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ORIGINAL ARTICLE / ÖZGÜN MAKALE

The effect of *panax ginseng* on intimal hyperplasia in rats with abdominal aortic intimal injury

Abdominal aortlarında intimal hasar yapılan sıçanlarda kullanılan panax ginsengin intimal hiperplazi üzerinde etkisi

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ABSTRACT

Background: This study aims to investigate the effects of *Panax ginseng (P. ginseng)* on intimal hyperplasia following intimal injury induced in the abdominal aortas of rats.

Methods: Twenty-four Wistar Albino rats were divided into four equal groups. Group A was designated as the control group and underwent laparotomy alone. In Group B, following laparotomy, the abdominal aorta was partially transected, and intimal injury was induced proximally using a 2F Fogarty catheter. Groups C and D received 20 mg/kg and 40 mg/kg of *P. ginseng*, respectively, and both groups underwent the same procedure as Group B. Two samples were collected from all rats with aortic injury: one from the primarily repaired aortic segment and another from the aortic segment with intimal injury caused by a Fogarty catheter. One sample was collected from the control group. The intima and media thicknesses of the collected aortic samples were histopathologically evaluated.

Results: No significant intimal hyperplasia was observed in the primarily repaired aortic segments, and *P. ginseng* did not have significant effect in these segments (p=0.394 and p=0.580, p=0.180, p>0.05). However, significant intimal hyperplasia developed in the aortic segments with injury induced by the Fogarty catheter (p=0.012, p<0.05). High-dose *P. ginseng* (40 mg/kg) significantly reduced intimal hyperplasia in these segments (p=0.036, p<0.05), while the low dose (20 mg/kg) did not show statistically significant effect (p=1.000, p>0.05).

Conclusion: Our study results showed that *P. ginseng* reduced intimal hyperplasia in a dose-dependent manner in rat abdominal aortas.

Keywords: Abdominal aorta, endothelial damage, intimal hyperplasia, *panax ginseng*.

ÖZ

Amaç: Bu çalışmada, sıçanların abdominal aortalarında oluşturulan intimal hasar sonrasında *Panax ginseng'in (P. ginseng)* intimal hiperplazi üzerine etkileri araştırıldı.

Çalışma planı: Yirmi dört Wistar Albino sıçanı dört eşit gruba ayrıldı. Grup A kontrol grubu olarak belirlendi ve yalnızca laparotomi yapıldı. Grup B'de laparotomi sonrası abdominal aorta, parsiyel kesildi ve proksimaline 2F Fogarty kateteri ile intimal hasar oluşturuldu. Grup C ve D'ye sırasıyla 20 mg/kg ve 40 mg/kg P. ginseng verildi ve her iki gruba da Grup B ile aynı prosedür uygulandı. Aort hasarı yapılan tüm sıçanlardan primer onarılan ve Fogarty kateteri ile intimal hasar yapılan aort segmentleri olmak üzere ikişer numune alındı. Kontrol grubundan bir numune alındı. Alınan aort örneklerinin intima ve media kalınlıkları histopatolojik olarak değerlendirildi.

Bulgular: Primer onarılan aort segmentlerinde anlamlı intimal hiperplazi gözlenmedi ve *P. ginseng*'in bu segmentlerde belirgin bir etkisi olmadı (p=0.394 ve p=0.580, p=0.180, p>0.05). Ancak, Fogarty kateteri ile hasar oluşturulan aort segmentlerinde anlamlı intimal hiperplazi gelişti (p=0.012, p<0.05). Yüksek doz *P. ginseng* (40 mg/kg) bu segmentlerde intimal hiperplaziyi anlamlı derecede azaltırken (p=0.036, p<0.05), düşük doz *P. ginseng* (20 mg/kg) istatistiksel olarak anlamlı bir etki göstermedi (p=1.000, p>0.05).

Sonuç: Çalışma sonuçlarımız sıçan abdominal aortlarında *P. ginseng*'in intimal hiperplaziyi doza bağlı olarak azalttığını gösterdi.

Anahtar sözcükler: Abdominal aort, endotel hasarı, intimal hiperplazi, *panax ginseng*.

