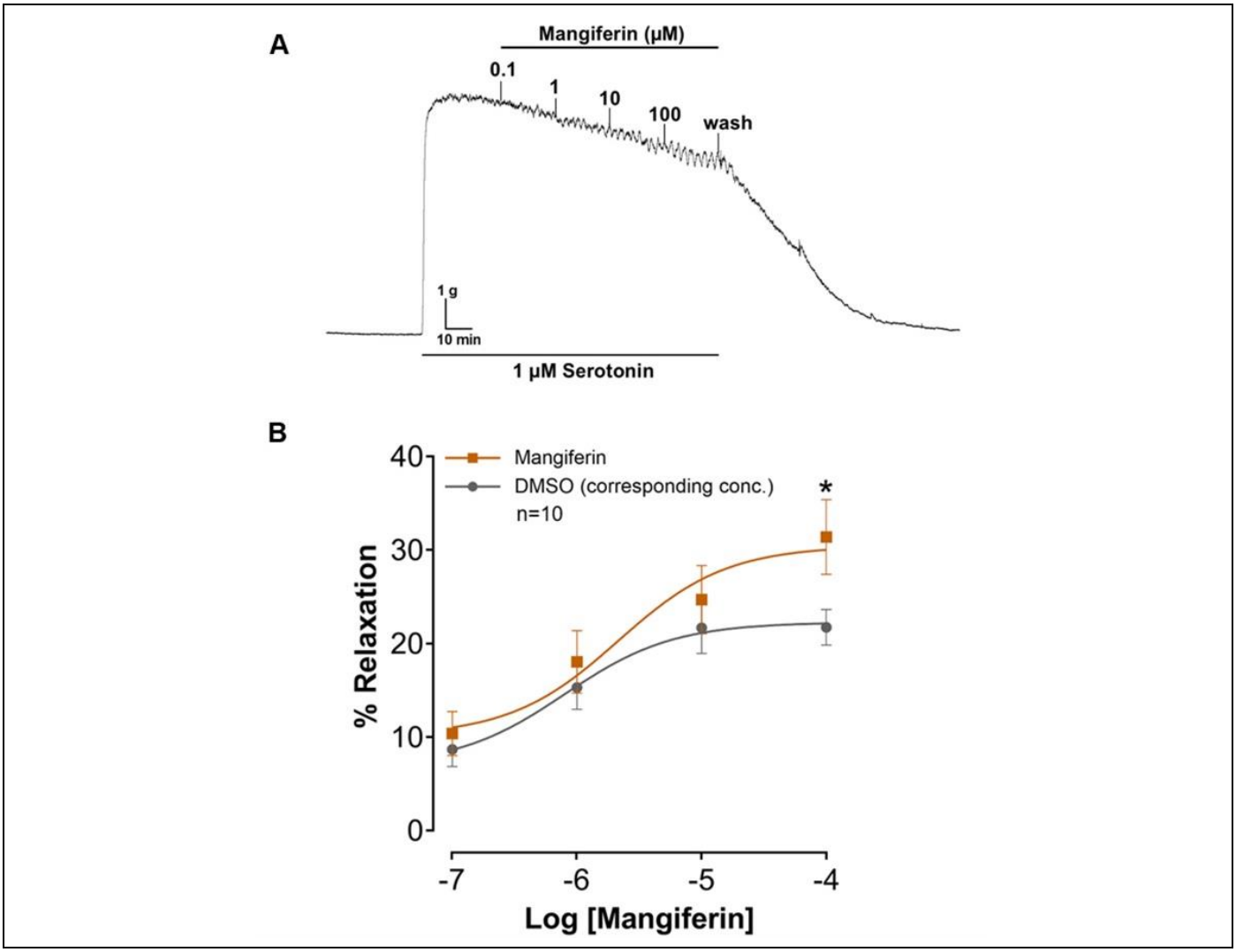

Figure 2 Mangiferin induced HUV relaxation**.** A) Representative trace showing the vasorelaxation effect of cumulative concentrations of mangiferin (0.1, 1, 10, and 100 µM) on 5-HT pre-contracted HUV. B) Concentration-response curve comparing mangiferin (orange squares) and vehicle control (DMSO, gray circles) on HUV relaxation, showing % Relaxation versus Log [Mangiferin]. Mangiferin significantly increased vasorelaxation at higher concentrations than the corresponding DMSO control (*p<0.05, unpaired t-test). Data are expressed as mean ± SEM (n=10 for each group).

