Evaluation of Antiasthmatic Effect of Aqueous Extract of Euphorbia Hirta and Lactuca Virosa on Ovalbumin and Ammonium Hydroxide Induced Asthma in Guinea Pigs

*1UWAYA, DO; 1OGIE, IE; 2FAYORIJU, OD; 1TAFAMEL, EG; 3OBINNA, UK; 4ATUGHARA, JC

1Department of Science Laboratory Technology, Faculty of Life Sciences, University of Benin, Benin City, Nigeria
2Department of Physiology, School of Basic Medical sciences, College of Medical Sciences, University of Benin, Benin City, Nigeria
3Gillott Road B16 0RS, Birmingham, United Kingdom, NO.346.
4Middlewood Street, Salford, United Kingdom, Post Code: M54LH, NO. 4.

*Corresponding Author Email: dickson.uwaya@uniben.edu; udickson4christ@yahoo.com
Co-authors Email: ogiewinosoa@gmail.com; glory.e.tafamel@gmail.com; atugharajohn@gmail.com; Obinna.kenan@gmail.com

ABSTRACT: Euphorbia hirta and Lactuca virosa are both powerful medicinal plants that are used in ethnomedicine to treat diarrhea, bacterial infections, inflammation, asthma, pain, fungus, cancer, and malaria. The aim of this study is to evaluate the antiasthmatic effect of the aqueous extracts of Lactuca virosa and Euphorbia hirta on ovalbumin and ammonium hydroxide induced asthma in guinea pigs model using standard procedures after dividing animals into 8 groups of 4 animals each. Lungs and trachea were collected for histology. The result obtained shows that the leaves of Lactuca virosa and the whole plant of Euphorbia hirta increased the latency to preconvulsing time and reduced the trachea wall thickness when compared to the ovalbumin and aluminum hydroxide control (**p<0.01, *p<0.05). Hematology parameters were not affected (P>0.05). The extract increased the level of superoxide dismutase in the blood and tissues of the animals (P<0.01). Data obtained shows that the leaves of Lactuca virosa and the whole plant of Euphorbia hirta possess antiasthmatic properties.

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Medicinal plants are plants that have gone through minor or no processing and are used to treat illnesses on a local or regional scale (Tilburt and Kaptchuk, 2008). Medicinal plants have medicinal benefits and are used in herbal preparations. Euphorbia hirta L. belongs to the family Euphorbiaceae. It inhabits open waste spaces, grasslands, road sides, and pathways in several portions of the world. It is a common weed found in most subtropical and tropical countries (Nyeem et al., 2017). In English, it is also known as asthma plant, asthma weed, garden spurge, pill-bearing spurge, and snake weed. Flavonoids, polyphenols, tannins, sterols, alkaloids, glycosides, and triterpenoids have all been shown to be present in the plant’s leaves. The plant was also used to treat bronchitis, asthma, dermatitis, dysentery, diarrhea, spasmodic pain, fever, fungal infection, viral infection, anxiety, malaria, amoebic infection, bacterial infection, helminthic infection, and hypertension, in addition to promoting breast milk production in females (Rahuman et al., 2007; Hore et al., 2006; Tona et al., 2000; Tona et al., 1999). The Asteraceae family includes Lactuca virosa. Common names for it include great lettuce, tall lettuce, opium
lettuce, bitter lettuce, laitue vireuse, wild lettuce, and wild lettuce (BSBI, 2007). It can be found in large quantities in central and southern Europe, the Punjab region of Pakistan, India, Australia, and some locations in eastern and western Nigeria. It is used to treat or control localized sleeplessness, muscular or articular aches, priapism, dysmenorrhea, nymphomania, pertussis, irritable cough, asthma, and restlessness in children (Heber, 2004). The aim of this study is to evaluate the antiasthmatic effect of the aqueous extracts of Lactuca virosa and Euphorbia hirta on ovalbumin and ammonium hydroxide induced asthma in guinea pigs model.

