

Effect of Pomegranate Extract (Punica Granatum L) on Pulmonary Arterial Pressure in Sprague Dawley rat with Pulmonary Arterial Hypetension

by Mahrus Abdur Rahman

Submission date: 20-Mar-2021 10:40AM (UTC+0800)

Submission ID: 1537521639

File name: re_in_Sprague_Dawley_rat_with_Pulmonary_Arterial_Hypetension.pdf (632.77K)

Word count: 3174

Character count: 18281

Effect of Pomegranate Extract (*Punica Granatum L*) on Pulmonary Arterial Pressure in Sprague Dawley Rat with Pulmonary Arterial Hypertension



MahrusAbdur Rahman¹, I Ketut Alit Utamayasa¹, Taufiq Hidayat¹

¹⁷ Department of Child Health, Faculty of Medicine University of Airlangga/Dr. Soetomo Hospital, Surabaya, Indonesia¹

Abstract— Congenital heart disease causes pulmonary arterial hypertension, heart failure, and early death. Pulmonary arterial hypertension causes pulmonary arterial wall remodeling, inflammation, deposition of extracellular matrix protein, collagen synthesis, and fibrosis. This study aims to analyze the effect of Pomegranate extract on pulmonary arterial pressure in Sprague Dawley rats with pulmonary arterial hypertension. Twenty-four Sprague Dawley rat age 3-month bodyweight 250-350 gram allocated randomly into Pomegranate extract and control group, 6 rats in each group. Pulmonary arterial hypertension was induced with monocrotaline 60 mg/kg body weight injected subcutaneously. Pulmonary arterial pressure both groups were measured at 2 weeks and 4 weeks of observation. Rats were euthanized after 2 and 4 weeks of observation. Mean pulmonary arterial pressure the Pomegranate extract group was significantly lower compared to the control group in two weeks and four weeks of observation, 27,57±9,17 mmHg vs 47,48±5,58 mmHg (p=0.001) and 32,43±9,64 mmHg vs 46,53±5,53 mmHg (p=0.001) respectively. Pomegranate extract can decrease pulmonary arterial pressure in Sprague Dawley rats with pulmonary arterial hypertension induced by monocrotaline. Pomegranate extracts effective preventing the progressivity of pulmonary arterial hypertension in the rat.

Keywords— Pomegranate extract, pulmonary arterial hypertension

1. Introduction

The incidence of congenital heart disease (CHD) is 2-9.4 per 1000 live births.[1] Non-cyanotic CHD if not corrected on time will result in pulmonary arterial hypertension (PAH). The pathogenesis of PAH is characterized by vasoconstriction, micro thrombosis, and pulmonary arteries remodeling. The triggers of vasoconstriction are hypoxia and hypertension of left atrium, causing calcium influx and calcium release from intracellular, and contraction of smooth muscle cells. Deficiency of protein C and S, and increase activity of von Willebrand factor causing micro thrombotic events. Arterial wall remodeling including increases apoptosis, endothelial cell loss, increased proliferative pathway activity, thickening of smooth muscle cells, and resistance to programmed cell death.[2] Collagen accumulation causes fibrosis, a stiff and narrow lumen of blood vessel walls which leads to an increase in pulmonary artery pressure and ultimately causes impaired right ventricular function.[3] A hallmark of pulmonary hypertension is an increased pulmonary vascular resistance which leads to progressive elevations in pulmonary artery pressure, resulting in compensatory right ventricular hypertrophy and, ultimately, heart failure.[4] Specific medications currently approved for therapy of PAH target three major pathways consist of nitric oxide, endothelin, prostacyclin pathway. Some PH centers use off-label drugs for PAH therapy.[5] PAH existing therapies are nothing can cure, so the search for new therapeutic strategies continues.[6]

