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Comparative in-vivo study of Anti-diabetic effect of Aqueous extracts of *Khadira* (*Acacia catechu* willd.) and *Arjuna* (*Terminalia arjuna* Roxb.).

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ABSTRACT

In Ayurveda *Khadira* and *Arjuna* are mentioned in *Kashayaskandha* (Group of astringents). Both possess *Sheet Veerya*, *Katu vipaka* and *Ruksha guna*, *Pramehagna* (anti- diabetic), *Shothhar* (anti-inflammatory) properties. The present study was performed to compare anti-diabetic activity of *Khadira* (Acacia catechu willd.) and *Arjuna* (Terminalia Arjuna Roxb.) in streptozotocin induced albino rats. Aqueous extracts of stem bark of *Khadira* and *Arjuna* were administered orally 6.75ml/kg/ body weight for 21 consecutive days to diabetic albino rats. Parameters likes Blood glucose level, OGTT, Hematology (WBC, RBC, Hemoglobin, HCT, and Platelet count), Biochemistry (Glucose, Total Protein, Urea, Creatinine, Triglyceride, HDL- Cholesterol, Cholesterol, SGPT, SGOT and ALP) , change in body weight performed for evaluation of hypoglycemic effects. Daily oral treatment with the aqueous extract of *Khadira* and *Arjuna* for 21 days significantly ($p<0.001$) reduced blood glucose in streptozotocin induced diabetic rats. The altered levels of biochemical parameters in diabetic animals as compared to normal indicating metabolic functions were also significantly improved by oral administration of *Khadira* and *Arjuna* extracts. The result suggests that aqueous extracts of *Khadira* and *Arjuna* revealed significant anti-diabetic activity. *Khadira* aqueous extract is more significant as anti-hyperglycemic agent than *Arjuna* aqueous extract in experimental rats.

KEYWORD – *Khadira, Arjuna, Prameha*, Diabetes.

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INTRODUCTION

Prameha (Diabetes) has become a global problem and also well described in the ancient Indian classics like *Vedas*. As of 2016, an estimated 387 million people have diabetes worldwide. This is equal to 8.3%of adult population, with equal rates in both women and men.[1] Insulin and oral hypoglycemic are the most widely used drugs for diabetes but they have various side effects like hypoglycemia, weight gain, lactic acidosis and they cause liver and renal damage. The controlling of diabetes without side effects is yet a challenge to the medical system. There is an increasing demand to use the natural products with anti-diabetic activity. Ayurvedic Samhitas mentioned *Arjuna* and *Khadira* in various formulation of Prameha Chikitsa. Also Nighantus like Bhavprakash nighantu, Kaiyadev nighantu,s Shodhal nighantu described *Arjuna* and *Khadira* as *Pramehaghna Dravya* That means both have Anti-diabetic properties.

Khadira **(***Acacia catechu willd*.**)** is a small or medium sized, thorny tree up to 15m tall, bark dark grey or greyish –brown, peeling off in long strips, brown or red inside. *Khadira* occurs naturally in mixed deciduous forests and savannas of lower mountains and hills.[2] It is especially common in drier regions on sandy soils of riverbanks and watersheds of India, Myanmar, Nepal, Pakistan and Thailand. Main chemical components of *Khadira* are Alkaloids, flavonoids, tannins and Saponins.[3] *Khadira* is used in *Dantaroga* (beneficial for teeth), *Mukharoga* (useful in mouth disease), *Kushtha, Raktapitta* (Urticaria), *Vatajkasa* (Dry cough), *Krimi*(worms), *Medoraga* (Obesity), *Prameha* (Diabetes).[4]

Arjuna (Terminalia arjuna Roxb.) is large tropical woody tree distributed throughout India. It is about 20-25 meters tall, usually has a buttressed trunk, and forms a wide canopy at the crown from which branches drop downwards.[5] The *Arjuna* is usually found growing on river bank or near dry river beds in Uttar Pradesh, Madhya Pradesh, West Bengal and South and Central India. Main chemical constituents of *Arjuna* are Tannins, Saponins, Flavonoids etc. [6] *Arjuna* is uses as cardio tonic and also uses in treating Hypertension, Diabetes, Cirrhosis of liver, Pulmonary tuberculosis, Uterine disorders, Venereal disease, Epilepsy, Chronic fever, Nausea, Diarrhea, Dysentery, Urticarial, Ulcers, Fractured bone and Diuresis.[7]