MATERIALS AND METHODS

Plant collection: Euphorbia hirta was collected in various fields within the University of Benin, Benin City, in Ovia, the north-east local government of Edo State, Nigeria. Lactuca virosa was collected from various fields at Ille-Ife in the Ife-East local government area of Osun State, Nigeria, and identified and authenticated at the department of plant biology and biotechnology by Dr. H.A. Akinnibosun.

Plant Preparation: The whole plant of Euphorbia hirta was washed, cut, and air-dried for 2 weeks in the Department of Science Laboratory Technology, University of Benin, Benin City. The plant was ground into powder and macerated for 24 hours with water. While the leaves of Lactuca virosa were washed, chopped, and blended. The macerated whole plant of Euphorbia hirta and the blended leaves of Lactuca virosa were filtered with a cheese cloth. Then the filtrates were freeze-dried using a freeze-dryer at the Energy Center at the University of Benin, Benin City.

Experimental Animals: Thirty-two (32) Guinea pigs of either sex weighing 200–500 g were bought from the animal house facility of the Department of Pharmacology, Ambrose Ali University, Ekpoma, Edo State, Nigeria. All the animals were allowed two weeks’ acclimatization in the animal facility of the Department of Animal and Environmental Biology, Faculty of Life Sciences, University of Benin, Benin City. They were allowed free access to pellets and tap water and were exposed to a natural light-dark cycle at room temperature. All animals were handled according to standard protocols for laboratory animals.

Experimental Procedure: The anti-asthmatic studies were carried out using ovalbumin and aluminum hydroxide-induced asthma models (a modified method of Ozolua et al. (2010). On the first and seventh days (I.P.), 10 mg of ovalbumin and 100 mg of aluminum hydroxide were given to 28 animals (groups 2–8) to make them more sensitive. The animals were then given water, salbutamol, and different doses of aqueous extracts of Euphorbia hirta and Lactuca virosa every day for 14 days (O, P). The 32 guinea pigs were allotted into 8 groups as follows:

- Group 1 was given 2 ml/kg of distilled water and did not have asthma.
- Group 2 were sensitized with ovalbumin and aluminum hydroxide and given distilled water.
- Group 3 were sensitized with ovalbumin and aluminum hydroxide and given 0.5 mg/kg salbutamol.
- Group 4 were sensitized with ovalbumin and aluminum hydroxide and given 50 mg/kg of Euphorbia hirta and 100 mg/kg of Lactuca virosa.
- Group 5 were sensitized with ovalbumin and aluminum hydroxide and given 0.5 mg/kg salbutamol.
- Group 6 were sensitized with ovalbumin and aluminum hydroxide and given 100 mg/kg of Euphorbia hirta and 100 mg/kg of Lactuca virosa.
- Group 7 were sensitized with ovalbumin and aluminum hydroxide and given Euphorbia hirta at a dose of 100 mg/kg.
- Group 8 were sensitized with ovalbumin and aluminum hydroxide and given Lactuca virosa 100 mg/kg.

After 14 days of treatment, the animals were exposed to 0.2% histamine aerosols with an ultrasonic nebulizer. They were then sacrificed using chloroform as an anesthesia, and their blood was put into sterile EDTA bottles with 5 ml syringes for hematology analysis. Lungs and trachea were collected for tissue histology, and the flow rate of the animals was also measured. Some of the trachea was homogenized for the antioxidant test.

Determination of Superoxide Dismutase (SOD): The assay is based on the reaction proposed by Idu et al. (2016). 2.5 ml of carbonate buffer was measured into the test tubes. 0.2 ml of tissue homogenate was added and labeled. 0.2 ml of distilled water was measured and added to the reference (Ref) tube. 0.3 ml of 0.3 mM epinephrine was added to each of the tubes and the reference tube. The UV-spectrophotometer (version T80+UV is Spectrometer, PG Instruments Ltd.) was used to read the mixtures at 420 nm absorbance every 30 to 120 s. Distilled water was used to zero the device.