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Cardiovascular disease (CVD) accounts for approximately 17.9 million deaths per year worldwide.[1] An important branch of CVD is occlusive vascular diseases such as coronary artery disease, cerebrovascular diseases, and peripheral artery disease.[2] Among cerebrovascular diseases, 85% of stroke cases are ischemic.[3] A common treatment of occlusive vascular diseases is revascularization procedures which include percutaneous transluminal balloon angioplasty, endovascular stent grafting, endarterectomy, Fogarty balloon thromboembolectomy, and vascular bypass surgery. The main goal of these revascularization procedures is to maintain the functions and vitality of the relevant organs by supplying more blood to the distal arterial segment. However, restenosis can occur in 10 to 50% of cases, resulting in a relapse of ischemic symptoms, consequently leading to organ failure and limb loss.[4]

The leading cause of vascular restenosis is intimal hyperplasia which occurs after revascularization.[5] Intimal hyperplasia is a physiological healing response to vascular wall injury; however, its precise pathophysiology remains unclear.[6] Intimal hyperplasia can occur due to endothelial injury following vascular interventions, and it may also develop as a result of non-surgical or physiological processes, such as the closure of the ductus arteriosus or atherosclerosis.[7]

The vascular endothelium secretes anticoagulants and plays a crucial role in coagulation homeostasis. Endothelial damage following vascular interventions leads to the loss of the normal homeostatic response of the endothelium. The damaged endothelium becomes an adhesive surface for circulating cells, such as leukocytes and platelets, which then accumulate and cause local aggregation. Endothelial damage also causes the normally anticoagulant endothelial surface to become procoagulant, thereby releasing numerous vasoactive molecules, such as cytokines and growth factors. If this inflammatory response is not neutralized, it can progress, resulting in extracellular matrix deposition in the vascular wall, along with smooth muscle cell migration and proliferation. This ultimately leads to intimal hyperplasia.[8,9] It is thought that suppressing intimal hyperplasia resulting from endothelial damage may increase vascular and graft patency. In this context, previous studies have examined the effects of various pharmacological agents to reduce or prevent intimal hyperplasia.[10,11]

Panax ginseng (P. ginseng) has been used as a traditional medicine in the treatment of diseases for thousands of years in Eastern Asian countries. Over the last three decades, its popularity has increased around the world.[12] In the literature, the role of *P. ginseng* in clearing free radicals, the protective effects of *P. ginseng* on atherosclerotic plaque formation, and its effective inhibition of endothelial vasomotor disorders has also described.[13] It has also been demonstrated that *P. ginseng* suppresses intimal hyperplasia and inhibits cell proliferation in vascular smooth muscle cells following intimal injury in rats.[14]

In the present study, we aimed to investigate the effects of *P. ginseng* on intimal hyperplasia following induced intimal damage of the abdominal aorta in a rat model.

MATERIALS AND METHODS

Experimental animals

A total of 24 male Wistar Albino rats, each weighing approximately 300 to 400 g, were used as experimental. The rats were randomly divided into four groups, each consisting of six animals. Prior to the experiment, the rats were housed in wire cages for seven days under a circadian rhythm, with 12 h of light and 12 h of darkness. The cages were maintained at an ambient temperature of 24 to 26°C and a humidity of 50 to 60%. The rats were fed with standard commercial pellet feed and tap water. After the surgical procedure, the rats were kept in individual cages for 14 days. All procedures were performed in compliance with the Principles of Laboratory Animal Care and the Guide for the Care and Use of Laboratory Animals, 8th Edition (Washington DC: National Academies Press; 2011). The study was approved by the İstanbul University Animal Experiments Local Ethics Committee (Date: 26.03.2021, No: 2021/09).

Panax ginseng supply and preparation

The *P. ginseng* was prepared and ground. The ground *P. ginseng* was dissolved in 96% ethanol at a ratio of 1:3. The resulting ethanol extract was evaporated to dryness using a rotary evaporator. After 48 h of maceration, the extract was weighed using a precision scale. A solution was then prepared by diluting the extract with 1 mL (or cc) of 0.9% sodium chloride (NaCl), adjusted according to the total amount required based on the weight of the rat.

