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Research on External Signs and Chemical Composition of Medicinal Plant Raw Material -Leaves of Ficus Elastica

Antiparasitic effect of Psidium guajava on promastigotes and axenic amastigotes of Leishmania

The Serum Formulation of Hati Tanah Tuber Ethanol Extract from Central Kalimantan

Job fulfilment and its related variables among pharmacy certificate holders in Jordan: A Cross-sectional Study

Chemical Profiling of Nonpolar Compounds of Onopardum Acanthium using GCMASS

Antioxidant, Antimicrobial, and Antiplasmodial Activities of Sonchus arvensis L. Leaf Ethyl Acetate Fractions

Senna Siamea Hexane Extract: Potent Antifungal Activity Against Candida albicans, Candida Krusei and Identification of Its Chemicals Content

DFT and Pharmacokinetic Study of Some Heterocyclic Aspirin Derivatives as The Cyclooxygenase Inhibitors: An In-Silico Approach

Fingerprint and Multivariate Analysis of Apium Graveolens L. From Different Geographic with Spectroscopic ATR-FTIR

Antibacterial Effect of Nigella sativa L. Seed from Indonesia

Successful Intrapericardial Fibrinolysis on Acute Recurrent Purulent Pericarditis with Impending Cardiac Tamponade during Pandemic Situation: A Rare Case Report

Bio-Evaluation, In-Vitro and In-Vivo Anti-Inflammatory Activity, Therapeutic Efficacy, and Genotoxicity of the Potentials of the Green Seaweed Valoniopsis Pachynema using Zebra Fish Larvae (Danio Rerio) as an Animal Model

Aquaporine 4 Expression on End Feet Astrocyte Before and After Cerebrospinal Fluid Drainage of Hydrocephalus Mice Model

Effects of Pomegranate Extract Supplementation (Punica granatum L.) on Clinical Manifestations of Pulmonary Arterial Hypertension in Children with Acyanotic Congenital Heart Disease

The Role of Breast Milk on Reducing the Risk of Neonatal Sepsis in Preterm and Low Birth Weight Infants: A Systematic Review and Meta-Analysis

Histopathological Perspectives of Multiple Organs in a Red- Footed Tortoise (Chelonoidis carbonaria) with Suspected Metabolic Bone Disease: A Case Report

Medicinal Plants Adopted to Treat Children's Diseases by Traditional Pediatrics "Women Healers" In The Souss Massa Region (Agadir Idaoutanan, Inzegane Ait Meloul and Chtouka Ait Baha) Morocco ›

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Research Article

Effects of Pomegranate Extract Supplementation (*Punica granatum* L.) on Clinical Manifestations of Pulmonary Arterial Hypertension in Children with Acyanotic Congenital Heart Disease

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ABSTRACT

Background: Pulmonary arterial hypertension (PAH) in congenital heart disease (CHD) mechanism includes vasoconstriction and vascular remodeling. In Indonesia, sildenafil as a vasodilator is the only standard treatment for PAH. Research on pomegranate extract showed its potential as an anti-inflammatory and anti-proliferative agent that could work synergically with sildenafil in reducing pulmonary arterial pressure (PAP) **Objective:** To investigate the effect of pomegranate supplementation in the clinical manifestation of PAH in children with acyanotic CHD. **Methods:** This study was a randomized controlled clinical trial that compared the clinical manifestation of PAH in children with acyanotic CHD who received standard therapy for PAH and pomegranate extract supplementation with the placebo group. Observations were carried out over three months, and pre-and post-test evaluations were conducted to assess changes in PAP, functional classification of PAH, body weight, systolic blood pressure, heart rate, respiratory rate, and oxygen saturation in both groups. Statistical analysis was undertaken using the Wilcoxon, Mann-Whitney, and Spearman correlation tests. **Results:** There was no significant difference in PAP reduction between the pomegranate and placebo groups (p = .44) and no significant difference in the functional classification of PAH in the placebo and pomegranate groups (p = .55). There was a considerable reduction in the respiratory rate in the pomegranate group (p = .017). Respiratory rate was positively correlated with the functional classification of PAH (p = .011). **Conclusion:** There was a significant reduction in the respiratory rate in the pomegranate group that correlated with the functional classification of PAH.

Key words: Heart disease, Pomegranate, Pulmonary hypertension, Sildenafil.