²¹ Studies in PAH treatment with drugs derived from natural plants have demonstrated unique advantages and broad application prospects. That natural plant products including *Ginkgo biloba leaf*, *Green tea*, *Salvia miltiorrhiza Bunge*, *Uncaria hynchophylla*, *Astragalus membranaceus*, *Panax notoginseng*, and *Anemarrhena asphodeloides*. Active substances in that plant are flavonoids, glycosides, diterpenoids, pyranocoumarins, and stilbenes.[7] Pomegranates use as a natural remedy due to their capability against pathogens. Every part of the pomegranate, the fruit juice, peel, arils, flowers, and bark have wide ranges of phytochemical properties therapeutic activity including anticancer, anti-inflammatory, anti-atherogenic, anti-diabetes, hepatoprotective, and antioxidant activity. Ellagic acid and hydrolyzable tannins, such as punicalagin, have the most activities.[8] Pomegranate juice effects in reduce blood pressure, improve endothelial function, reduce stiffness, and slow or reverse the progression of atherosclerosis.[9] Until now, there have not been many studies that prove the effect of PGE on the improvement of pulmonary arterial

pressure on PAH. PGE is expected to be used in clinical research as an adjunct drug for therapy and inhibits the progression of PAH. The study aimed to prove the effect of pomegranate extract on pulmonary artery pressure reduction in Sprague Dawley rats with pulmonary artery hypertension.

2. Method

This study was the laboratory experimental research³⁷ conducted on 24 Sprague Dawley rats. PAH was induced by subcutaneous monocrotaline injection at a dose of 60 mg/kg body weight. The rats meet the study requirements: 3 months old, body weight 250-350 grams, and healthy. Rats were grouped randomly into 2 study groups and 2 control groups, six rats in each group. The study group was treated with pomegranate extract, extracted from all parts of pomegranate fruits in powder form and has been standardized to contain 40% ellagic acid produced by Xi'an Biof Bio-Technology Co., Ltd. (Room 1-1111, High-tech Venture Park, No. 69 Jinye Road, Gaoxin District of Xi'an, People Republic of China). The PGE 150 mg / kg body weight suspended in a 0.3% CMC solution of 0.3% 2 ml. The control group was given a 0.3% sodium carboxymethylcellulose solution 2 ml. PGE and CMC were given once daily, start after 3 days of monocrotaline injection. Evaluation of pulmonary arterial pressure was done after 2 weeks and 4 weeks of observation. Pulmonary arterial pressure measurement was made after the following steps: rats were anesthetized, intubated via tracheostomy using a 16G IV catheter, connected with an oxygen tube through a three way with an oxygen flow of 0.5 L / minute. A left lateral thoracotomy was performed at 3-4th intercostal space, widened with a spreader, and the heart exposed. The 20G IV catheter was inserted into the main pulmonary artery through the right ventricular outlet under the pulmonary artery valve, and connected to the pressure gauge monitor hose. On the monitor screen, pulmonary arterial pressure waves appear in the systolic and diastolic phases. Pulmonary artery pressure was recorded at least 3 times. The best pressure trace was chosen and the mean pressure was calculated. The rats were euthanized by exsanguination after the measurement of pulmonary arterial pressure.[10]

Statistic analysis of MANOVA and Least Significant Difference (LSD) were used and the level of significance of < 0.05 using SPSS. This study was approved by Animal Care and Use Committee Veterinary Faculty of Universitas Airlangga (No. 400-KE December 23rd 2014).

3. Result

Two rats died on the 7th and 11th day of observation, both included in the control group 2 weeks and 4-weeks observation. The pulmonary arterial pressure was as shown in table 1.

Table 1. Pulmonary arterial systolic and diastolic pressures

Group	Systolic BP(mmHg)	Diastolic BP(mmHg)
	Mean ± SD (Min-Maks)	Mean ±SD (Min-Max)
Control 2 weeks	66.64 ± 11.07 ^a (45.9-79.1)	37.90 ± 4.26 ^a (30.9-42.8)
PGE 2 weeks	41.47 ± 13.47 ^b (20.5-57.4)	20.62 ± 7.25 ^b (10.7-32.6)
Control 4 weeks	65.03 ± 5.50 ^a (59.5-71.4)	37.28 ± 7.99 ^a (26.9-44.1)
PGE 4 weeks	44.73 ± 12.66 ^b (26.0-60.6)	26.28 ± 9.15 ^b (13.7-38.2)
p	0.002*	0.002*

Note: * significant at $\alpha = 0.05$. The same a,b, superscript shows no differences between groups (based on multiple LSD comparisons)