Experimental model

A total of 24 rats were used in this study, divided into four equal groups of six.

- Group A: Control group with only laparotomy performed
- Group B: A group of rats in which the abdominal aorta was partially transected after laparotomy, and intimal injury was induced using a 2F Fogarty catheter positioned 1 cm proximal to the incision
- Group C: A group of rats which underwent the same procedure as Group B and received a preoperative dose of 20 mg/kg of *P. ginseng*, followed by postoperative administration of *P. ginseng* for 14 days
- Group D: A group of rats that underwent the same procedure as Group B and received a preoperative dose of 40 mg/kg of *P. ginseng*, followed by postoperative administration of *P. ginseng* for 14 days.

Surgical procedure

Similar to the previous study,[15] all rats underwent a median laparotomy incision following intraperitoneal administration of 75 mg/kg of ketamine hydrochloride (Ketalar®, Pfizer, Istanbul, Türkiye) and 10 mg/kg of xylazine hydrochloride (Rompun®, Bayer, Istanbul, Türkiye). The infrarenal abdominal aortas of the rats in Group A were identified and held in place using a silk suture to form a vascular loop. For rats in Group B, after identifying the infrarenal abdominal aorta, 100 units per kg (U/kg) of heparin (Heparin Sodium, Sandoz, Kocaeli, Türkiye) were administered intravenously. Five minutes later, the infrarenal abdominal aorta was clamped with an atraumatic bulldog clamp, and the abdominal aorta was partially transected using an ophthalmic scalpel. Intimal injury was then created with a 2F Fogarty balloon catheter (Edwards Lifesciences, CA, USA) positioned 1 cm proximal to the incision. The abdominal aorta was subsequently repaired with 8.0 prolene sutures (Prolene, Ethicon, Johnson&Johnson, Somerville, NJ, USA) and the layers were closed according to the anatomical structure of the rats. The rats in Group C were administered 20 mg/kg of *P. ginseng* (Korea Ginseng Corp., Jung-gu Seoul, South Korea) via oral gavage (the extract was mixed with 1 mL of 0.9% NaCl solution) before the procedure. This group underwent the same procedures as those in Group B. The rats in Group D received 40 mg/kg of *P. ginseng* by oral gavage before the procedure, and the same procedures performed on Group B were applied to this group as well. Oral *P. ginseng* treatment was continued at the indicated doses for 14 days after the procedure in Groups C and D.[16] All rats were euthanized 14 days later through intraperitoneal administration of 135 mg/kg of sodium pentothal (Abbott Laboratories, Istanbul, Türkiye). Two samples were collected from the aortic segments that were primarily repaired and subjected to intimal injury using a Fogarty catheter in all rats, except for the control group (Group A). One sample was collected from each rat in Group A. These samples were, then, placed in formaldehyde (Merck KGaA, Darmstadt, Germany) solution for histopathological evaluation.

Pathology protocol

The samples were fixed in 10% buffered formaldehyde solution for three days. After fixation, the aortic vessels were dissected by taking transverse sections through the suture line and the balloon-applied areas proximally. These sections were, then, subjected to routine tissue processing. After processing, 3-µ thick sections taken from the paraffin blocks were stained with hematoxylin and eosin (H&E) and examined under a light microscope. Intima and media thicknesses were measured in millimeters using the Olympus analySIS 5 (Olympus Corp., Tokyo, Japan) image analysis program, based on the digital photographs taken during the examinations.[17]

Statistical analysis

Statistical analysis was performed using the NCSS version 21.0.3 (2021) software (NCSS LLC., Kaysville, UT, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max), or number and frequency, where applicable. The Kruskal-Wallis test and Dunn-Bonferroni test were used for comparisons between groups with more than two quantitative variables that did not show a normal distribution. The Bonferroni-adjusted Wilcoxon signed-rank test was used for binary comparisons of quantitative variables that did not show a normal distribution. A p value of <0.05 was considered statistically significant.