INTRODUCTION

In children with acyanotic CHD, PAH is a pulmonary vascular disease that causes severe morbidity and mortality. It is a problem for clinicians to manage as part of CHD management. Cardiovascular surgery and catheterization to repair the underlying anatomic defect are the definitive treatments for PAH caused by CHD. Due to inadequate resources for cardiac surgery and catheterization, managing PAH in developing countries remains difficult. Thus, pharmacological therapy is essential to reduce the mortality and morbidity of the disease.[1]

According to the National Registries of the United Kingdom, the incidence of PAH is.48 percent per 1 million children each year. In cases of CHD, 4-15 percent progress to PAH, and 5-10% progress to Eisenmenger's syndrome.[2] The Registry to Evaluate Early and Long-Term PAH (REVEAL) estimates a survival rate of 1.3, and the 5-year survival rate in PAH patients is predicted to be 96 +/- 4%, 84 +/- 5%, and 74 +/- 6%. Survival rates were significantly worse in CHD without shunts and in PAH that persisted after surgery.[3]

PAH etiology is characterized by two mechanisms: vasoconstriction and pulmonary vascular remodeling. In individuals with left-to-right shunt CHD, increasing flow and pressure to the pulmonary blood arteries decreases vasodilators such as NO-cGMP and prostacyclin (PGI2) while boosting vasoconstrictors such as endothelin (ET-1), Rho GTPases, and thromboxane. Endothelial damage promotes matrix metalloproteinase breakdown and the release of FGF and TGF-1. These factors cause smooth muscle cell hypertrophy and proliferation. Endothelial injury also activates pro-inflammatory cytokines and macrophages (e.g., IL-6, IL-1b, MCP-1, and TNF-a), which promote remodeling and the creation of the neointima layer. As a result, effective pharmacological therapy of PAH CHD must include vasodilators as well as anti-remodeling medicines.[4]

Currently, the standard pharmacological therapy for children with PAH CHD in Indonesia is a class of medications known as phosphodiesterase-5 [PDE-5] inhibitors (sildenafil), which acts as a vasodilator in the pulmonary arteries. As a result, anti-remodeling medicines that work in tandem with vasodilators to achieve appropriate pulmonary vascular pressure are still required.[5]

Pomegranate has been demonstrated in studies to be an anti-inflammatory and anti-proliferative agent that can lower oxidative stress, lipid peroxidase, and foam cell formation.[6] According to Rahman MA's 2016 research, pomegranate extract showed an anti-remodeling impact by decreasing the advancement

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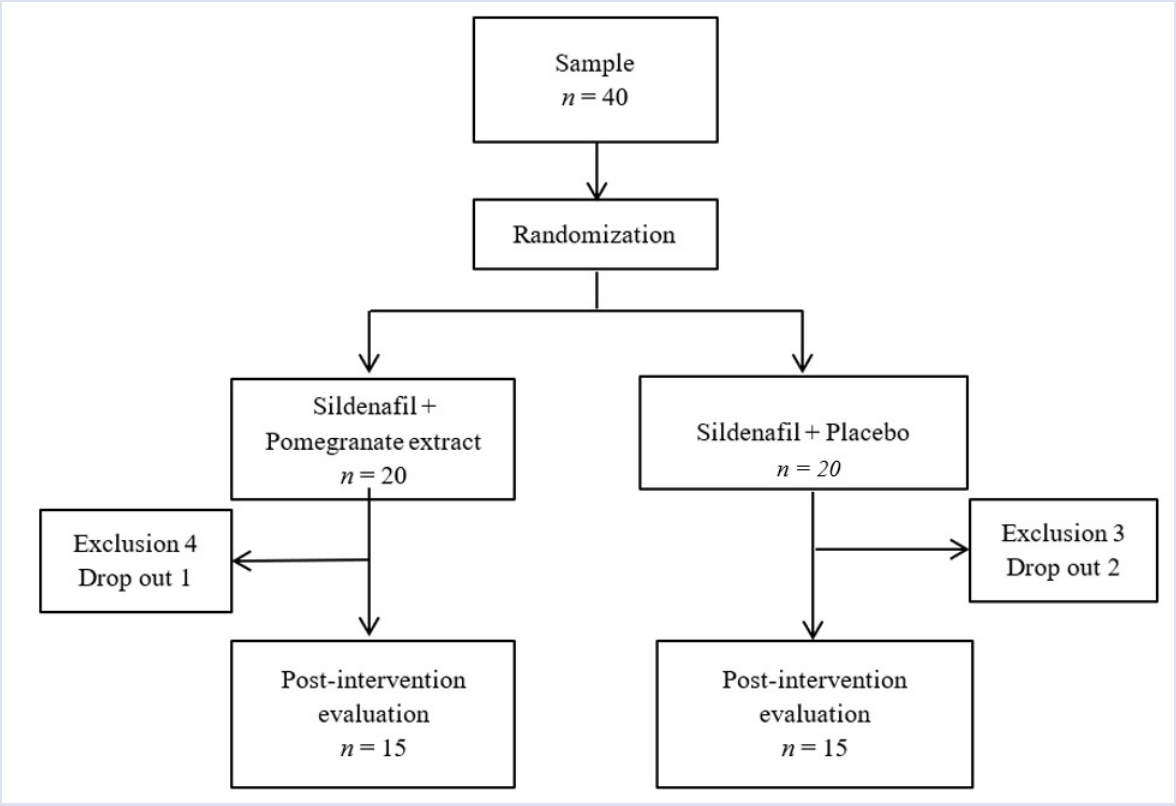