The mean systolic and diastolic pulmonary arterial pressure in the PGE group was significantly lower than in the control group 2 weeks ($p = 0.001$ and $p = 0.001$) and 4 weeks ($p = 0.014$ and $p = 0.032$) observations. The mean systolic and diastolic pulmonary arterial pressure in the PGE group 2 weeks and 4 weeks observation was not significantly different ($p = 0.631$ and $p = 0.196$). Meanwhile, the mean systolic and diastolic pulmonary arterial pressure in the control group 2 weeks and 4 weeks observation was not significantly different ($p=0.831$ and $p=0.222$) (Figure 1)

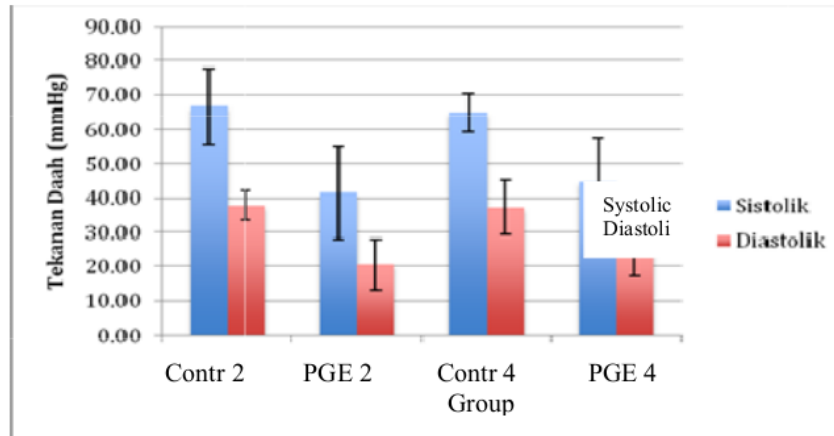


Figure 1. Average pulmonary arterial systolic and diastolic pressure
 Notes: Blue bar chart = mean pulmonary arterial systolic pressure.
 Red bar chart = mean pulmonary arterial diastolic pressure.

The mean pulmonary arterial pressure in the PGE group and the control group was as shown in table 2.

Table 2. Mean pulmonary arterial pressure

Group	n	Mean pulmonary arterial pressure (mmHg)				OnewayA nova p
		Mean	SD	Minimum	Maximum	
Control 2 weeks	5	47.48 ^b	5.58	39.03	53.63	0.001*
PGE 2 weeks	6	27.57 ^a	9.17	13.97	40.87	
Control 4 weeks	5	46.53 ^b	5.53	40.50	53.20	
PGE 4 weeks	6	32.43 ^a	9.64	20.47	41.67	

Note: * significant at $\alpha = 0.05$. The same superscript shows no differences between groups (based on multiple LSD comparisons)

The mean pulmonary arterial pressure in the PGE group was significantly lower than the control group 2 weeks and 4 weeks of observations ($p=0.000$ and $p=0.013$). The mean pulmonary arterial pressure in the PGE group 2 and 4 weeks observation was not significantly different ($p=0.302$). The mean pulmonary arterial pressure in the control group 2 and 4 weeks observation was not significantly different ($p=0.854$).

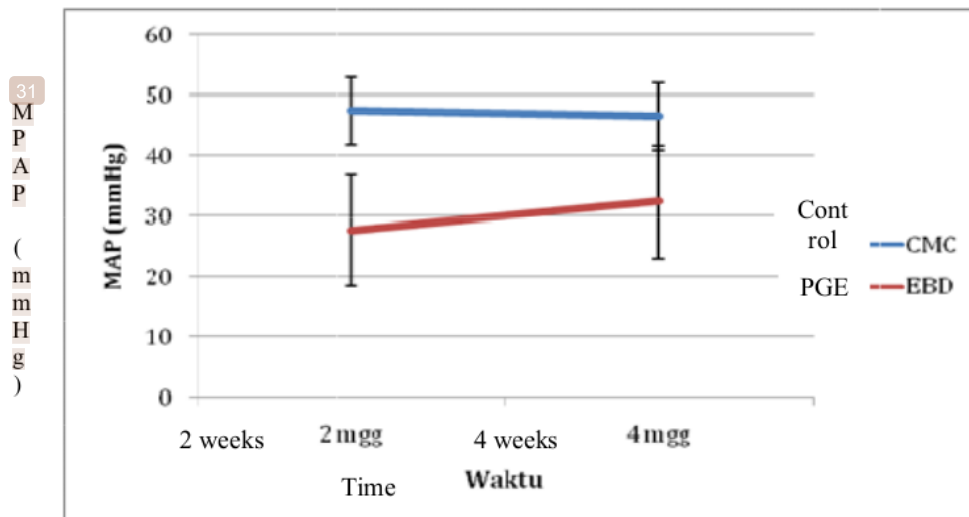


Figure 2 .Mean pulmonary arterial pressure (MPAP). Note Blue line = mean pulmonary arterial pressure control group. Redline = mean pulmonary arterial pressure PGE group.