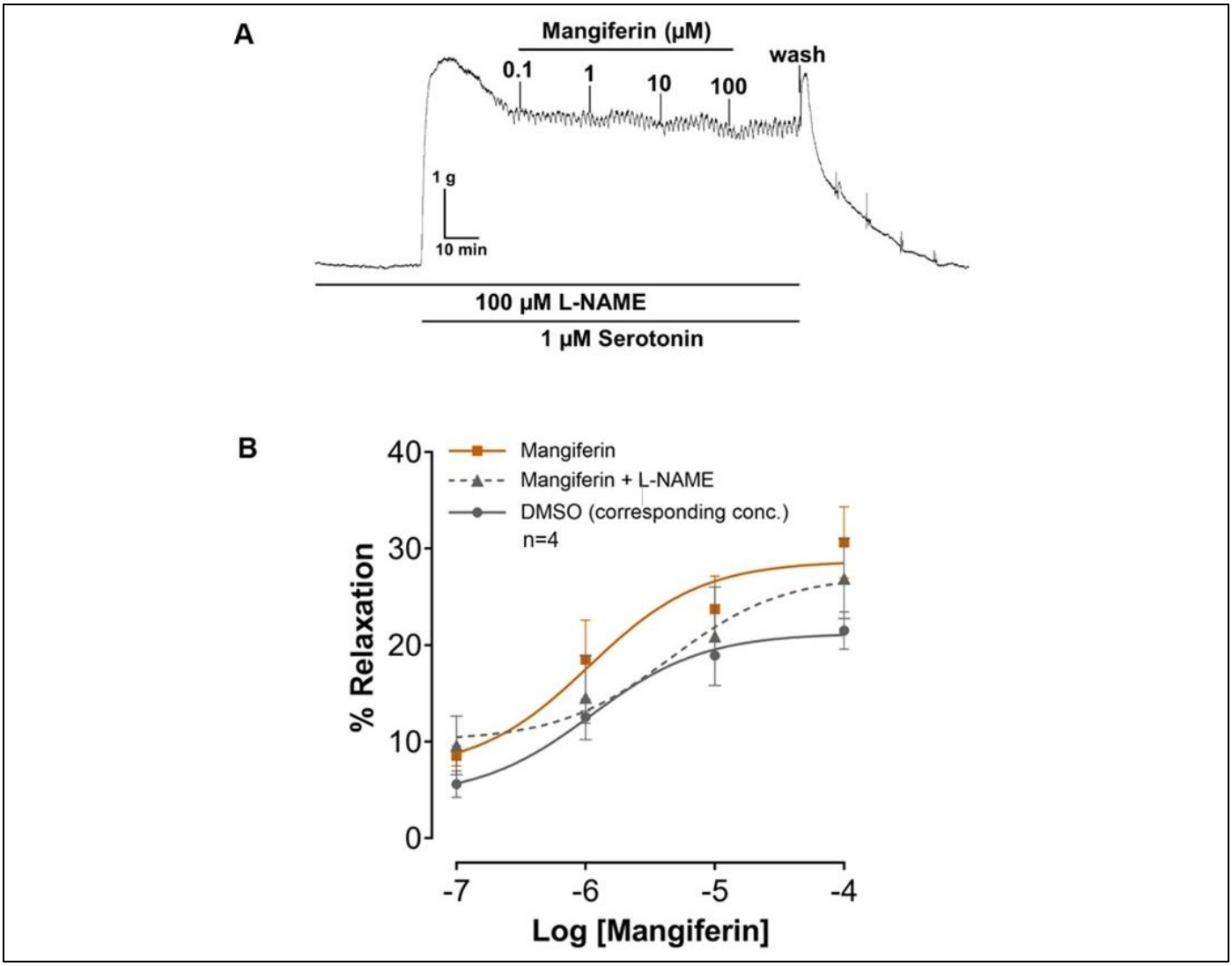

Figure 3 Mangiferin-induced HUV relaxation likely mediated via eNOS activation**.** A) Representative trace showing the vasorelaxation effect of cumulative concentrations of mangiferin (0.1, 1, 10, and 100 μM) in the presence of 100 μM L-NAME**.** B) Concentration-response curve comparing the % Relaxation response to mangiferin (orange square), mangiferin in the presence of 100 μM L-NAME (gray triangle), and the corresponding DMSO vehicle control (gray circle) versus Log [Mangiferin]. The results indicate that mangiferin induces dose-dependent vasorelaxation, which is partially attenuated by L-NAME, suggesting a role for nitric oxide in its mechanism of action. Data are expressed as mean ± SEM (n = 4 for each group).

2.5 Statistical analysis

All statistical analyses were performed using GraphPad Prism 8 (GraphPad Software, San Diego, CA, USA). All data were demonstrated as the mean ± SEM. Relaxation of the HUV segment was expressed as the percentage of the contraction induced by 1 μM 5-HT. The EC50 and Emax values were derived from the fitted concentration-response curves and analyzed using an unpaired t-test for comparison. 95% Confidence Interval (CI) were used to compare EC_{50} values between groups. Group differences were assessed using either an unpaired t-test or one-way ANOVA followed by Tukey's post hoc test, as appropriate. Statistical significance was considered when $p < 0.05$, or when 95% CI did not overlap.

3. RESULTS

3.1 Mangiferin enhances vasodilation in HUV

Various concentrations of mangiferin were used to investigate its vasodilation effect on HUV, which was measured as the percent relaxation compared to the 5-HT-induced constriction of the HUV. Representative vascular tension tracing of HUV when treated with 5-HT and mangiferin is shown in Figure 2A. The vasodilatory effects of 0.1, 1, 10, and 100 μM mangiferin, when fitted to a concentration-response curve, was shown and produced an EC_{50} of 2.14±0.46 μM and a maximum relaxation (E_{max}) of 30.49±3.31% (n=10, Figure 2B). A significant vasodilation effect of 100 μM mangiferin was observed, showing a percent relaxation increase to 145.08±14.60% (n=10, p<0.05,

