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# EVALUATION OF CARDIOVASCULAR ACTIVITIES OF AN AYURVEDIC PREPARATION 'KHADIRARISHTA' IN RAT MODEL

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## ABSTRACT

In recent medical treatment for various diseases, traditional or alternative medicines such as Ayurvedic drugs are getting importance and reputation day by day because they have fewer side effects and give necessary pharmacological actions. But prolonged and excess usage may lead to harmful effects such as damage of the heart muscle leading to various types of arrhythmia and coronary artery diseases. "Khadirarishta", an Ayurvedic drug, is being traditionally used for heart diseases along with jaundice, anemia and abdominal tremor. The electrocardiographical (ECG) parameters were measured in rat model before and after administration of Khadirarishta. It was observed that Khadirarishta at a dose of 800 mg/kg was safe but 1600 mg/kg and 3200 mg/kg produced abnormal activities in the heart.

**KEYWORDS:** Khadirarishta, ECG, Heart disease, Rat model, Traditional medicines.

## INTRODUCTION

Plants and human beings are inseparable, because plants not only provide us food, shelter and medicines but also the life sustaining oxygen gas. Since, disease, decay and death always co-exist with life; the early man had to think about disease and its treatment at the dawn of intellect. Thus the race started using plants as of a means of treatment of diseases and injuries from the early days of civilization on earth and its long journey from ancient time to modern age the human race has successfully used plants and products as effective therapeutic tools for fighting against disease and various health hazards.[1] Medicinal plants are the principal healthcare resources for the majority of people all over the world. The healing properties of herbal medicines have been recognized in many ancient cultures. The traditional medical systems such as Ayurveda, Siddha and Unani are part of a time-tested culture and honored by people till today. Pharmaceutical importance of plants has led to the discovery and adoption of plant extracts which were commonly used in traditional medicine as alternative source of remedy.[2] Herbal medicines, also called botanical medicines or phytomedicines, refer to the use of any plant seed, berries, roots, leaves, bark or flower for medicinal purposes.[3] The economic significance of medicinal plants stems from the fact that the number of patients suffering from chronic ailments is on the rise and drugs from medicinal plants are more effective in treating such disorders.[4] Plants are utilized as therapeutic agents since time immemorial in both organized (Ayurveda, Unani) and unorganized (folk, tribal, native) forms.[5] The widespread use of herbal remedies and healthcare preparations, as those described in ancient texts such as the Vedas and the Bible, and obtained from commonly used traditional herbs and medicinal plants, has been traced to the occurrence of natural products with medicinal properties.[6] Medicinal and aromatic plants (MAPs) are produced and offered in a wide variety of products, from crude materials to processed and packaged products like pharmaceuticals, herbal remedies, teas, spirits, cosmetics, sweets, dietary supplements, varnishes and insecticides.[7-9] Ayurvedic medicine is still the mainstream of the world's populations for primary healthcare because of better cultural acceptability, better compatibility with the human body and fewer side effects. Now a day's many Ayurvedic preparations are used for the different disease purpose, but have no proven scientific evidence about their proper action and lethal dose. In the present days, the World Health Organisation (WHO) emphasizes on concomitant use of traditional drugs which are based on plant materials to ensure the total health coverage. A large number of plants are known to be used in the treatment of cardiovascular disorders in different corners of the world.

Ayurvedic is a traditional system of medicine which is also called *Ayurveda*[10] and used as a wide range of modalities to create health and well being. *Ayurveda* is used to restore the physical, mental and emotional balance in patients, thereby improving health, preventing disease (prophylaxis) and also treating any current illness.[11] *Ayurveda* is a Sanskrit term, made up of the words *ayus* and *veda*. *Ayus* means life and *Veda* means knowledge or science. The term *Ayurveda* thus means the knowledge of life or the science of life.[12] World Health Organization and National Institute of Health, USA have also recommended the use of Ayurvedic drugs in the name of complementary/alternative medicine (CAM) system, because these drugs have fewer side effects and give necessary pharmacological actions.[13-15] Khadirarista is an Ayurvedic preparation. It is also known as Khadirarisht. It is used in all sorts of skin diseases, heart diseases, jaundice, anemia, worms, abdominal tumor and leprosy. It is manufactured as liquid by arista process.[16]

## MATERIALS AND METHODS

### Drug

Khadirarista was purchased from Shree Kundeshwari Oushadhalaya, Dhaka. It was presented as 500 mL in glass bottle.