Bark of *Arjuna* and *Khadira* are used in Ayurveda in treatment of diabetes. *Arjuna and Khadira* have multi targeted effects on various physiological system of human body. During the intense search in classical texts of Ayurveda, it is found that *Arjuna* and *Khadira* are one the common drug has *Pramehaghna* (Anti-Diabetic) property And *Arjuna* and *Khadira* showed its wide acceptance as an anti-diabetic effect.[8] Ayurveda described *'Bahudravashleshma'* as a causative Factor of *Prameha*. That is, in

Prameha Kapha dosha is predomenative aggrevated due to increasing *Drava Guna* of *Kapha dosha* which causes *Dhatushaithilya*. *Kashaya rasa* has a *Kaphghna* property and reduces *Dhatushaithilya*. In Ayurveda classics, Acharya Charka has mentioned *Arjuna* (*Terminalia arjuna* Roxb.) and *Khadira* (*Acacia catechu* Willd.) in *Kashayskandha* and described as a *Pramehgna*. That means both have Anti-diabetic properties. Both possess same *Kashaya Rasa*, *Sheet Virya*, *Katu Vipaka* and bark as a useful part. So, it is necessary to find out whether the bark of *Arjuna* is more effective or bark of *Khadira* or both equally act as anti-diabetic agents.

MATERIAL AND METHODS

Plant material

The botanically identified samples, bark of *Terminalia arjuna Roxb.(Arjuna)* and bark of *Acacia catechu willd. (Khadira)* were collected. The sample was authenticated for its botanical identity, row drugs and Physico-chemical standardization is carried out in well-known research laboratory Dr. Bhide foundation, SP college in Pune, Maharashtra.

Drug standardization-

Organoleptically, both drugs have Astringent in taste and Characteristic Odour. *Khadira* was rough in touch, Greyish brown in Colour while *Arjuna* was Smooth in touch, whitish in Colour. In microscopic study, it was found that the transverse section of bark of *Khadira,* showed numerous, uni-to-bi-seriate medullary rays, vessels occurring isolated or in small group of two to four, xylem fibers. And T.S. of *Arjuna* showed a few outer layers filled with brown coloring matter; phloem Parenchyma and phloem fibers, rosette crystals of calcium oxalate, starch grains, mostly simple to compound.

Physico-chemical standardization –

In *Khadira*, Alcohol soluble and water soluble extractive values are 26.17% and 28.63% respectively. Total ash value was 3.22%, Moisture content was 2.67% and pH values was 5.61 which was found to be within limit as specified in API. In *Arjuna*, Alcohol soluble and water soluble extractive values are 10.68% and 23.31% respectively. Total ash value was 1.71%, Moisture content was 3.02% and pH values was 5.23 which was found to be within limit as specified in API.

Preparation of aqueous extracts and standardization

Aqueous extracts of *Khadira* and *Arjuna* were prepared in APT research center, Pune. For Preparation of aqueous extract of bark of *Khadira* and *Arjuna* Standard method (Soxhlet extraction) was used. These extracts were used for pre-clinical study. Phytochemical tests revealed the presence of tannin and alkaloids in both drugs extracts. Also HPTLC profile of Aqueous extracts of both drugs tested using different solvents confirmed the presence of Tannin and flavonoids in both *Arjuna* and *Khadira*. In Khadira, Saponin, Triterpinoids, bitter principle were found in high intense than *Arjuna*.

Experimental animals

The experimental protocol was approved by institutional animal ethical committee in APT testing and research private limited, Research project no.36/1819. Rats of strain Sprague Dawley were used for the study. All animals taken were of same sex i.e. Male rats. Body weight of rats was ranging from 200.0 gm to 250.0 gm. Total animals used for study were 30. The rats were housed in their cages for five days prior to start of dosing in the experimental room after veterinary examination.

Induction of diabetes mellitus

All rats except Normal control group were fasted overnight for 16 hrs before the induction of diabetes. All rats except Normal control group were injected with single dose of 35 mg/kg Streptozotocin (STZ) subcutaneously on back. After 4 hours; 5% glucose solution was given to rats orally for 78 hours. After a period of 8 days blood glucose levels were checked by snipping the tail of STZ treated fasted rats. Rats showing the blood glucose levels more than 200 mg/dl were taken into the study.