Figure 2B), relative to corresponding DMSO concentration. Therefore, mangiferin had the potential to induce vasodilation in HUV effectively.

3.2 NO signaling likely mediates mangiferin-induced vasodilation

To demonstrate if mangiferin-induced vasodilation was indeed mediated by eNOS activation, HUV was pretreated with 100 µM L-NAME, a NOS inhibitor, followed by the application of 5-HT and mangiferin, respectively. Figure 3A shows the vascular tension tracing recorded from a representative HUV when treated with L-NAME, 5-HT, and the various concentrations of mangiferin. In the presence of L-NAME, the concentration-relaxation curve for mangiferin exhibited an EC50 shift to 4.55±0.66 µM, whereas without L-NAME pretreatment, the EC50 was 1.06±0.66 µM (n=4, Figure 3B). A slight overlap of the 95% CIs between the mangiferin-treated group (95% CI: 1.431×10^{-7} to 7.913×10^{-6}) and the L-NAME pretreated group (95% CI: 1.655×10^{-7} to 1.249×10^{-4}) was noted, suggesting that the difference between the groups may not reach statistical significance. Nevertheless, a rightward shift of the dose–response curve was observed, indicating a decrease in the potency of mangiferin-induced relaxation in HUV. On the other hand, the maximum relaxation in both groups was equal (Emax=28.71±2.84% in mangiferin and 27.21±4.82% in with L-NAME), suggesting the competitive inhibition of L-NAME on mangiferin's action. Thus, the ability of the aforementioned eNOS inhibitor to block mangiferin's action provided evidence that NO signaling likely accounts for mangiferin-induced vasodilation in HUV.

3.3 Cytotoxicity of mangiferin on HUVEC

The cytotoxicity of mangiferin on HUVEC was determined using the MTT assay. Figure 4 shows that mangiferin incubation at concentrations ranging from 0.1-100 µM for 72 hours conclusively did not impact the viability of HUVEC (n=4, p=0.8323), demonstrating that mangiferin had no cytotoxic effects on human vascular endothelial cells, indicating its safety and capacity to effectively induce vasodilation.