Figure 2 showed that mean pulmonary arterial pressure in the PGE group maintained lower in 2 weeks period of observation compared with the control group.

4. Discussion

Our study investigated the effect of pomegranate extract for the treatment of pulmonary arterial hypertension in Sprague Dawley rat induced with monocrotaline. The results showed that pomegranate extract effectively reduced/suppressed the pulmonary arterial pressure and slowing its progressivity. The mean pulmonary arterial pressure was significantly lower compared to the control after two weeks of treatment. Increasing mean pulmonary arterial pressure from two weeks until four weeks of observation was not significant. These results revealed that Pomegranate extract can reduce and prevent the progressivity of pulmonary arterial hypertension.

Pulmonary arterial hypertension is a chronic and progressive disease characterized by a persistent increase in pulmonary artery pressure accompanied by right ventricular hypertrophy. The definition of PH in children has been the same as in adults, as $mPAP > 20$ mmHg and $PVR \geq 3$ WU.[11] Pulmonary arterial hypertension is still an important cause of morbidity and mortality in children. The survival of children with idiopathic PAH remains poor. The treatment of PAH has changed, improved, and led to the approval of 10 drugs from three main pharmacological pathways in the last two decades. Therapy with modern drug improves the symptoms of PAH and slows down the clinical deterioration. However, therapeutic strategies in children have not been sufficiently studied. PAH therapy in pediatric is vastly based on experience and trial data from adults.[5,12]

The use of natural plant products has confirmed in the clinical efficacy and showed unique advantages for PAH treatment. *Ginkgo biloba leaf*, *Green tea*, *Salvia miltiorrhiza Bunge*, *Uncaria rhynchophylla*, *Astragalus membranaceus*, *Panax notoginseng*, and *Anemarrhena asphodeloides*, are the natural plant products that have been used in the treatment of PAH.[7] The effects of herbs and phytochemicals used to treat PH through six mechanisms, including vasodilatory, antiproliferative, anti-vascular remodeling, antioxidant, apoptosis-inducing actions, and anti-inflammatory. Many of these medicinal plants and phytochemicals can have more therapeutic effects than chemical drugs if used appropriately.[12] Pomegranate has been used for thousands of years. It is described as a treatment for tapeworm and other parasites in records dating from around 1500 BCE. Pomegranate has been used for high blood pressure, athletic performance, heart disease, diabetes, and many other conditions.[13] Pomegranates have a wide range of capabilities and use as a natural remedy to chemical treatment. Every part of the pomegranate has

therapeutic activity including antioxidant, anticancer, anti-inflammatory, anti-atherogenic, anti-diabetes, hepatoprotective, and antimicrobial.[8]Pomegranate has several pharmacological actions as an anti-inflammatory, antioxidant, and anticarcinogenic. A growing number of studies of pomegranate apply it to solve medical problems.[14]Punicalagin therapy in rats can protect against endothelial dysfunction and pulmonary hypertension induced with hypoxia. It is induced via anti-oxidant actions, improved nitric oxide (NO)-cGMP signaling, and reduced oxidative stress. Decrease of superoxide generation, phytochemical reduces oxidative stress and raises mRNA expression of MMP-9, HIF-1 α , VEGFA, NF- κ B, and TNF- α in lung tissue of animals are the indicator of reducing oxidative stress. Punicalagin therapy can be used as an effective treatment for PH.[15]Punicagranatum supplementation of chickens fed had the potential to improve growth performance, increasing plasma nitric oxide concentration. and prevent Pulmonary Hypertension Syndrome, significantly suppressed the expression of ET-1 in the liver.[16]