RESULTS

No surgical complications occurred during the procedure, and postoperatively, all rats were observed to wake up after anesthesia. In Group B, one rat died 24 h after the procedure, and another died on the third day. Two replacement rats were obtained from the unit, and similar procedures were performed on them. At the end of the two weeks, no infections or complications were noted during the collection of samples.

In our study, two samples were collected from the aortic segments which were primarily repaired and subjected to intimal injury using a Fogarty catheter in all rats, except for the control group. Since the rats in Group A were the control group, one sample was collected from each of them. The aortic samples which were primarily repaired and subjected to intimal injury using a Fogarty catheter were examined separately, and compared to the control group.

According to the histopathological and statistical analysis of the samples taken from the aortic segments damaged by the Fogarty catheter, the excised abdominal aortas were normal in Group A (control group) (Figure 1). In the sections obtained from Group B, the intimal layer exhibited prominent and irregular thickening in certain areas. Elastic tissue staining revealed an irregular lamina elastica interna in regions with abnormal intimal thickening, and a lack of continuity was observed in some areas (Figure 2). The aortas of rats in Group C exhibited thickening in the intima layer in certain areas, but no irregular papillary thickening was observed. The lamina elastica interna appeared regularly in most sections (Figure 3). In Group D, minimal thickening was observed in the intima layer, while the internal elastic lamina appeared normal in nearly all sections (Figure 4). Statistically significant differences were observed among the groups while comparing the intima/media ratios of aortas with intimal injury induced by the Fogarty catheter (Figure 5, Table 1). A statistically significant difference was observed between Group A and Group B (p=0.012)..

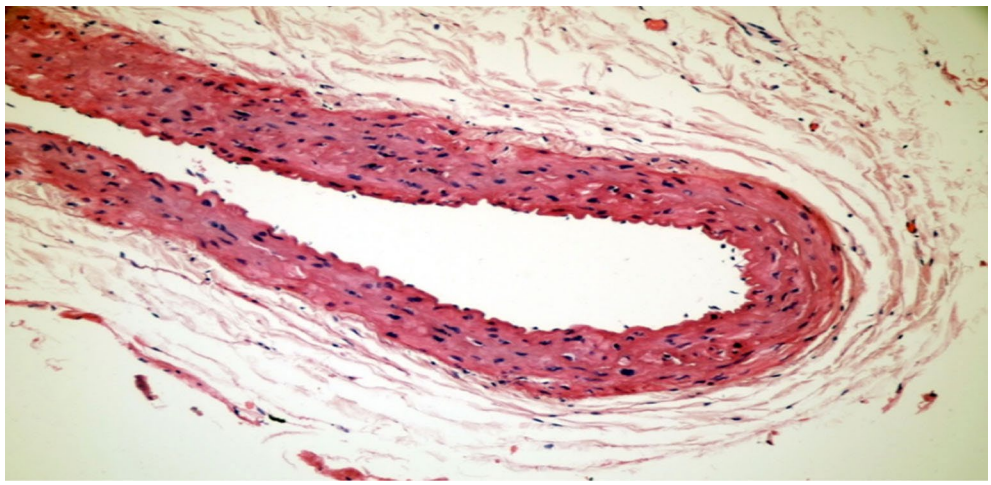

Figure 1. Aortic section with normal structure in Group A (control group) (H&E, ×200).