Figure 1: Research flowchart.

of fibrosis in the tunica adventitia of the pulmonary arteries in PAH model rats by inhibiting the expression of TGF-1, type I collagen, and an increase in the MMP-1 /TIMP-1 ratio.[7] Previous research on the use of pomegranate extract in the treatment of PAH CHD was still in the process of proving its efficacy in an animal model. However, additional research is needed to assess the effect of pomegranate extract supplementation as a therapy for PAH CHD in children.

METHODS

This study was a double-blind and randomized controlled trial with a pre-and post-test control group, which compared the clinical manifestation of PAH in children with acyanotic CHD who received sildenafil and supplementation of pomegranate extract. The samples were children aged one month to 10 years old with PAH CHD at Dr. Soetomo General Hospital's Pediatric Cardiology Outpatient Clinic from February 2022 to October 2022. The Health Research Ethics Committee of Dr. Soetomo General Hospital Surabaya approved this research with ethics certificate 0353/KEPK/I/2022.

Selection of participants

The inclusion criteria were children aged one month to 10 years with CHD with left-to-right shunts (ASD, VSD, PDA, or a combination) who received standard therapy for PAH and parents with completed consent forms. The exclusion criteria included those who had undergone heart surgery or catheterization, those with chronic lung parenchymal disease, autoimmune diseases, impaired thyroid function, connective tissue diseases, chromosomal abnormalities, neuromuscular disorders, and those who could not be contacted to come during the observation.

Pomegranate

The pomegranate extract used in this study resulted from the whole pomegranate fruit (*Punica granatum L*), which contains 40 percent ellagic acid. The dose was 120 mg/kg/day with an ellagic acid content of 48 mg/kg/day.[7,11-13]

Intervention and measurement

Patients who fulfilled the requirements criteria completed the informed consent and had measurements of their height, weight, systolic blood pressure, pulse, respiratory rate, peripheral oxygen saturation, and echocardiogram to determine the estimated PAP. Afterward, patients were randomly assigned to the pomegranate or placebo groups. We gave sildenafil 0.5-2mg/kg/dose 3-4 times daily and 120 mg/kg/day of pomegranate extract to the patients in the intervention group. Sildenafil and placebo capsules were given to patients in the control group. After three months of observation, evaluations of body weight, systolic blood pressure, heart rate, respiratory rate, peripheral oxygen saturation, and echocardiographic examination were carried out. The measurements were carried out blindly without knowing whether the study subjects were included in the intervention or control groups.

Statistical analysis

The Kolmogorov-Smirnov test was used to determine the normality of all data. The Wilcoxon statistical test was used to compare changes before and after treatment in each test group. The Mann-Whitney test was used to compare the clinical symptoms of the intervention and control groups. The Spearman correlation test was used to assess the relationship between clinical manifestation of PAH and functional classification of PAH.

RESULTS

Of the forty patients who met the inclusion criteria during the study period, only 30 completed the post-test evaluation at the end of the research. Four patients in the intervention group and three in the control group were excluded because these patients had heart defects closed.