Our study showed pulmonary arterial pressure decreased significantly after PGE administration for two and four weeks. This pressure drop was likely to be through several pathways of inhibition mechanism by PGE. PGE has the ability of anti-oxidant and strong anti-inflammatory properties. The beneficial effects of PGE are related to the active substances; ellagic acid, ellagitannins, puniceic acid, and other fatty acids, flavonoids, anthocyanins, anthocyanidins, flavones, and estrogenic flavonols.[17]Punicagranatum extract supplementation had the potential to improve growth, prevent pulmonary hypertension syndrome, higher plasma nitric oxide concentration, and suppressed the expression of ET-1 in the liver of chickens fed Punicagranatum.[16]Pomegranate-derived compounds exhibit a wide range of vasculoprotective effects through reducing oxidative stress, lipid peroxidation, and generation of foam cells, attenuate platelet aggregation, vasculo-protective effects result in improve vascular function, increased the expression of endothelial nitric oxide synthase (eNOS), protects the generated nitric oxide (NO) against its oxidative destruction, activation of the protein kinase B (Akt) / eNOS pathway and attenuation of vascular inflammation.[18-20]Increase the growth of *Bifidobacterium breve* and *Bifidobacterium infantis* and the production of short-chain fatty acids caused by Pomegranate byproducts and punicalagin have beneficial effects through the activation of peroxisome proliferator-activated receptors (PPARs). PPARs regulate inflammation, metabolism, and immunity.[17]Punicalin, and punicalagin which are constituents of PGE that can increase the production of short-chain fatty acids (SCFAs) by the metabolism of commensal bacteria in the intestine. SCFAs are absorbed and activate peroxisome proliferator-activated receptor γ (PPAR γ), which will inhibit the transcription of pro-inflammatory molecules by NF- κ B, AP-1, and STAT, and produce anti-inflammatory effects. There are elevated levels of cytokines IL-1 β , IL-18, IL-6, IL-13, and TNF- α which contribute to vasoconstriction which causes an increase in pulmonary artery pressure and proliferation of pulmonary artery smooth muscle.[21]The inhibition of the inflammatory process by PGE through inhibition of pro-inflammatory cytokines causes vasodilation and inhibition of pulmonary artery smooth muscle proliferation causing a decrease in pulmonary artery pressure on PAH. In conclusion; Pomegranate extract can decrease pulmonary arterial pressure in Sprague Dawleyrats with pulmonary arterial hypertension induced by monocrotaline.

The limitation of our study was the complexity of the measurement of pulmonary arterial pressure. Our methods used left lateral thoracotomy and direct measurement of pressure through puncture of the heart. These methods traumatic enough, sometimes puncture needle stack on the right ventricle wall and can influence the pressure result recorded.

5. Conclusion

This study has demonstrated that Pomegranate extracts effective in decreasing and preventing the progressivity of pulmonary arterial hypertension in the rat. Our results showed the mean pulmonary arterial pressure in the PGE group significantly lower than the control group. The result also showed the increase of mean pulmonary arterial pressure during observation from two weeks to four weeks of treatment was not significantly different. It is important to note that this finding can be an alternative mode of treatment for pulmonary arterial hypertension. Future clinical study effects of PGE can be arranged in children with pulmonary arterial hypertension.