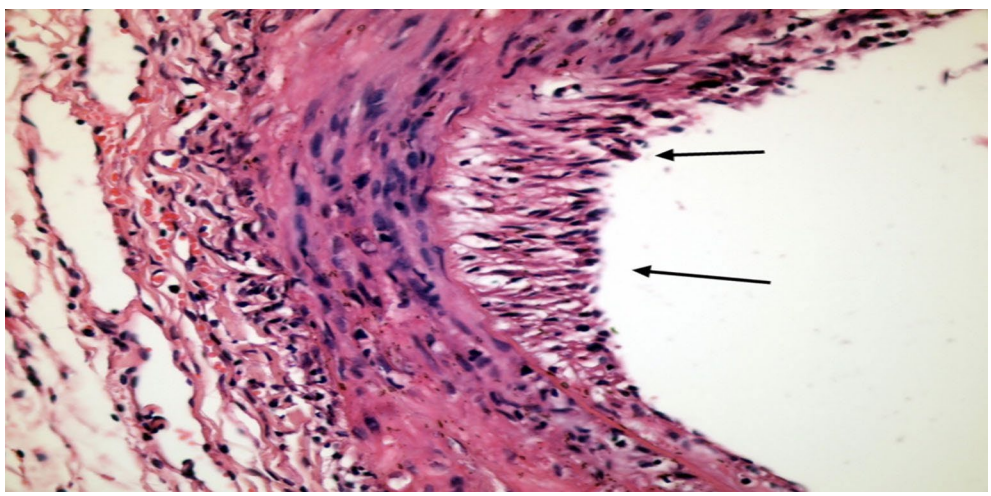

Figure 2. Media disorder and intima thickening in Group B (H&E, ×400).

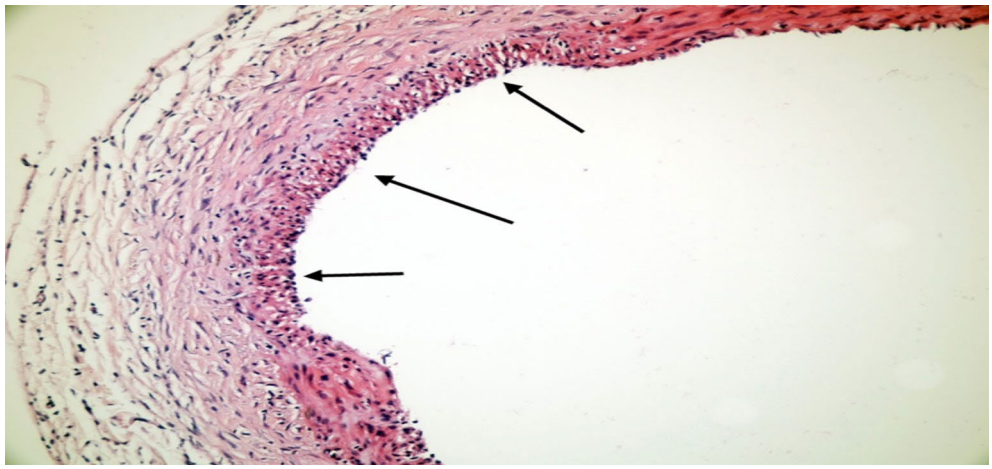

Figure 3. Slightly thickened layer of intima in Group C (H&E, ×200).

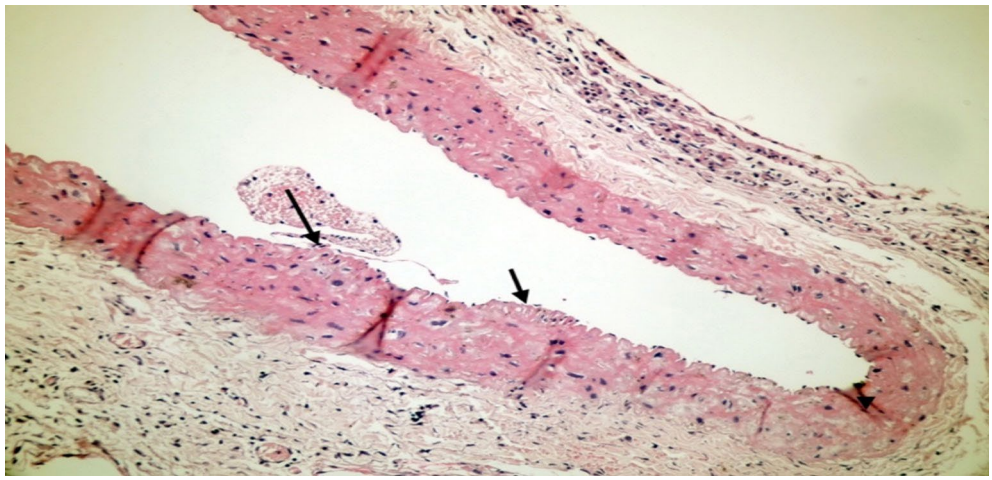

Figure 4. Indistinct thickened areas in the intima and media layers in Group D (H&E, ×200).