Table 1 shows that there were no significant differences in the age range, gender proportion, nutritional status, mean systolic blood pressure, heart rate, respiratory rate, peripheral oxygen saturation, type of heart defect, and size of heart defect, as well as severity degree of PAH in both test groups before the intervention with a $p > 0.05$.

Table 2 compares echocardiographic features, decreasing PAP, and functional classification of PAH before and after three months of intervention. This study showed no significant difference in pre-test and post-test PAP reduction ($p = 0.44$). There was no significant difference in the functional classification of PAH between the study subjects who received standard therapy and pomegranate compared to those who received standard therapy and placebo ($p = 0.55$).

Table 3 compares changes in clinical manifestations, including body weight, systolic blood pressure, heart rate, respiratory rate, and oxygen saturation, in both test groups. In this table, there was a significant increase in the body weight of the research subjects in the pomegranate group ($p = 0.012$) and the placebo group ($p = 0.005$). This table also shows a significant decrease in the average respiratory rate in the pomegranate group ($p = 0.017$). In contrast, in the placebo group, there was no significant decrease in the average respiratory rate ($p = 0.361$). Respiratory rate was positively correlated with the functional classification of PAH ($p = 0.011$).

Out of fifteen study samples, no side effects occurred in the placebo group during the three months of observation. In the pomegranate group, out of fifteen study samples, one patient was found with complaints of diarrhea, and two patients complained of vomiting during the first month of the study. In the three patients, dosage adjustments and medication schedules were adjusted to minimize side effects. No severe complication of pomegranate supplementation, including hypotension, was reported in this study.

Table 1: The characteristic of the participants.

	Pomegranate n (%)	Placebo n (%)	p
Age			
0-5 months	1 (6.7)	1 (6.7)	0.29
6-11 months	1 (6.7)	2 (13.3)	
1-2 years	2 (13.3)	3 (20)	
<2 – 5 years	4 (26.7)	5 (33.3)	
>5 – 10 years	7 (46.7)	4 (26.7)	
Mean age	4.86	4.12	0.91
Gender			
Male	7 (46.7)	7 (46.7)	1
Female	8 (53.3)	8 (53.3)	
Nutritional status			
Normal	4(26.7)	8(53.5)	0.91
Moderate malnutrition	11(73.3)	2(13.3)	
Severe malnutrition	0(.0)	5(33.3)	
Systolic blood pressure (mmHg)	85.4 ± 6.8	87.47 ± 14.0	0.61
Heart rate (x/minutes)	113.4 ±18.1	104.1 ± 17.1	0.16
Respiratory rate (x/minutes)	31.6 (20-60)	32 (20-60)	0.98
Oxygen saturation (%)	98 (86-99)	98 (90-99)	0.52
Type of congenital heart defect			
ASD	4 (26.7)	5 (33.3)	0.81
VSD	7 (46.7)	6 (40.0)	
PDA	2 (13.3)	2 (13.3)	
ASD + VSD	0 (0.0)	1 (6.7)	
ASD + PDA	2 (13.3)	0 (.0)	
VSD + PDA	0 (.0)	0 (.0)	
ASD + VSD + PDA	0 (.0)	1 (6.7)	
Size of the heart defect			
Small	2 (13.3)	1 (6.7)	0.87
Moderate	5 (33.3)	6 (40.0)	
Large	8(53.3)	8(53.3)	
Degree of PAH			
Mild	7(46.7)	1 (6.7)	0.078
Moderate	2(13.3)	5 (33.3)	
Severe	6(40)	9(60)	

Table 2: Comparison of the effect of pomegranate supplementation vs placebo.

	Pomegranate n (%)	Placebo n (%)	p
Degree of PAH			
Normal	3 (20.0)	3 (20)	0.25
Mild	5 (33.3)	1 (6.7)	
Moderate	3 (20.0)	4 (26.7)	
Severe	3(26.7)	7 (53.3)	
Change in degree of PAH			
Improved	5(33.3)	7(46.7)	0.71
Not improved	10(66.7)	8(53.3)	
Reduction of PAP (mmHg)	-12.02± 32	-14 ±19.46	0.44
Functional classification of PAH			
I	4 (26.7)	6 (40)	0.55
II	9 (60.0)	7 (46.7)	
IIIa	2 (13.3)	2 (13.3)	
IIIb	0 (.0)	0 (.0)	
Change in functional classification of PAH			
Improved	3(20)	2(13.3)	1
Not improved	12(80)	13(86.7)	

DISCUSSION

There was no significant difference in pre-test and post-test PAP reduction between the pomegranate and placebo groups. Moreover, there was no significant difference in the functional classification of PAH after three months of pomegranate supplementation.