6. References

- [1] Liu Y, Chen S, Zühlke L, Black GC, Choy M, Li N, et al. Global birth prevalence of congenital heart defects 1970–2017: updated systematic review and meta-analysis of 260 studies. *Int J Epidemiol* 2019;48:455–63.
- [2] Huber L, Bye H, Brock M. The pathogenesis of pulmonary hypertension – an update. *Swiss Med Wkly* 2015.
- [3] Schreier D, Hacker T, Song G, Chesler N. The role of collagen synthesis in ventricular and vascular adaptation to hypoxic pulmonary hypertension. *J Biomech Eng* 2013;135:021018.
- [4] Sysol JR, Machado RF. Classification and pathophysiology of pulmonary hypertension. *Contin Cardiol Educ* 2018;4:2–12.
- [5] Hansmann G, Aplitz C. Treatment of children with pulmonary hypertension. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. *Heart* 2016;102:ii67–85.
- [6] Ghofrani HA, Barst RJ, Benza RL, Champion HC, Fagan KA, Grimminger F, et al. Future perspectives for the treatment of pulmonary arterial hypertension. *J Am Coll Cardiol* 2009;54:S108–117.
- [7] Xiang L, Li Y, Deng X, Kosanovic D, Schermuly RT, Li X. Natural plant products in treatment of pulmonary arterial hypertension. *Pulm Circ* 2018;8:2045894018784033.
- [8] Bassiri-Jahromi S. *Punica granatum* (Pomegranate) activity in health promotion and cancer prevention. *Oncol Rev* 2018;12:345.
- [9] Tziomalos K, Doumas M, Athyros VG. Non-pharmacological intervention: Pomegranate Juice for the Management of Hypertension and the Improvement of Cardiovascular Health. *The Open Hypertension Journal* 2013;5:23-26.
- [10] Morimatsu Y, Sakashita N, Komohara Y, Ohnishi K, Masuda H, Dahan D, et al. Development and characterization of an animal model of severe pulmonary arterial hypertension. *J Vasc Res* 2012;49:33–42.
- [11] Rosenzweig EB, Abman SH, Adatia I, Beghetti M, Bonnet D, Haworth S, et al. Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management. *Eur Respir J* 2019;53:1801916.
- [12] Jasemi SV, Khazaei H, Aneva IY, Farzaei MH, Echeverría J. Medicinal Plants and Phytochemicals for the Treatment of Pulmonary Hypertension. *Front Pharmacol* 2020;11(145):1-21.
- [13] WebMD. Vitamine & Supplement: Pomegranate. Available at: <https://www.webmd.com/vitamins/ai/ingredientmono-392/pomegranate>. Accessed at July 9, 2020.
- [14] Elnawasany S. Clinical Applications of Pomegranate. In: Soneji JR, Nageswara-Rao M, editors. *Breed. Health Benefits Fruit Nut Crops*, InTech; 2018. Available at: <https://doi.org/10.5772/intechopen.75962>. Accessed at July 9, 2020.
- [15] Shao J, Wang P, Liu A, Du X, Bai J, Chen M. Punicalagin Prevents Hypoxic Pulmonary Hypertension via Anti-Oxidant Effects in Rats. *Am J Chin Med* 2016;44:785–801.
- [16] Ahmadipour B, Pat S, Khajali F. The Protective Effect of Pomegranate peel Powder on Pulmonary Hypertension in Broiler Chickens. *JSM Biomar.* 2018;4(1):1-6.
- [17] Viladomiu M, Hontecillas R, Lu P, Bassaganya-Riera J. Preventive and prophylactic mechanisms of action of pomegranate bioactive constituents. *Evid Based Complement Alternat Med* 2013;2013:1–18.
- [18] Wang D, Özen C, Abu-Reidah IM, Chigurupati S, Patra JK, Horbanczuk JO, et al. Vasculoprotective effects of Pomegranate (*Punica granatum* L.). *Front Pharmacol* 2018;9.
- [19] Rahimi HR, Arastoo M, Ostad SN. A Comprehensive review of *punica granatum* (Pomegranate) properties in toxicological, pharmacological, cellular and molecular biology researches. *Iran J Pharm Res IJPR* 2012;11:385–400.
- [20] Usta C, Ozdemir S, Schiariti M, Puddu PE. The pharmacological use of ellagic acid-rich pomegranate fruit. *Int J Food Sci Nutr* 2013;64:907–13.
- [21] Groth A, Vrugt B, Brock M, Speich R, Ulrich S, Huber LC. Inflammatory cytokines in pulmonary hypertension. *Respir Res* 2014;15:47.



This work is licensed under a Creative Commons Attribution Non-Commercial 4.0 International License.

Effect of Pomegranate Extract (Punica Granatum L) on Pulmonary Arterial Pressure in Sprague Dawley rat with Pulmonary Arterial Hypetension

ORIGINALITY REPORT

22%

SIMILARITY INDEX

15%

INTERNET SOURCES

17%

PUBLICATIONS

1%

STUDENT PAPERS

PRIMARY SOURCES

1

publicatio.bibl.u-szeged.hu

Internet Source

2%

2

Patrick Crosswhite. "Nitric oxide, oxidative stress and inflammation in pulmonary arterial hypertension :", Journal of Hypertension, 02/2010

Publication

1%

3

Pulmonary Hypertension, 2016.