### Instrument

Veterinary ECG machine (EDAN VET 300 model) was used to carry out the experiment. The EDAN VET-300 is suitable equipment for laboratory working with animals for measuring ECG. It is simple and easy to use, lightweight and portable. Interpretative analysis included in the form of automatic measurement calculation.

### Selection of animals

A total 40 rats of either sex, weighing about 130-150 g, aged 2 months were purchased from animal house of the Department of Pharmacy, Jahangirnagar University, Savar, Dhaka, Bangladesh. All the rats were acclimatized to the new environment for a period of one week. During the experiment period the rats were kept in a well ventilated animal house at 25 $^{o}$C. They were supplied with standard pellets and fresh drinking water. All the rats were kept in cage and maintained with natural 12 h light and dark cycle in the animal house of Department of Pharmaceutical Chemistry, University of Dhaka, Bangladesh.

**Preparation of dose**

The dose was calculated from human dose of 5-10 mL. The dose calculation is given in the **Table 1**.

**Table 1. Calculation of dose ('X' is body weight of the rats) where normal human dose is 200 mg/kg.**

| Concentration (as expressed by 'X') | Concentration (as expressed by mg/kg) | Action sought |
|---|---|---|
| 1/16 X | 100 | Less action |
| 1/12 X | 133 | Less action |
| 1/8 X | 200 | Less action |
| 1/4 X | 400 | Less action |
| ½ X | 800 | Proper action |
| X | 1600 | Slightly toxic |
| 2 X | 3200 | More toxic |
| 4 X | 6400 | Lethal dose |
| 8 X | 12800 | Lethal dose |

**Experimentation**

For anesthesia 50mg/kg Ketamine was administered as intraperitoneal injection. The electrodes were connected to the left arm, right arm, left leg, right leg and rib joint. Auto option was selected to get rhythm from standard limb lead I, II, III, avR, avL, avF, V. Finally standard limb lead I and II were used for characterization of ECG. Rhythm mode was also used and standard limb lead II recording were used for calculation of ECG parameters.

**ECG parameters**

ECG parameters were recorded and analyzed to find the effect of drugs. The ECG parameters are summarized in **Table 2**. A schematic tracing of ECG record is shown in **Figure 1**. These tracing were used as a standard to calculate the measured values of ECG parameters.

**Table 2. ECG Parameters.**

| Parameters of ECG | Standard Duration (ms) |
|---|---|
| P wave | ≤100 |
| QRS complex | 80-110 |
| Q wave | 40 |
| R wave | 200 |
| S wave | 60-10 |
| T wave | 160 |
| U wave | 80 |
| PR interval | 120-200 |
| ST segment | ≤200 |
| R-R interval | 600-1200 |