4. DISCUSSION

This study demonstrates that 1) mangiferin enhances HUV relaxation; 2) the vasodilation effect of mangiferin tends to be exerted through NO signaling; and 3) The treatment of mangiferin does not show any signs of cytotoxicity on HUVEC. This study represents the first investigation of mangiferin's vasodilatory effects on human-isolated vessels, revealing its involvement with NO signaling—a crucial pathway for inducing vasodilation, and highlighting its potential physiological significance.

HUV from fetal origin was widely recognized as a dependable *in vitro* model for investigating human vascular tension[15]. Similarly, HUVEC, an endothelial cell line derived from HUV, was valuable for research into the general characteristics of human endothelium, particularly in studies related to endothelial toxicity[16].

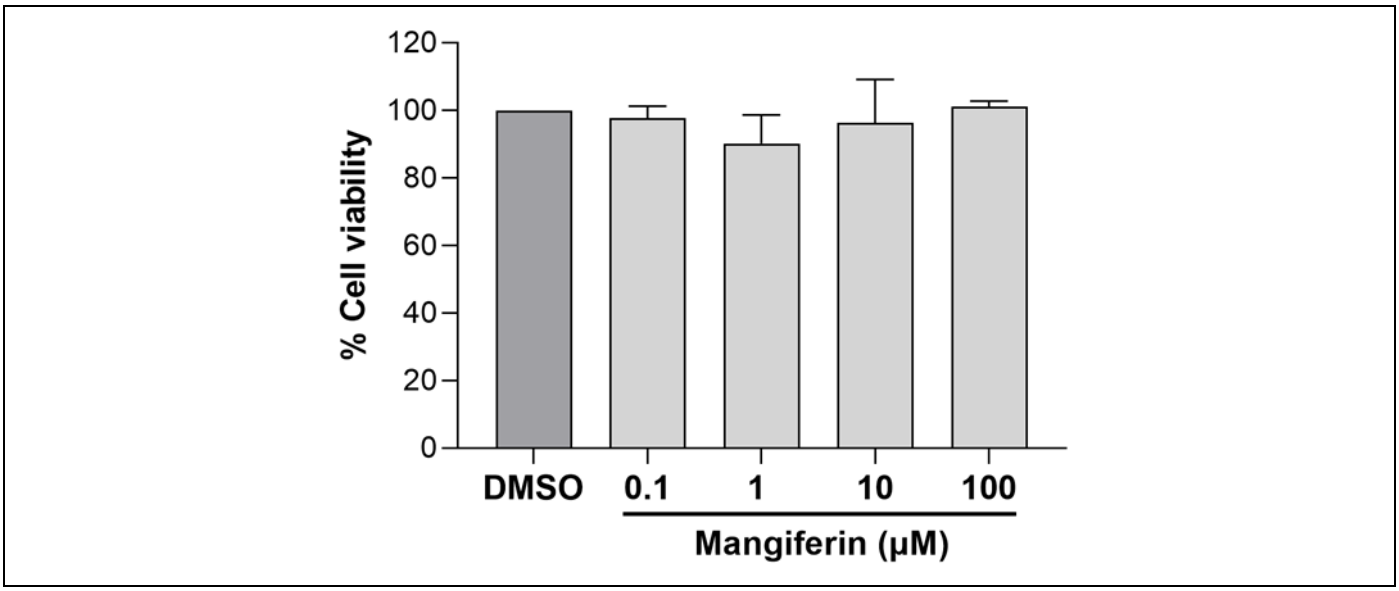

Figure 4 Effect of mangiferin on HUVEC viability. HUVECs were treated with various concentrations of mangiferin (0.1, 1, 10, and 100 µM) for 72 hours, and cell viability was compared to the vehicle control (DMSO). Results are presented as mean ± SEM (n=4), indicating that mangiferin did not exhibit any significant cytotoxicity at the tested concentrations.

Unlike other animal cell models, HUV and HUVEC minimized potential species-specific variations in response to drugs or stimuli, rendering them an ideal tool for researchers seeking to obtain more accurate experimental data.