The mean value in Group B was significantly higher. A statistically significant difference was observed between Group D and Group B (p=0.036). No statistically significant difference was observed between Group C and Group B (p=1.0). Similarly, no statistically significant differences were observed among the other groups (p>0.05).

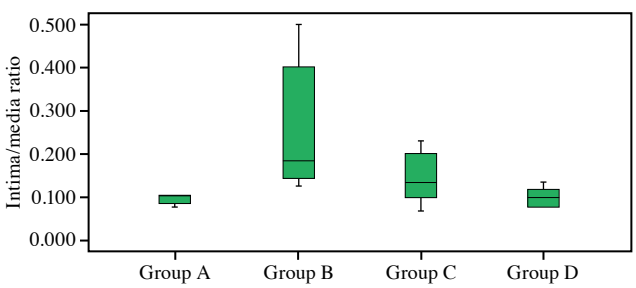

Figure 5. Distribution of intima/media ratios of aortas with fogarty catheter-induced intimal injury.

According to the histopathological and statistical analysis of the samples taken from the primarily repaired aortic segments, there were no significant irregularities in the intima and media layers of the groups, and no statistically significant differences were observed among the groups while comparing he intima/media ratios of partially transected and primarily repaired aortas (p>0.05) (Table 2).

DISCUSSION

The response process of blood vessels following damage to the endothelial wall involves a complex biological mechanism. Although restenosis is

Table 1. Comparison of intima/media ratios of aortas with Fogarty catheter-induced intimal injury

	Mean±SD	Median	Min-Max	*p*
Group A	0.09±0.009	0.95	0.07-0.10	**0.008****†
Group B	0.25±0.15	0.18	0.12-0.50	
Group C	0.14±0.60	0.13	0.06-0.22	
Group D	0.10±0.02	0.09	0.07-0.13	
	p			
A-B	0.012*†			
A-C	0.510†			
A-D	1.000†			
B-C	1.000†			
B-D	0.036*†			
C-D	1.000†			

† Kruskal Wallis test & post-hoc Dunn-Bonferroni test; * p<0.05; ** p<0.01.

Table 2. Comparison of intima/media ratios of partially transected and repaired aortas

	Mean±SD	Median	Min-Max	*p*
Group A	0.09±0.009	0.09	0.07-0.1	0.410†
Group B	0.27±0.20	0.27	0.06-0.55	
Group C	0.11±0.07	0.09	0.06-0.25	
Group D	0.09±0.04	0.07	0.06-0.16	
	p			
A-B	0.394†			
A-C	0.697†			
A-D	1.000†			
B-C	0.580†			
B-D	0.180†			
C-D	1.000†			

† Kruskal Wallis test & post-hoc Dunn-Bonferroni test.

recognized as a key response after endothelial injury, its pathophysiology remains largely unknown.[6] Endothelial cells secrete various vasoactive substances which regulate vascular tone. These cells respond with vasoconstriction or vasodilation of the endothelium as a normal reaction, either due to changes in blood vessel lumen pressure and shear stress or as a result of the release of vasoactive mediators by blood cells.[18] Intimal injury following vascular interventions triggers a complex sequence of events, including endothelial denudation, the exposure of prothrombotic intima, subsequent inflammation, the release of growth factors and cytokines, platelet activation, and smooth muscle cell proliferation and migration. These processes may lead to either healing or pathological outcomes, such as neointimal hyperplasia or neoatherogenesis, which ultimately contribute to the development of restenosis.[19]

Various pharmacological agents are used to prevent intimal hyperplasia and maintain long-term patency of blood vessels, including antiplatelet agents (acetylsalicylic acid, clopidogrel, dipyridamole), antiproliferative agents (sirolimus), statins, inhibitors

of the renin-angiotensin-aldosterone system, and calcium channel blockers.[20] In addition to pharmacological agents, various herbal medicines derived from plants or foods have also been used to prevent intimal hyperplasia.[21] Natural compounds found in plants generally have a lower side effect profile compared to pharmacological agents and are better tolerated during long term use. Therefore, in our study, the effects of the herbal product *P. ginseng* on intimal hyperplasia have been investigated.