Study design

Table 1: Experimental study design

GROUP NO.	GROUP NAME	SPECIFICATION (N=6)
1.	Normal Control	-
2.	Disease Control	Streptozotocin (35 mg/kg)
3.	STD	STZ + Glibenclamide (10 mg/kg)
4.	TEST 1	STZ + Khadira Aqueous extract (6.75 ml/kg bw)
5.	TEST 2	STZ + Arjuna Aqueous extract (6.75 ml/kg bw)

Administration of drug

Dosing of Standard and test drug was started after confirming induction of diabetes in animals. Day on which first dose given was considered as 0 day.

Standard drug-After induction of diabetes; Standard drug was administered for the duration of 28 days to rats in standard drug group. Glibenclamide was given as a standard drug at the dose of 10 mg/kg orally.

Test drug-After induction of diabetes; test drugs were administered for the duration of 28 days to evaluate its anti-hyperglycemic activity. The Aqueous extract of *Khadira* and *Arjuna* (Test drug) at the concentrations 6.75 ml/kg bw were administered to each rat of two groups (i.e. Test 1, Test 2) respectively by a single oral gavage. The animals were dosed using a stainless steel intubation needle fitted onto a suitably graduated syringe. For administration of doses; respective doses of aqueous extract *Khadira* and *Arjuna* were mixed together in 10 ml of distilled water and given to animals according to its most recently recorded body weight.(2ml to 200gm rat)

Testing parameters- Body weight, Blood glucose level, OGTT, Hematology (WBC, RBC, Haemoglobin, HCT, Platelet count), Biochemistry (Glucose, Total Protein, Urea, Creatinine, Triglyceride, HDL- Cholesterol, Cholesterol, SGPT, SGOT and ALP), Histopathology of major organs like Liver, Kidney and Pancreas was performed of two animals of each group.

Statistical method- For analysis of data obtained from in-vivo evaluation of Aqueous extract of *Acacia catechu* willd. And *Terminalia Arjuna* Roxb. Were calculated by using one way ANOVA test. Results are expressed as the mean $\pm$SD. A value of $P< 0.05$ was considered significant.

OBSERVATION AND RESULTS

1. *Glucose* (MG/DL)

After diabetes induction, the animals have shown significant increase in the fasting blood glucose levels ($p< 0.001$) as compared to Normal Control animals. Rats showing the blood glucose levels more than 200 mg/dl were taken into the study. These animals were then randomly divided into three groups viz. Disease control, Standard and Aqueous extract of *Khadira* and *Arjuna Kwath* respectively. The Glucose levels were weekly monitored in all animals.

On 28th day of experiment, the glucose levels were found to be significantly decreased in STD ($p<0.01$), *Arjuna* Aqueous extract ($p<0.001$) and *Khadira* Aqueous extract ($p<0.001$) treated groups in comparison with Disease control animals.

2. **OGTT (Oral glucose tolerance test)**

The oral glucose tolerance test was performed on Day 14 and Day 28.

28th day, there was reduction in the glucose levels of Khadira aqueous extract treated animals as compared to Disease control animals but the difference was not statistically significant. There is no significant difference observed in animal group treated with Arjuna aqueous extract as compared to Disease control animals

3. *Hematology*

Table 2: Hematology Study

GROUP	MEAN VALUE				
	WBC (10^9/L)	**RBC** (10^{12}/L)	**HGB** (gm/dl)	**HCT** (%)	**PLT** (10^{12}/L)
Normal control Group	8.55	8.17	15.82	63.07	114.8
Disease control group	12.23	7.83	13.67	57.87	402.7
STD	11.75	6.24	11.32	47.43	188.5
Test 1(*Khadira*)	9.48	5.71	10.40	45.85	680.5
Test 2(*Arjuna*)	5.96	6.21	11.28	49.50	727.4

In hematological parameters there was no statistically significant change observed in all groups when compared to Disease control animals.