| | |
|---|---|
| Q-T interval | 350-430 |

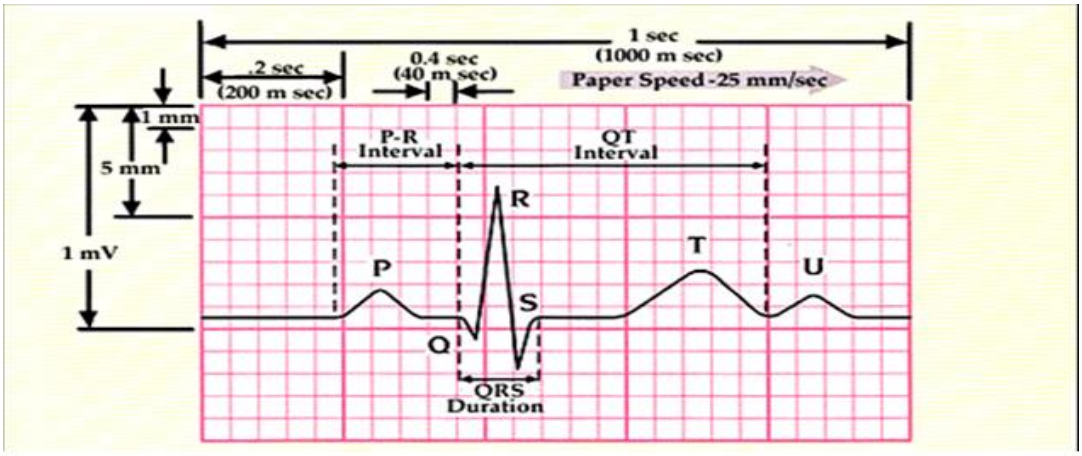



**Figure 1: Schematic presentation of an ECG tracing.**

| Vertical Axis | Horizontal Axis |
|---|---|
| 1 small square = 1 mm (0.1 mV) | 1 small square = 0.04 s (40 ms) |
| 1 Large square = 5 mm (0.5 mV) | 1 small square = 0.2 s (200 ms) |
| 2 Large square = 10 mm (1 mV) | 5 small square = 1 s (1000 ms) |

**ECG paper speed**

The paper moved at a rate of 25 mm/second. Time was measured horizontally. Each small block is 1 mm equal to 0.04 seconds and equal to 0.1 mV. Each bold block is equal to 0.2 seconds. Amplitude was measured vertically in mV.

**RESULTS AND DISCUSSION**

In control mode, the normal heart rate of rats was within 203-284 bpm (the range being 250-350 bpm), and ECG tracing showed that every parameters were within the normal range (**Figure 2**).

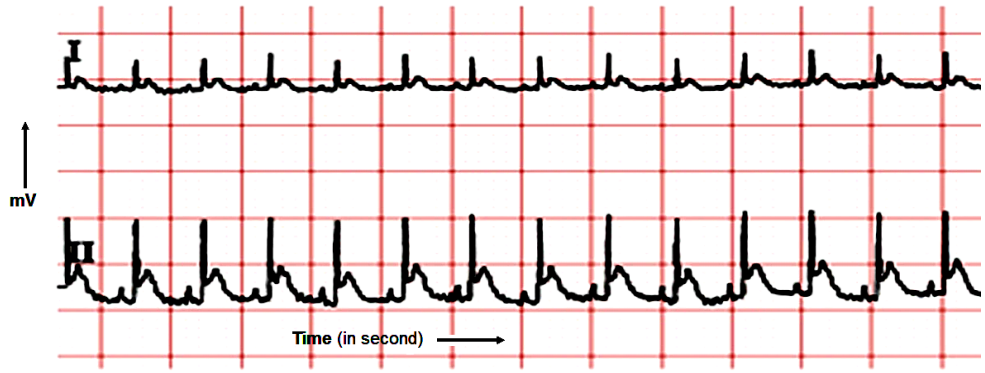



**Figure 2. Normal sinus rhythm (NSR) of the rat heart.**

When Khadirarishta was administered at a dose of 800 mg/kg, no change in the heart rate and other ECG parameters were observed. It was indicated that 800 mg/kg is quite safe dose for

the rats. After administration of 1600 mg/kg then it showed some diseases such as SA nodal block which was an evident from missing beats.

After administration of 3200 mg/kg of the drug, the heart rate decreased to about 65 bpm. It indicated that Khadirarishta produced marked bradycardia and ultimately leading to the death of the animals [**Figures 5(a) to (e)**] producing various types of severe arrhythmias looking likes that of ventricular fibrillation.