Pomegranate was proven by Shao *et al.* to produce pulmonary vascular vasodilation by raising levels of acetylcholine acting on endothelial receptors and correcting endothelial dysfunction *via* the NO-cGMP signaling pathway. This study also showed that punicalagin exhibited antioxidant and anti-inflammatory properties, as seen by lower levels of MMP-9, TNF-a, and VEGF.[14] Previous research revealed that pomegranate could decrease the fibrosis process that occurs in the right ventricle and pulmonary arteries during PAH.[7] According to Rahman MA's study, pomegranate extract could slow the advancement of fibrosis in the tunica adventitia of the pulmonary arteries in PAH model rats by inhibiting the expression of TGF-1, type I collagen, and increasing the MMP-1/TIMP-1 ratio.[13,21]

The average age in this study was 4.5 years old. According to Egito *et al.*', which included 26 children with PAH who underwent open lung biopsy as well as intracardiac defect closure surgery, patients who had thickening of the tunica media consisting of vascular smooth muscle cells, as well as thickening Collagen layer in the tunica adventitia, had persistent PAH after surgical closure of the defect. The thickening of this tunica media and adventitia were indicators of an irreversible state in pulmonary vascular remodeling. Collagen layer thickening in the tunica adventitia was discovered as early as 12 months of life and was most common in patients aged two years. The likelihood of irreversible tunica media and pulmonary vascular adventitia remodeling increases with age.[9]

In this trial, the pomegranate and sildenafil intervention lasted three months. In 2014, Barst *et al.* conducted a research on children aged

Table 3: Comparison of clinical manifestation after pomegranate supplementation vs. placebo.

	Pomegranate			Placebo		
	Pre-test	Post-test	p	Pre-test	Post-test	p
Body weight (kg)	14.6 ± 8.5	15.5 ± 8.3	0.012	11.9 ± 7.3	12.5 ± 7.1	0.005
Systolic blood pressure (mmHg)	85 (71-97)	88 (74-119)	0.308	87 (67-115)	90 (70-120)	0.335
Heart rate (x/minute)	110 (92-150)	110 (84-144)	0.77	110 (76-130)	98 (60-140)	0.353
Respiratory rate (x/minute)	31.6 ± 9.8	28.3 ± 5.8	0.017	32.4 ± 10.8	29.9 ± 7.7	0.361
Oxygen saturation (%)	96.8 ± 3	94.4 ± 8	0.86	97.4 ± 3.3	96.8 ± 5	0.529

Table 4: Correlation analysis of clinical manifestation of PAH and functional classification of PAH.

	p
Body weight	0.055
Systolic blood pressure	0.182
Heart rate	0.504
Respiratory rate	0.011
Oxygen saturation	0.97
Side effect	0.681

1-17 years with PAH, demonstrating that sildenafil successfully reduced PAP after 16 weeks of sildenafil medication. Clinical improvement and exercise capacity, on the other hand, improved within 12 months of treatment.[15] Pomegranate extract was administered to male Sprague-Dawley rats for two weeks in previous studies to establish a vasculoprotective effect.[7,11,12,16] According to Sengupta's prior research from 2013, one year in human life was nearly similar to two weeks in mouse life (13.8 days).[17] Based on this literature, it could be concluded that in human research subjects, pomegranate extract showed a vasculoprotective effect after administration for one year.

This study showed a significant decrease in respiratory rate after administering pomegranate extract compared to the respiratory rate in the placebo group. From the correlation test analysis, the respiratory rate was positively correlated with the functional classification of pulmonary hypertension, which means that the higher the respiratory rate in the study subjects, the more severe the functional classification of PAH.