4. *Organ weight* (GRAM)

Table 3: Table Showing Organ Weights

GROUP	MEAN VALUE				
	ADRENALS	HEART	KIDNEYS	LIVER	SPLEEN
Normal control Group	0.07	0.97	2.29	9.86	1.57
Disease control group	0.06	0.98	2.60	10.56	1.42
STD	0.10	0.94	2.27	9.92	1.28
Test 1(*Khadira*)	0.07	1.1	3.00	11.1	1.06
Test 2(*Arjuna*)	0.07	0.89	2.62	10.4	0.92

GROUP	MEAN VALUE			
	LUNGS	GONADS	BRAIN	PANCREAS
Normal control Group	1.86	2.67	1.21	0.66
Disease control group	2.00	2.66	1.23	0.57
STD	2.06	2.56	1.33	0.62
Test 1(*Khadira*)	1.77	2.73	1.55	0.47
Test 2(*Arjuna*)	1.96	2.46	1.45	0.50

The relative organ weight data has also shown non-significant changes in the organ weights of animals in comparison with Disease control animals.

5. *Biochemistry*

Table 4a: Biochemistry Study

GROUP	MEAN VALUE				
	ALP (U/L)	SGPT (U/L)	SGOT (U/L)	TGL (mg/dl)	Cholesterol (mg/dl)
Normal control Group	303.3	55.3	188.5	130.5	142.2
Disease control group	406.3	123.0	236.0	110.7	60.0
STD	304.7	80.2	202.3	209.2	66.5
Test 1(*Khadira*)	259.0	76.1	244.5	142.5	86.5
Test 2(*Arjuna*)	236.8	86.0	248.4	142.6	79.6

Table 4b: Biochemistry Study

GROUP	MEAN VALUE			
	HDL (mg/dl)	TP (g/L)	Creatinine (mg/dl)	Urea (mg/dl)
Normal control Group	30.3	7.9	0.5	42.6
Disease control group	18.5	4.9	0.6	36.8
STD	33.4	6.0	0.5	49.7
Test 1(*Khadira*)	20.7	7.5	0.5	55.8
Test 2(*Arjuna*)	21.3	6.5	0.5	44.4

There was no significant change observed in levels of SGOT, TGL, HDL, Cholesterol, Creatinine and Urea in any treatment when compared to Disease control animals. On the contrary, the ALP levels were found to be decreased in *Khadira* Aqueous extract ($p<0.05$) and *Arjuna* Aqueous extract ($p<0.05$) as compare to DC. SGPT levels were found to be decreased in STD ($p<0.01$), *Khadira* Aqueous extract ($p<0.01$) and *Arjuna* Aqueous extract ($p<0.001$) as compared to DC Animals. Total protein content was found to be increased in *Khadira* Aqueous extract ($p<0.01$) and *Arjuna* Aqueous extract ($p<0.05$) as compared to DC animals.

6. *Histopathology*

After scarification of animals; some tissues were preserved in 10% formalin for Histopathological tests. Histopathology of major organs like liver, kidney and pancreas was performed of two animals of each group. No major abnormality was detected in kidney, liver, pancreas. of animals treated with test drugs as compared to animal in disease control group.

DISCUSSION

Effect on body weigh

STZ induced diabetes is considered by severe loss in body weight. Body weight was measured weekly during the study period of 28 days. In disease control group, there was statistically reduction of body weight observed on day 21 ($p<0.05$) and on Day 28 ($p<0.01$) as compared to Normal Control group. In STD group, Test 1 (*Khadira*) group, Test 2(Arjuna) group showed improvement in body

weight on 28th day. The increase in body weight could be due to amelioration of glycaemic control and structural protein synthesis.

Effect on glucose (mg/dl) level

Glucose test is one method for measuring the amount of Glucose or sugar circulating in a blood. Disease control group showed increase in blood sugar level as compare to normal control group. On 28th day of experiment, the glucose levels were found to be significantly decreased in STD ($p<0.01$), *Arjuna* Aqueous extract ($p<0.001$) and Khadira Aqueous extract ($p<0.001$) treated groups in comparison with Disease control animals. Khadira and Arjuna treated group exhibits significant reduction in blood glucose level which may be attributed to the regeneration of β-cells due to antioxidant effect of both drugs.

Effect on oral glucose tolerance test (ogtt)-

From OGTT test, we can determine that how body actually processes glucose. The oral glucose tolerance test was performed on Day 14 and Day 28. 28th day, there was reduction in the glucose levels of *Khadira* aqueous extract treated animals as compared to Disease control animals but the difference was not statistically significant. There is no significant difference observed in animal group treated with *Arjuna* aqueous extract as compared to Disease control animals.