Mangiferin was selected for testing on HUV and HUVEC based on previous findings showing that it promoted vascular relaxation and exhibited low toxicity in rat vessels, which encouraged us to investigate its effects in human vessels. The 5-HT which was reported its receptor expression on HUV smooth muscle, was used to induce HUV constriction[17]. Our findings demonstrate that mangiferin induces vasodilation in 5-HT-contracted HUV, consistent with previous reports in rat mesenteric arteries[13]. However, the magnitude of relaxation is slightly lower in HUV, suggesting tissue-specific differences in vascular responsiveness. This discrepancy may stem from variations in receptor expression, endothelial function, or the expression of eNOS, which may be higher in rat mesenteric arteries[18]. Species-specific differences in vascular smooth muscle sensitivity and receptor density, such as muscarinic or adrenergic receptors, could also contribute[19]. Moreover, structural and functional distinctions between resistance arteries and conduit veins may affect responsiveness to mangiferin[20]. Further molecular investigations, along with pharmacokinetic and clinical studies, are warranted to clarify these mechanisms.

One possible mechanism involving mangiferin-induced vasorelaxation was an eNOS activation, which had been described for many plant-derived phenolic compounds such as resveratrol, quercetin, and epigallocatechin gallate[21]. Activation of human eNOS was a key mechanism in vascular endothelial cells, where it maintained vessel tone through nitric oxide (NO) generation[22]. This mechanism supported increased blood flow in healthy vessels and enhanced function in compromised vessels affected by conditions such as inflammation, diabetes, and cardiovascular diseases[23, 24]. Inhibition of eNOS by L-NAME was reported to decrease vascular relaxation due to reduced NO production[25]. We use the L-NAME expecting that the mechanism of mangiferin-induced HUV relaxation may occur through eNOS stimulation. Our findings suggest that L-NAME tends to competitively inhibit the actions of mangiferin, as evidenced by the rightward shift in the concentration–response curve observed in the L-NAME-pretreated group. This suggests a potential mechanism by which mangiferin modulates eNOS activity and NO production to exert its vasorelaxant effects in human vessels. These results are consistent with previous studies reporting that mangiferin's vasorelaxant effects are at least partially mediated through the NO signaling pathway[8,11,12]. Further investigations with larger sample sizes and additional molecular analyses are necessary to clarify this mechanism more definitively.

It is essential to evaluate the toxicity of mangiferin before its use in clinical trials. All dosage of mangiferin used to induce relaxation in our study, were assessed for cytotoxicity on HUVECs, the primary site of eNOS synthesis in HUV, showing no cytotoxicity. This finding indicates that our mangiferin preparation is not harmful to HUVECs. This is consistent with our previous study, which demonstrated that mangiferin at the same dosage exhibited no toxicity in isolated rat smooth muscle cells[13]. Animal research had shown that mangiferin exhibits no acute or sub-chronic toxicity, with no clinical symptoms or hematological alterations observed[26]. Beyond its non-toxic nature, mangiferin previously demonstrated notable properties in improving vascular cell function and vascular reactivity in metabolic conditions such as hypertension, hyperlipidemia, and hyperglycemia[27]. Together, these highlight the potential of mangiferin to be safely developed as a vasodilatory agent or a supplement to support vascular health, while also providing a basis for determining reference dosages in future clinical trials.

5. CONCLUSIONS

This study is the first to investigate the vasodilatory effects of mangiferin on human-isolated vessels, demonstrating its action partially through the NO pathway and confirming its safety with no observed cytotoxic effects on human vascular tissues.

6. ACKNOWLEDGEMENTS

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Author contribution

Kritsana Tipcome and Kitinat Rodthongdee were responsible for conceptualizing, designing, and conducting all experiments, analyzing the data, and drafting, revising, and finalizing the manuscript. Kitinat Rodthongdee also provided reagents, materials, experimental equipment, and analytical tools. Patcharada Amatyakul and Chutarat Sirichareon handled umbilical cord collection and transfer. Katesirin Ruamyod conducted the cell experiment. Krongkarn Chootip and Anjaree Inchan provided experimental equipment and mentorship.

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Conflict of interest (If any)

none to declare

Ethics approval

All experiment protocols were approved by an ethical committee of NU-IRB, under COA number 521/2020.

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