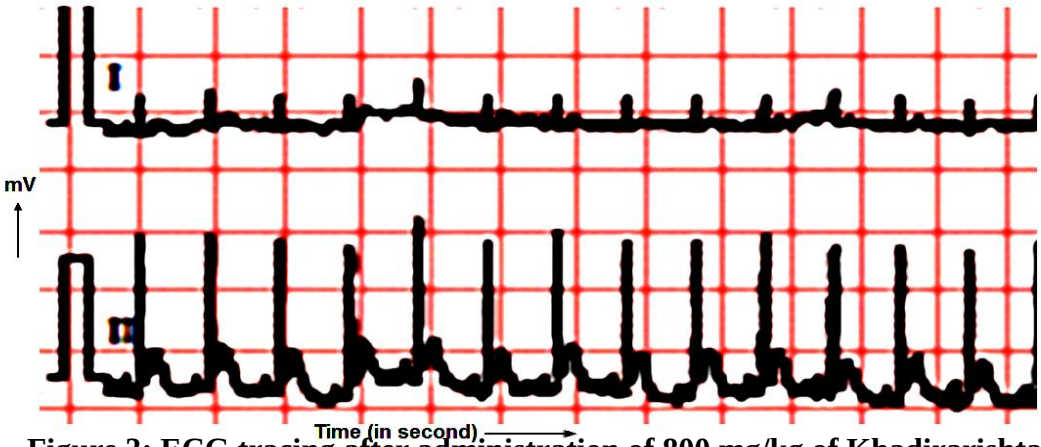



**Figure 3: ECG tracing after administration of 800 mg/kg of Khadirarishta.**

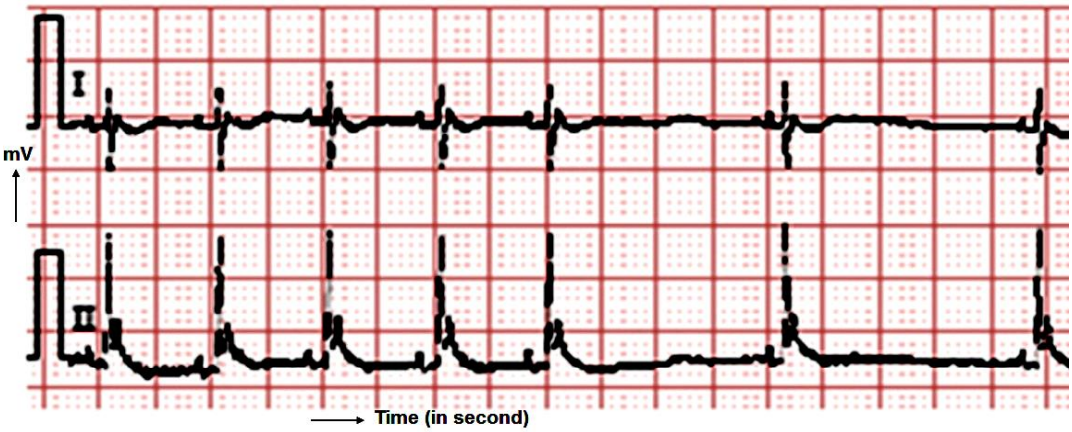
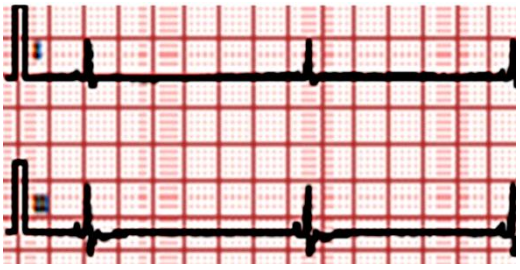
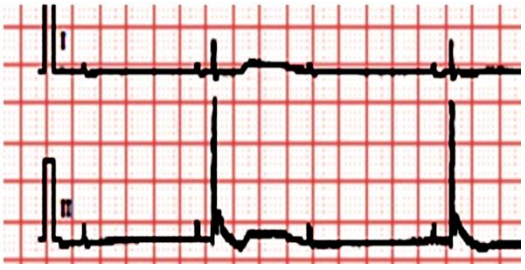


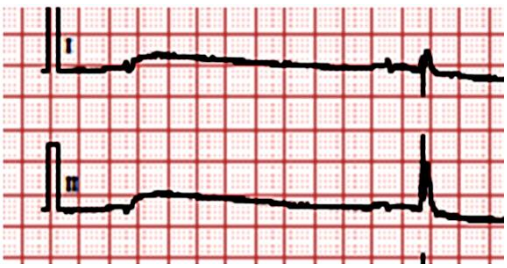

**Figure 4: Typical ECG tracings of the standard limb lead I and II after intraperitoneal administration of 1600 mg/kg of drug.**