Effect on hematological parameters

Hematological Parameters provides valuable information on the health status of animals. The study blood was collected for hematology and serum was analyzed for various parameters viz. WBC, RBC, HGB, HCT, PLT etc.

WBC is for scanning hidden infections. RBC, HGB and HCT for determine the oxidative stress and percentage of blood by volume that is compose of red blood cells. PLT for determine abnormalities of platelet functions.

On day 28, in hematological parameters there was no statistically significant change observed in all groups when compared to Disease control animals. This indicates that there was no much interference on red blood cell and Hb production. RBC and Hb are important in transporting respiratory gases. That there were no significant treatment related effect on RBC and Hb implies that the aqueous extract of *Khadira* and *Arjuna* did not adversely affect the oxygen carrying capacity of the blood and the amount

of oxygen delivered to the tissues. No significant change of WBC and Platelets counts indicates no hidden infection and no any coagulation problem and platelet hyper-reactivity respectively.

Organ weight **(GRAM)-** The relative organ weight data has also shown non-significant changes in the organ weights of animals in comparison with Disease control animals. This indicates that no inflammation and enlargement of internal organs were occured.

Biochemistry- At the end of the study blood was collected for Biochemistry and serum was analyzed for various parameters viz. ALP, SGOT, SGPT, TGL, HDL, Cholesterol, Total Protein, Creatinine and Urea. ALP, SGOT, SGPT test for determination of liver damage. TGL, HDL, Cholesterol, Total Protein test to determine dyslipidemia. Creatinine and Urea test for tracking the progression of diabetic kidney.

On 28^{th} day of study, there was no significant change observed in levels of SGOT, TGL, HDL, Cholesterol, Creatinine and Urea in any treatment when compared to Disease control animals. On the contrary, the ALP levels were found to be decreased in *Khadira* Aqueous extract ($p<0.05$) and *Arjuna* Aqueous extract ($p<0.05$) as compare to Disease control animals. SGPT levels were found to be decreased in STD ($p<0.01$), *Khadira* Aqueous extract ($p<0.01$) and *Arjuna* Aqueous extract ($p<0.001$) as compared to Disease control Animals. Total protein content was found to be increased in *Khadira* Aqueous extract ($p<0.01$) and *Arjuna* Aqueous extract ($p<0.05$) as compared to Disease control animals. This indicates that aqueous extract of *Khadira* and *Arjuna* has the ability to heal hepatic tissue damage.

Discussion on histopathology

No major abnormality was detected in kidney, Liver and Pancreas of animals treated with test drugs as compared to animal in disease control group. This indicates that no toxic effect of both drugs on internal organs.

Based on the above results it is observed that both test samples, *Khadira* aqueous extract *and Arjuna* aqueous extract act as anti-hyperglycemic agent but between them Khadira aqueous extract is more effective as anti-hyperglycemic agent than Arjuna aqueous extract in experimental rats at the given dose.

MODE OF ACTION

Mode of action of aqueous extract of khadira and arjuna as anti-diabetic agent according to ayurveda.

The diseases *Prameha* defined in classics as the *Kaphavata* predominance. Even though all three *Dosha* are involved in the *Prameha* manifestation, The *Vata* predominance is understood with hypo functioning of *Agni* (*Mand*) or *Vishamagni*. This improper *Agni* influence the *Kapha* and *Aam* production into the body. Further, due to unwholesome diet and regimen (*Apathyaaharavihara*) *Kapha*, *Mamsa*, *Meda* get aggravated and cause the obstruction. (*Margavarodha*) *Khadira* and *Arjuna* with *Kashaya rasa* clears the channels due to *kaphashoshan* (Absorbtion of kapha) as well as decreases the *Kleda*. *Katu vipaka* helps to increases the digestion. Thus it stimulates the *Jatharagni* and regularizes the *Mandagni* which is the main cause of *Prameha*. *Laghu* and *Ruksha* guna clears the *Mala*, *Kleda* from *strotas* and alleviates. So the *Khadira* and *Arjuna* are capable of correcting the *Dhatu* vitiatison (*Saithilyata*). Thus, helps in breakdown of *Prameha sampranti* and reduces related symptoms. Due to Kashaya rasa, sheet Veerya and Ruksha guna, it acts as sthambhaka hence performs *Mutrasangrahaniya karma* ie. Reduces the amount of Mutra thus restore the normal Ambu. Kashaya rasa, sheet Veerya, Ruksha guna are kapha pitta shamaka. They help in rectifying *atipravrutti* of *mutra* by directly and indirectly. Though both drugs are mentioned in *Kashayaskanda*. *Khadira* has '*Tikta'* rasa in addition to *Kashaya rasa*. *Tikta rasa* has predominace of *Akasha* and *Vayu mahabhoota*. So it has ability of permeate to *sushma strotasas*. Due to this drug can reach at cellular level and help to reduce *meda* and *Kleda*. Thus, *Khadira* is more effective in treating *Prameha* than *Arjuna*. In this way, Ayurvedic claim that *Khadira* and *Arjuna* are *Pramehagha Dravya* (Anti-diabetic drugs) has been proven with the help of animal diabetic models.