Determination of Malondialdehyde (MDA): Malondialdehyde was analyzed with the method by Idu et al. (2016). A quantity (0.5 ml) of the tissue homogenate was added to 1 ml (1:1 v/v) of TCA-TBA, HCL reagent (thiobarbituric acid 0.375% w/v, 15% TAC w/v, 0.25N HCl). Solutions were heated for 15 minutes in a boiling water bath. The solution was
cooled and centrifuged at 1000 rpm for 10 min. The absorbance of the supernatant was measured against a reference blank at a wavelength of 535 nm. The malondialdehyde concentration of the sample was calculated using extinction for efficient use of 1.5×105M-1cm-1.

Statistical Analysis: Data were expressed as mean ± standard error of mean (SEM), and ‘n’ represents the number of guinea pigs per experimental group. A one-way analysis of variance (ANOVA) was performed with Newman Keul’s post hoc test. All data were analyzed using Graph Pad Prism (UK) software, version 6. P<0.05 indicates a significant difference between the compared data.

RESULT AND DISCUSSION
Preconvulsing time, flow rate and trachea wall thickness in ovalbumin and aluminium hydroxide sensitized Guinea pigs: The result in Figure 1 shows that salbutamol (0.5 mg/kg) and an aqueous extract of Euphorbia hirta (50 mg/kg) + Lactuca virosa (100 mg/kg) increased the latency to preconvulsing time (*p<0.05), and Euphorbia hirta (100 mg/kg) + Lactuca virosa (50 mg/kg) also increased the latency to preconvulsing time when compared to the ovalbumin control (**p<0.01).

The result in Figure 2 shows that the flow rate of the animals was not affected at all dose levels of the aqueous extract of Euphorbia hirta and Lactuca virosa extracts and the standard (0.5 mg/kg salbutamol) compared to the ovalbumin control (p > 0.05). In Figure 3, it can be seen that the trachea wall was thinner after treatment with salbutamol (0.5 mg/kg), 50 mg/kg EH + 100 mg/kg WL, 100 mg/kg EH + 50 mg/kg WL, 100 mg/kg EH + 100 mg/kg WL, and 100 mg/kg WL (*p > 0.05). 100 mg/kg EH reduced the trachea wall thickness when compared to ovalbumin and aluminum hydroxide. Plates A to H show the trachea wall thickness of the animals in the various groups.
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Plate A: Trachea wall thickness for Group 1. [Arrow showing the diameter of trachea wall thickness. d= diameter]

Plate E: Trachea wall thickness for Group 5 [Arrow showing the diameter of trachea wall thickness. d= diameter]

Plate B: Trachea wall thickness for Group 2. [Arrow showing the diameter of trachea wall thickness. d= diameter]

Plate F: Trachea wall thickness for Group 6 [Arrow showing the diameter of trachea wall thickness. d= diameter]

Plate C: Trachea wall thickness for Group 3. [Arrow showing the diameter of trachea wall thickness. d= diameter]

Plate G: Trachea wall thickness for Group 7 [Arrow showing the diameter of trachea wall thickness. d= diameter]

Plate D: Trachea wall thickness for Group 4 [Arrow showing the diameter of trachea wall thickness. d= diameter]

Plate H: Trachea wall thickness for Group 8. [Arrow showing the diameter of trachea wall thickness. d= diameter]

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The result in Figure 5 shows that salbutamol (0.5 mg/kg), 50 mg/kg EH + 100 mg/kg WL, 100 mg/kg EH + 50 mg/kg WL, 100 mg/kg EH + 100 mg/kg WL, 100 mg/kg EH + 100 mg/kg WL, and 100 mg/kg EH increased the superoxide dismutase activity in the blood of the animal compared to the ovalbumin control ($P<0.0001$).