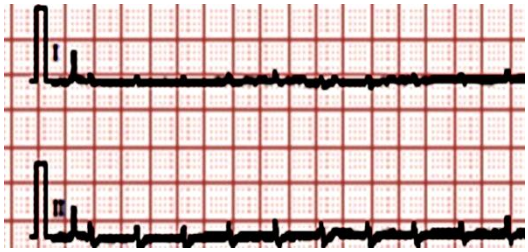
**(a)**



**(b)**




(c)




(d)


(e)

**Figure 5. Typical ECG tracings of the standard limb lead I and II after intraperitoneal administration of 3200 mg/kg of drug. Panels (a) and (b) show AV nodal block as well as SA nodal block, Panel (c), Panel (d) and Panel (e) show ventricular fibrillation and dying conditions of the animals. The vertical line indicates mV and the horizontal line indicates time in second (s).**

It indicated that 3200 mg/kg is a very lethal dose and this dose of the drug produced all types of arrhythmia. Tables 3 and 4 show the ECG parameters in duration.

**Data from auto mode**

The auto mode was that mode where heart rate, P wave, PR interval, QRS duration was shown. Using the auto mode it could be known about increase or decrease heart rate. The data obtained from machine after administration 800 mg/kg in auto mode showed in the **Table 3**.

**Table 3: Different ECG parameters after administration of Khadirarista at a dose of 800 mg/kg. The data were shown as mean of 10 similar experiments (n=10) in auto mode.**

| Time (min) | HR (bpm) | P dur (ms) | PR interval (ms) | QRS dur (ms) |
|---|---|---|---|---|
| Pretreatment | 248.5 | 51.8 | 94.25 | 113.66 |
| 10 | 243.3 | 31.3 | 92.5 | 134 |
| 15 | 268.2 | 30 | 52.3 | 103.5 |
| 20 | 277.3 | 31.6 | 77.3 | 114.8 |
| 25 | 281 | 42.3 | 78 | 138.3 |
| 30 | 279.6 | 44.5 | 90 | 168.2 |
| 35 | 272 | 50.3 | 84 | 154 |
| 40 | 249.8 | 44.6 | 92.6 | 142.5 |

| | | | | |
|---|---|---|---|---|
| 45 | 239.2 | 30 | 98.5 | 163 |
| 50 | 255.5 | 58.3 | 109.7 | 117.8 |

**Table 3** shows the ECG parameters after administration of 800 mg/kg of Khadirarista. Pretreatment row shows the values in control condition. ECG parameters were calculated after 10 min of administration of drug. At this dose, the heart rate increased, P duration decreased, PR interval decreased followed by increased for some time and then came to normal value. All these indicated that 800 mg/kg was safe dose for animal.

The data of auto mode obtained from machine after administration 3200 mg/kg in auto mode shown in the **Table 4**.

**Table 4. Different ECG parameters after administration of khadirarista at a dose of 3200 mg/kg. The data were shown as mean of 10 similar experiments (n=10) in auto mode.**

| Time (min) | HR (bpm) | P dur (ms) | PR interval (ms) | QRS dur (ms) |
|---|---|---|---|---|
| Pretreatment | 248.5 | 51.8 | 94.25 | 113.66 |
| 10 | 242 | 38.6 | 61.3 | 156.2 |
| 15 | 231.8 | 57.3 | 96 | 174 |
| 20 | 216.3 | 44 | 61.5 | 144.5 |
| 25 | 232 | 61.5 | 81.5 | 139.6 |
| 30 | 197 | 59 | 92.3 | 105 |
| 35 | 133.3 | 144.5 | 215 | 104.5 |
| 40 | 123 | 87 | 166 | 120 |
| 45 | 107.7 | 25.5 | 82.5 | 96.7 |
| 50 | 65 | 37 | 54 | 96 |

**Table 4** shows the numerical values of different ECG parameters after administration of 3200 mg/kg of Khadirarista. Pretreatment row shows the normal values. The ECG parameter values were calculated after 10 min. It was observed that heart rate decreased severely; P duration, PR interval and QRS duration also decreased dramatically. All these indicated that 3200 mg/kg was a lethal dose leading to dyeing condition of animals.