The effects of *P. ginseng* on intimal hyperplasia are based on the ability of its saponins to reduce this pathological process by inhibiting the proliferation of vascular smooth muscle cells.[22] The reduction of intimal hyperplasia by *P. ginseng* has been supported by numerous studies in the literature. It was shown that phenolic acid extract obtained from *P. ginseng* have a protective effect on free fatty acid-induced endothelial dysfunction by inhibiting intracellular lipid accumulation and overexpression of endothelin-1.[23] In the carotid artery damage model using a balloon catheter by Gao et al.,[24] after ginsenoside Rg1 treatment for 14 days, phosphorylated extracellular signal-regulated kinase2 (p-ERK2) signal was inhibited and mitogen-activated protein kinase phosphatase-1 (MKP-1) expression increased, thereby demonstrating suppression of vascular neointimal hyperplasia caused by balloon injury. In a similar experimental model conducted by Chai et al.,[13] ginsenoside Rb1 reduced intimal hyperplasia induced by homocysteine. Another study by Zhang et al.[25] showed that the extract obtained from *P. notoginseng* inhibited intimal hyperplasia.

Although many experimental and clinical studies have examined the pharmacological properties of *P. ginseng*, systematic reviews on this subject are insufficient and lack strong evidence for clinical efficacy.[26] In this context, in this experimental study, we investigated the effects of *P. ginseng* on intimal hyperplasia in rat abdominal aortas. Previous studies have shown a statistically significant turning point in intimal hyperplasia within a two-week period.[27] Based on these findings, the rats in our study were maintained under appropriate conditions for 14 days to ensure sufficient intimal hyperplasia formation. No statistically significant intimal hyperplasia was observed in the primarily repaired aortic segments, and the effect of *P. ginseng* was not notable in this subgroup. In contrast, a statistically significant intimal hyperplasia developed in aortic segments subjected to intimal injury induced by the Fogarty catheter. While low-dose *P. ginseng* had no significant inhibitory effect, high-dose administration, on the contrary, demonstrated a statistically significant inhibitory effect. Our experimental findings support previous studies suggesting that *P. ginseng* reduces intimal hyperplasia.

Nonetheless, there are some limitations to this study. First, this study was carried out in a rat mode. Such models may not fully reflect human biology, and the results obtained may have limited generalizability to human populations. Second, the study only covers a 14-day period, which does not provide sufficient information on the long-term safety and efficacy of the drug, necessitating studies with longer observation periods. Third, the use of only two doses of *P. ginseng* (20 mg/kg and 40 mg/kg) limits the opportunity to thoroughly investigate the effects of different doses, making it difficult to determine the optimal dosage range. Fourthly, although histopathological measurements used to assess intimal hyperplasia are unbiased, they are susceptible to human error, potentially leading to variability in results. Finally, the creation of intimal injury through surgical procedures, particularly in small animal models such as rats, presents technical challenges, and consistency may vary depending on the surgeon's experience, which may have limited the generalizability of the results. Highlighting these limitations underscores important factors which must be considered while interpreting the findings of the study and emphasizes the need for standardization of surgical techniques in future research.

In conclusion, in our experimental model on endothelial damage in rat abdominal aortas, *Panax ginseng* reduced intimal hyperplasia in a dose-dependent manner. Taken together, we believe that further comprehensive studies should be conducted to determine the therapeutic dose range and the use of herbal-derived *Panax ginseng*, which is cost-effective, readily available, and has fewer side effects, may help reduce intimal hyperplasia and increase the duration of vessel patency following vascular interventions.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept, design, literature review: D.Y., I.B.; Control/supervision: I.B., N.V.O.; Data collection and/or processing, analysis and/or interpretation, writing the article, critical review, references and fundings, materials: D.Y., I.B., N.V.O.

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