Probable mode of action of aqueous extract of khadira and arjuna as anti-diabetic agent according to modern.

The compounds identified from the Aqueous extracts of Khadira and Arjuna with the help of HPTLC. These compounds have been classified in appropriate chemical groups and data are reported on their pharmacological activities, mechanism of actions which have hypoglycemic effect. Identified compounds are Flavonoids, Saponins, Triterpenoids, Tannins and bitter principle etc. which are responsible for anti-diabetic activity of Khadira and Arjuna. Activities of these compounds against diabetes are follows:

Flavonoids- It is important antioxidant and promotes several health effects. Flavonoids in Diabetes usually alternate the diabetes treatment by reducing the aldose rudctase, regenerating the pancreatic cells, enhancing insulin release and increasing calcium ion uptake.[9] The role flavonoids are quite important in fighting with complications of diabetes mellitus than any other method of treatment.[10] Also, Flavonoids stimulated glycogen synthesis in rats soleus muscle through mechanisms well known to insulin signal transduction.[11]

Saponins- Saponins have been found having Pharmaceutical properties of anti- inflammatory, anti-fungal, anti-bacterial, antiviral and anti-diabetes.[12] In the aspect of anti-diabetes, saponins activates AMPK in a calcium-dependent manner, thus regulating gluconeogenesis and glucose uptake.[13] Saponins effectively alleviated hyperglycemia in diabetic rats by up- regulating the expression of glucose transporter type 4(GLUT4) while down- regulated the expression of G6P in insulin signal pathway.[14]

Triterpenoids- The therapeutic approach of Triterpenoids to treating DM is to decrease postprandial glucose levels. It can be achieved through the inhibition of α- glucosides and α- amylases which delay the absorbance of carbohydrates in postprandial insulin level.[15]

Bitter principle- Compound stimulate peripheral and skeletal muscle glucose utilization and inhibites intestinal glucose uptake and shows hypogyacemic effect.[16]

Discussion on efficacy of aqueous extract of khadira more than arjuna.

Aqueous extract of *Khadira* and *Arjuna* both responded significantly in animal model Sprague Dawley rats. Thus both of them have showed anti-diabetic effect. Based on observation**,** Between them *Khadira* aqueous extract is more significant as anti-hyperglycemic agent than *Arjuna* aqueous extract in experimental rats. It is due to *khadira* extract has shown statically highly significant anti-hyperglycemic activity as compare to disease control group and well as *Arjuna* aqueous extract due to presence of Saponin, Triterpinoids, bitter principle in high intense than *Arjuna*.

CONCLUSION

Aqueous extract of *Khadira* and *Arjuna* both responded significantly in animal model Sprague Dawley rats. Thus both of them have showed anti-diabetic effect. Based on observation**,** between them *Khadira* aqueous extract is more significant as anti-hyperglycemic agent than *Arjuna* aqueous extract in experimental rats. It is due to *khadira* extract has shown statically highly significant anti-hyperglycemic

activity as compare to disease control group and well as *Arjuna* aqueous extract. The observed phytochemical results of *Arjuna* and *Khadira* bark are similar to the standard values which are available in A.P.I. In *Khadira* and *Arjuna*, class of compounds Saponin, Triterpinoids, bitter principle were found in high intense in *Khadira* than *Arjuna*. These results are stated on the basis of pre-clinical trials and clinical trials are needed.

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