**Fig 5:** Effect of the aqueous extract of *Euphorbia hirta* and *Lactuca virosa* on S.O.D. activity in blood of ovalbumin and aluminium hydroxide sensitized guinea pigs. Salbutamol (0.5 mg/kg), 50 mg/kg EH + 100 mg/kg WL, 100 mg/kg EH + 50 mg/kg WL, 100 mg/kg EH + 100 mg/kg WL, and 100 mg/kg EH increased the SOD activity in the blood of the animal compared to the ovalbumin control ($P<0.0001$). SOD: superoxide dismutase, EH: *Euphorbia hirta*, WL: *Lactuca virosa*. Data are presented in the form of mean ± standard error of mean (n = 4).

The superoxide dismutase activity in the tissues of the animals was not affected (p > 0.05) Figure 6. Figures 7 and 8 show that MDA activity in the blood and tissue of the animals was not affected when compared to the ovalbumin control (p > 0.05). In Table 2, organ-to-body
weight ratios were not affected by the aqueous extract of *Euphorbia hirta* and *Lactuca virosa* when compared to the ovalbumin control and the normal control (P>0.05). The pictures on Plates A–H show how the water extract of *Euphorbia hirta* and *Lactuca virosa* changed the lung histology of the different animal groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Control</th>
<th>Ovalbumin+AloH</th>
<th>50EH+100WL</th>
<th>100EH+50WL</th>
<th>100EH+100WL</th>
<th>100EH</th>
<th>100WL</th>
<th>Salbutamol(0.5mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (10^3/µl)</td>
<td>13.10±2.03</td>
<td>8.38±0.55</td>
<td>11.88±1.33</td>
<td>6.78±1.45</td>
<td>11.33±1.23</td>
<td>8.75±1.35</td>
<td>9.50±2.21</td>
<td>18.90±4.41</td>
</tr>
<tr>
<td>RBC (10^6/µl)</td>
<td>4.31±0.33</td>
<td>3.68±0.05</td>
<td>4.14±0.36</td>
<td>3.95±0.37</td>
<td>3.56±0.35</td>
<td>2.99±0.59</td>
<td>6.88±0.71</td>
<td>3.28±0.63</td>
</tr>
<tr>
<td>GRAN (%)</td>
<td>6.23±0.79</td>
<td>5.85±0.85</td>
<td>6.23±0.66</td>
<td>9.09±2.71</td>
<td>5.5±0.64</td>
<td>7.08±0.50</td>
<td>9.93±2.71</td>
<td>10.13±1.54</td>
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<tr>
<td>HCT (%)</td>
<td>37.00±2.89</td>
<td>30.83±0.31</td>
<td>32.40±3.40</td>
<td>25.43±2.85</td>
<td>28.48±2.95</td>
<td>24.85±0.60</td>
<td>364.80±117.30</td>
<td>364.80±117.30</td>
</tr>
<tr>
<td>HGB (g/dl)</td>
<td>10.75±0.90</td>
<td>8.3±0.20</td>
<td>9.73±1.72</td>
<td>7.40±0.86</td>
<td>8.45±0.99</td>
<td>7.08±0.43</td>
<td>364.80±117.30</td>
<td>364.80±117.30</td>
</tr>
<tr>
<td>PLT (10^3/µl)</td>
<td>641.00±54.60</td>
<td>596.60±112.80</td>
<td>694.80±113.20</td>
<td>397.00±88.62</td>
<td>553.00±67.32</td>
<td>364.80±117.30</td>
<td>25.43±2.85</td>
<td>397.00±88.62</td>
</tr>
<tr>
<td>PCT (%)</td>
<td>0.67±0.06</td>
<td>0.51±0.11</td>
<td>0.70±0.13</td>
<td>0.37±0.12</td>
<td>0.58±0.07</td>
<td>0.39±0.02</td>
<td>68.08±3.29</td>
<td>0.70±0.13</td>
</tr>
<tr>
<td>LYMP (%)</td>
<td>77.53±8.44</td>
<td>78.88±2.82</td>
<td>79.10±1.42</td>
<td>71.60±2.25</td>
<td>80.48±2.57</td>
<td>76.55±4.01</td>
<td>68.08±3.29</td>
<td>71.95±3.28</td>
</tr>
<tr>
<td>MID (%)</td>
<td>16.25±4.17</td>
<td>16.18±2.06</td>
<td>14.68±1.33</td>
<td>17.10±4.05</td>
<td>14.03±2.36</td>
<td>15.10±2.92</td>
<td>23.10±1.88</td>
<td>19.18±1.83</td>
</tr>
</tbody>
</table>