The standard therapy for pulmonary arterial hypertension, the phosphodiesterase-5 [PDE-5] inhibitor class (sildenafil), acted as a vasodilator in the pulmonary vessels. Pomegranate extract had the potential to act as an anti-inflammatory and anti-proliferative agent by lowering oxidative stress, lipid peroxidase, and the development of foam cells, all of which functioned as anti-remodeling agents. Pomegranate extract supplementation may improve the efficacy of PAH management. Pomegranate and sildenafil may work together to reduce PAP. In comparison to the group receiving standard therapy and placebo, the group receiving standard therapy plus pomegranate supplementation had a superior functional classification of PAH.[6,19,22]

This was the first study to investigate at the effect of pomegranate supplementation on pediatric patients with PAH caused by acyanotic CHD. After three months of pomegranate consumption, there were no serious side effects such as hypotension or anaphylaxis. There was no prior evidence on the combination of anti-failure medicines and standard therapy for pulmonary arterial hypertension with pomegranate supplements that could be utilized to provide information about the rules for using these drugs. More research with age grouping, frequency of administration, dosage, and longer duration of pomegranate supplementation is required to provide data on the proper dose and duration of pomegranate administration in children to achieve the desired anti-remodeling effect. More research is also needed to investigate the interaction of pomegranate extract with sildenafil and other anti-failure medicines taken by study participants.

CONCLUSION

A significant reduction in the respiratory rate in the pomegranate group is correlated with the functional classification of PAH in children with PAH caused by acyanotic CHD. There are no severe side effects, such as hypotension or anaphylaxis, after consuming pomegranate for three months.

REGISTRATION

This research has been reviewed and approved by the Thai Clinical Trials Registry (TCTR) with the identification number: TCTR20221006005. The entire clinical trial protocol can be accessed at http://www.thaiclinicaltrials.org/show/TCTR20221006005

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DISCLOSURE

The author reports no conflicts of interest in this work.

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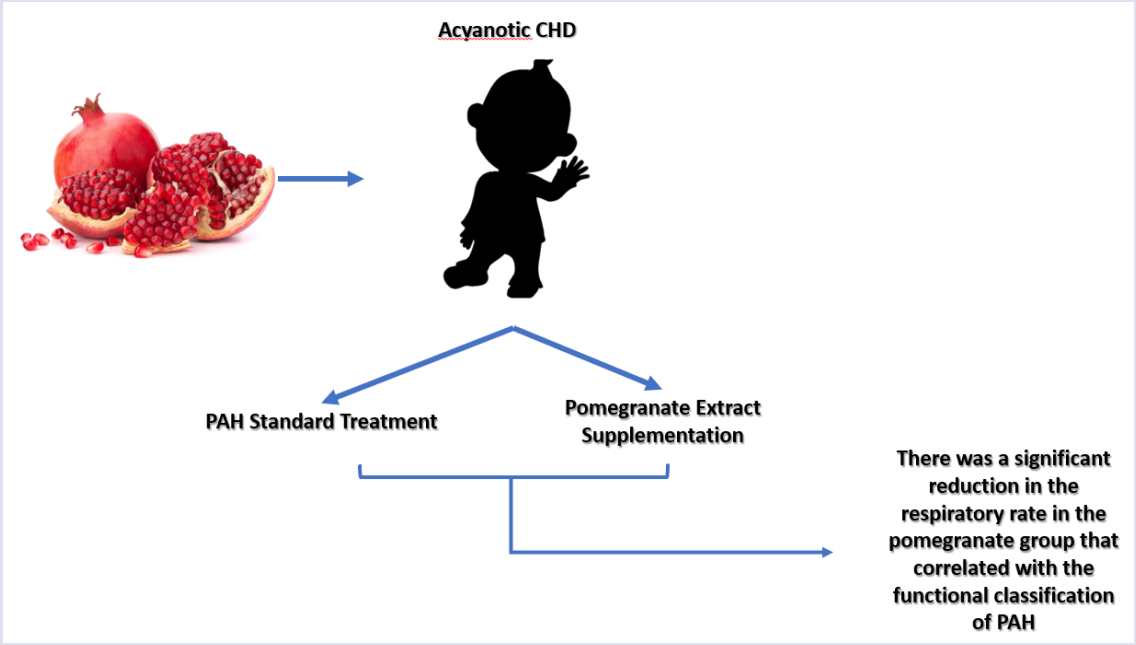
GRAPHICAL ABSTRACT



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