Publication

1%

4

onlinelibrary.wiley.com

Internet Source

1%

5

serval.unil.ch

Internet Source

1%

6

www.jscimedcentral.com

Internet Source

1%

7

www.tandfonline.com

Internet Source

1%

8

respiratory-research.biomedcentral.com

Internet Source

1%

9

Jingyun Shao, Peng Wang, An Liu, Xusheng Du, Jie Bai, Mingwei Chen. "Punicalagin Prevents Hypoxic Pulmonary Hypertension via Anti-Oxidant Effects in Rats", The American Journal of Chinese Medicine, 2016

Publication

1%

10

[Submitted to Universitas Airlangga](#)

Student Paper

1%

11

Tapan Behl, Anita Kotwani. " Proposed mechanisms of in hyperglycaemia and associated diabetic complications ", Journal of Pharmacy and Pharmacology, 2017

Publication

1%

12

doaj.org

Internet Source

1%

13

www.alliedacademies.org

Internet Source

1%

14

Malik, A.B.. "Catecholamine-induced pulmonary edema", General Pharmacology, 1983

Publication

1%

15

Yu Wen, Yin-he Han, Huining Gu, Mingzheng Zhang, Bin Li. "Differential expression of related molecules after acute injury of rabbits' anterior cruciate ligament and medial collateral

1%

ligament", Research Square, 2021

Publication

16

circ.ahajournals.org

Internet Source

<1%

17

unsri.portalgaruda.org

Internet Source

<1%

18

www.bioxorio.com

Internet Source

<1%

19

www.freepatentsonline.com

Internet Source

<1%

20

Georg Hansmann. "Pulmonary Hypertension in Infants, Children, and Young Adults", Journal of the American College of Cardiology, 2017

Publication

<1%

21

Lili Xiang, Ying Li, Xu Deng, Djuro Kosanovic, Ralph Theo Schermuly, Xiaohui Li. "Natural plant products in treatment of pulmonary arterial hypertension", Pulmonary Circulation, 2018

Publication

<1%

22

MRM Elghorori. "A study of maternal plasma β -endorphin in pre-eclamptic women during labour", Journal of Obstetrics and Gynaecology, 2009

Publication

<1%

23

f1000research.com

Internet Source

<1%

24	www.ncbi.nlm.nih.gov Internet Source	<1%
25	Sally Elnawasany. "Chapter 7 Clinical Applications of Pomegranate", IntechOpen, 2018 Publication	<1%
26	Mohamad Nasser, Ziad Damaj, Akram Hijazi, Othmane Merah et al. "Pomegranate Juice Extract Decreases Cisplatin Toxicity on Peripheral Blood Mononuclear Cells", Medicines, 2020 Publication	<1%
27	content.karger.com Internet Source	<1%
28	smw.ch Internet Source	<1%
29	www.dovepress.com Internet Source	<1%
30	www.spandidos-publications.com Internet Source	<1%
31	core.ac.uk Internet Source	<1%
32	mafiadoc.com Internet Source	<1%

33

res.mdpi.com

Internet Source

<1%

34

Mervin Chávez-Castillo, Ángel Ortega, Pablo Duran, Daniela Pirela et al. "Phytotherapy for Cardiovascular Disease: A Bench-to-Bedside Approach", Current Pharmaceutical Design, 2020

Publication

<1%

35

"Critical Care of Children with Heart Disease", Springer Science and Business Media LLC, 2020

Publication

<1%

36

José L. Sánchez-Gloria, Horacio Osorio-Alonso, Abraham S. Arellano-Buendía, Roxana Carbó et al. "Nutraceuticals in the Treatment of Pulmonary Arterial Hypertension", International Journal of Molecular Sciences, 2020

Publication

<1%

37

Tingting Zhang, Nanako Kawaguchi, Kenji Yoshihara, Emiko Hayama et al. "Silibinin efficacy in a rat model of pulmonary arterial hypertension using monocrotaline and chronic hypoxia", Respiratory Research, 2019

Publication

<1%

Exclude quotes On

Exclude matches Off

Exclude bibliography On

Effect of Pomegranate Extract (Punica Granatum L) on Pulmonary Arterial Pressure in Sprague Dawley rat with Pulmonary Arterial Hypetension

GRADEMARK REPORT

FINAL GRADE

/100

GENERAL COMMENTS

Instructor

PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6