**Tables 5** and **Table 6** show abnormal total R number, RR average, RR maximum interval, RR minimum interval. In the ECG interpretation curve were shown in control mode, the normal heart rate of rats which was 203-284 bpm. But when Khadirarista was administered at a dose of 800 mg/kg, no change in the heart rate was observed. After administration of 1600 mg/kg then it showed some disease such as SA nodal block, Atrial filbrilation, AV nodal block, Right bundle branch block, Left bundle branch block. After administration of 3200

mg/kg of the drug, the heart rate decreased to 65 bpm. It indicated that Khadirarista produced marked bradycardia and ultimately leading to the death of the animals.

**Data from rhythm mode**

The rhythm mode was that mode where lead I, II, III, aVR, aVL, aVF, V was located. This mode showed RR average interval, RR maximum interval, RR minimum interval. The data obtained from machine after administration 800 mg/kg in rhythm mode were shown in the **Table 5**.

**Table 5. Different ECG parameters after administration of Khadirarista at a dose of 800 mg/kg. The data were shown as mean of 10 similar experiments (n=10) in rhythm mode.**

| Time (min) | Total R number | RR avg interval | RR max interval | RR min interval |
|---|---|---|---|---|
| Pretreatment | 243.16 | 248.83 | 428.33 | 190 |
| 10 | 207.85 | 234.5 | 342.16 | 199.83 |
| 15 | 266.16 | 230.16 | 382.5 | 188.16 |
| 20 | 272.3 | 188.4 | 350.3 | 184.8 |
| 25 | 269.7 | 227.7 | 314 | 184.17 |
| 30 | 260 | 233.83 | 347 | 187 |
| 35 | 259.7 | 230.3 | 341.7 | 202.8 |
| 40 | 255.8 | 234.7 | 275 | 219.3 |
| 45 | 246.7 | 242.5 | 312.5 | 225.7 |
| 50 | 249.7 | 240.3 | 323 | 200.8 |

In the **Table 5**, pretreatment row shows the results in control condition. The calculation of data started after 10 min. It was observed that total R number, RR average interval, RR maximum interval and RR minimum interval all remained static after administration of 800 mg/kg of the drug.

**Table 6** shows the results of ECG parameters after administration of 3200 mg/kg. It was observed that total R number decreased but RR average interval, RR maximum interval and RR minimum interval increased drastically. These results showed that 3200 mg/kg was a lethal dose and it affected all parameters of ECG tracings which indicated that the dose produced all types of arrhythmia.

The data obtained after administration 3200 mg/kg in rhythm mode were shown in the **Table 6**.

**Table 6. Different ECG parameters after administration of Khadirarista at a dose of 3200 mg/kg. The data were shown as mean of 10 similar experiments (n=10) in rhythm mode.**

| Time (min) | Total R number | RR avg interval | RR max interval | RR min interval |
|---|---|---|---|---|
| Pretreatment | 243.16 | 248.83 | 428.33 | 190 |
| 10 | 211.16 | 250.83 | 318.66 | 209 |
| 15 | 232.6 | 262 | 284 | 239.4 |
| 20 | 259.8 | 232.5 | 312.8 | 197 |
| 25 | 194.2 | 389.2 | 943 | 187.7 |
| 30 | 283 | 215.7 | 415.3 | 223 |
| 35 | 110 | 625.5 | 1145.5 | 495.5 |
| 40 | 40 | 1501 | 231 | 822 |
| 45 | 48 | 1243 | 480 | 961 |
| 50 | 65 | 923 | 1008 | 858 |

## DISCUSSION

Traditional medicines are relatively safe and effective medication. But very large dose may cause injury to the related organ (heart, liver, kidney; heart was considered in this study) and produce drug induced effects which might prove lethal to the subjects. This finding is quite similar to our previous findings.[17,18]

## CONCLUSION

In the present work, the experiments were performed in rat model with the drug at different doses in intraperitoneal route and ECG tracing were recorded to explore the cardiac activity. It was found that 800 mg/kg was quite normal dose, 1600 mg/kg was slightly toxic but 3200 mg/kg was lethal dose in rats. So, it could be concluded that Khadirarista is a safe drug at a dose of 800 mg/kg. But at long time use or at a high dose it could induce different cardiac diseases. Study at cellular and molecular level with this drug is necessary to get more insight about mechanism of this drug.