**Table1:** The effect of the aqueous extract of *Euphorbia hirta* and *Lactuca virosa* on hematology parameters of ovalbumin and aluminum hydroxide induced asthma in guinea pigs.

The same data were represented as mean ± S.E.M, n = 4.

**Table2:** The effect of *Euphorbia hirta* and *Lactuca virosa* on organ to body weight ratio of ovalbumin and aluminium hydroxide induced asthma in guinea pigs.

The organs were not affected by the aqueous extract of *Euphorbia hirta* and *Lactuca virosa* when compared to the ovalbumin and the normal control (P > 0.05). EH: Euphorbia hirta, WL: Lactuca virosa. Data were represented in the form of mean±standard error of the mean. n=4.

In traditional medicine, the plants *Euphorbia hirta* and *Lactuca virosa* are well known and frequently used to cure ailments like malaria, bacterial, fungal, and viral infections, inflammation, cancer, cough, and asthma (Nyeem et al., 2017). Asthma affects many people and affects the airways. It is a complicated disease with different and recurring symptoms, bronchi that are overactive, and inflammation at the root (Busse and Lemanske, 2001). In this research, 50 mg/kg *Euphorbia hirta* + 100 mg/kg *Lactuca virosa*, 50 mg/kg *Euphorbia hirta* + 50 mg/kg *Lactuca virosa*, and 0.5 mg/kg Salbutamol all made the time it took for seizures to start longer after histamine aerosols were present (Figure 1).

Plate A: Histopathology of the lungs demonstrating fluid accumulation in the lungs’ wall under normal circumstances (distilled water). × 100

Plate B: Histopathology of the lungs of the negative control (Ovalbumin+aluminum hydroxide) demonstrating the presence of fluidy material obstructing the airway. × 100
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**Plate C:** Histopathology of the lungs for the standard group (0.5 mg/kg salbutamol) of 100 patients shows fluid accumulation in the lung wall.

**Plate D:** Histopathology of the lungs for the first extract group (50 mg/kg EH + 100 mg/kg WL) demonstrates fluid accumulation in the lungs' wall. × 100

**Plate E:** For the second extract group (100mg/kg EH+50mg/kg WL), the histopathology of the lungs (Plate E) demonstrates fluid accumulation in the lung wall.

**Plate F:** Histopathology of the lungs demonstrating fluid and inflammatory buildup in the lung wall (100mg/kg EH and WL).

**Plate G:** Lung histopathology demonstrating fluid accumulation in the lung wall (100 mg/kg EH)

**Plate H:** Histopathology of the lung showing fluid and inflammatory buildup in the lung wall at (100mg/kg WL) 100

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Histamine brings calcium ions to the H1 receptors, which makes smooth muscles contract, capillary permeability rise, and pain happen (Criado et al., 2010). Histamine causes bronchoconstriction in asthmatic situations by binding to the H1 receptor in the bronchi. The patient gasped for air as a result of this constriction, which set off a pre-convulsion. Euphorbia hirta and Lactuca virosa's capacity to lengthen the latency of the preconvulsive period is evidence of their anti-asthmatic properties. Euphorbia hirta and Lactuca virosa have anti-asthmatic properties similar to salbutamol, a well-known common asthma medication (Figure 1).

Asthma and chronic obstructive pulmonary disease are treated with salbutamol, a short-acting β2 receptor agonist (COPD). The primary receptors in bronchial smooth muscle, the β2 adrenergic receptors, are stimulated. The β2 receptors are stimulated, which activates the adenyl cyclase enzyme, which produces cyclic adenosine monophosphate (cAMP). A rise in cAMP relaxes bronchial smooth muscle and lowers airway resistance by reducing intracellular ionic calcium concentrations. Higher cAMP levels also stop mast cells in the airway from releasing histamine and leukotriene, which narrow the airways (O'Shaughnessy, 2012). At all dosage levels, salbutamol and the extracts reduce the thickness of the trachea wall. The ability of the extract and salbutamol to lower the thickness of the tracheal wall indicates that the plant extract's mode of action may involve bronchodilation. At all dosing levels, the animals' tracheal flow rate was unaffected. 50 mg/kg Euphorbia hirta and 100 mg/kg Lactuca virosa, 50 mg/kg Lactuca virosa, and 100 mg/kg each boosted the blood's superoxide dismutase activity. 100 mg/kg of Lactuca virosa, 100 mg/kg of Euphorbia hirta, and 100 mg/kg of Euphorbia hirta. A natural enzyme in the body called super-oxide dismutase helps break down the super-oxide radical into O2 and H2O2. Superoxide radicals are by-products of oxygen metabolism that, if unchecked, can result in various forms of cell damage. Asthma, cancer, and arthritis are just a few of the ailments that hydrogen peroxide damages and causes. Therefore, it serves as a crucial defense mechanism in almost all living cells that are exposed to oxygen (Younus, 2018). The levels of malondialdehyde in the animals' blood and tissues were unaffected by any dose of the plant extracts. At all doses of the extracts, the animals' hematological parameters were unaffected. The distribution of oxygen and nutrients to various body areas depends on red blood cells. Brecher (2005) notes that platelets aid in hemostasis, and white blood cells are crucial for the production of antibodies that fight infections. Diseases may develop if these parameters are elevated or lowered in the blood. However, the fact that the hematological parameters remained unaffected indicates that plant extracts are safe and effective for treating disorders. The aqueous extracts of Euphorbia hirta and Lactuca virosa did not have any negative effects on the animals' organs at any dose level. An indication of liver cirrhosis is the presence of inflammation in certain body organs, such as the liver, while an indication of nephritis is the presence of inflammation in the nephron. The size of the body's organs tends to rise as a result of this inflammation. The fact that the plant extracts had no effect on the organs' weight indicates that using plants to cure illnesses is safe (Analia et al., 2006). On a histopathological slide, fluid was shown accumulating for normal control in the lung's wall (Plate A). Plate B demonstrated that the negative control (ovaalbumin and aluminum hydroxide) had fluidly material obstructing its airway. For the standard group (0.5 mg/kg salbutamol), Plate C depicts fluid accumulation in the lungs' wall. Plate D depicts fluid accumulation in the lungs' wall for the first extract group (50 mg/kg EH + 100 mg/kg WL). For the second extract group (100 mg/kg EH+50 mg/kg WL), Plate E depicts fluid accumulation in the lungs' wall. Plate F depicts a fluid and inflammatory buildup in the lung wall (100 mg/kg EH and WL). Plate G depicts fluid accumulation in the lungs' wall (100 mg/kg EH). Plate H depicts a fluid and inflammatory buildup in the lungs' wall (100 mg/kg WL). The histology slides demonstrated the degree of lung inflammation for the various groups, and the animals in the extract groups had some reduction in lung inflammation.

Conclusion: The study's results showed that taking the aqueous extracts of Lactuca virosa and Euphorbia hirta by mouth had strong effects on reducing asthma. Even though the water-based extracts of Euphorbia hirta and Lactuca virosa can help with asthma when used separately, using them together might make the treatment more effective.

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