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**REFERENCES**


1. Ghani A (1998). Text book of pharmacognosy, 2(1): 240.
2. Suresh Kumar, Rohit Kumar and Altaf Khan (2011). Medicinal plant resources: Manifestation and prospects of life-sustaining healthcare. *Continental J. Biological Sciences*, 4 (1): 19-29.
3. Baquar, S.R (2001). Textbook of economic botany, Ferozsons (Pvt.) Ltd., Lahore, Pakistan.
4. Deshpande, R.S., Neelakanta, N.T. and Hegde, N (2006). Cultivation of medicinal crops and aromatic crops as a mean of diversification in agriculture: *eIX/ADRT/115*.
5. Girach R.D., Khan, H. and Ahmad, M (2003). Botanical identification of Thuhar seldom used as Unani medicine. *Hamdard Medicus*. XLVI(1): 27-33.
6. Hoareau, L. and DaSilva, E. J (1999). Medicinal plants: a re-emerging health aid. *Electronic Journal of Biotechnology* 2 (2): 56-70.
7. Ohrmann, R (1991). Pflanzenextrakte in Haushaltsprodukten. Dragoco Report (Holzminden) 3: 67-76.
8. Gorecki, P (2002). Vitafoods und Kosmetika: Arzneipflanzen erobern sich neue Wirkungsbereiche. Drogenreport 28: .9-15.
9. Lange, D (1996). Untersuchungen zum Heilpflanzenhandel in Deutschland. ein Beitrag zum internationalen Artenschutz. Bundesamt für Naturschutz, Bonn-Bad Godesberg.
10. Courson WA (2008). State licensure and ayurvedic practice: planning for the future, managing the present. *Newsletter of the National Ayurvedic Medical Association* [online journal].
11. Mazumder Papiya Mitra ; Das Saumya ; Das Sanjita ; Das Manas Kumar (2011). Phyto-Pharmacology of *Berberis aristata* DC. *A Review Journal of Drug Delivery & Therapeutics* 1(2): 46-50.
12. Lakshmi T, Anitha Roy, Geetha RV (2011). *Acacia Catechu* Willd –A Gift From Ayurveda To Mankind –A Review. *The Pharma Research* (T. Ph. Res.) 5(2): 273-293.
13. Chopra A and Doiphode VV (2002). Ayurvedic medicine—core concept, therapeutic principles, and current relevance. *Medical Clinics of North America* 86(1): 75-88.
14. Dodds JA (2008). Know your CAM provider. *Bulletin of the American Academy of Orthopedic Surgeons/American Association of Orthopedic Surgeons* [online journal].
15. Gogtay NJ, Bhatt HA, and Dalvi SS (2002). The use and safety of non-allopathic Indian medicines. *Drug Safety* 25(14): 1005-1019.

16. Bangladesh National Formulary of Ayurvedic Medicine (1992). (Approved by the Government of Bangladesh vide Ministry of Health and Family Welfare Memo No. Health- 1/Unani-2/89/ (Part-1) 116 dated 3-6-1991): 83-84.
17. Most. Shammi Rahman, Shahana Jahan, Kamrun Nahar, Nazia Islam, Danis Rahman, Ridwan Bin Rashid, Abu Asad Chowdhury, Rebecca Banoo and Mohammad Shah Amran (2013). Evaluation of cardiovascular activity of an Ayurvedic product 'Mrityunjay' in rat model; *Bangladesh Pharmaceutical Journal* 16(1): 99-105.
18. Md. Tauhid-Ul Islam, Md. Abdus Samad Bhuiyan, Md. Musfequr Rahman Shajjad, Md. Taimuzzaman Sharif, Md. Zakir Sultan, Asma Rahman, Md. Akter Hossain, Abu Asad Chowdhury and Mohammad Shah Amran. A study of prophylactic effect against diabetes of two Ayurvedic drugs 'Jambadyarista' and 'Bohumutrantak Ras' in normal as well as alloxan-induced diabetic rats. *British Journal of Pharmaceutical Research 4(16): 1945-1955, 2014.*