ANTI-TUBERCLE ACTIVITY OF PHOENIX DECTYLEFERA (DATE PALM) FRUIT EXTRACT-IN VITRO STUDY

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ABSTRACT

The tuberculosis was described by the terms like Consumption, Phthisis, Scrofula, Pott's disease, and the White Plague in the history. This was focused attention of killer disease from ancient times around over the world. The human being tried to fight with the disease and discovered tools and techniques for combating the disease and to overcome the problem. Treatment for tuberculosis (TB) depends on the type of tuberculosis, although a long course of antibiotics is most often used. While TB is a serious condition that can be fatal if left untreated, deaths are rare if treatment is completed. For most people, hospital admission during treatment is not necessary. The drugs administered for the treatment of tuberculosis includes H: Isoniazid (600 mg), R: Rifampicin (450 mg), Z: Pyrazinamide (1500 mg), E: Ethambutol (1200 mg), S: Streptomycin (750 mg). All these drugs have various side effects and strong need for herbal alternative is needed for treatment. Keeping this point Phoenix dectylefera were extracted in solvent and dried extracts incorporated in Lowenstein Jensen's Medium for Anti tubercle testing. Two strains of Mycobacterium tuberculosis standard strain H37 Rv (SSM) and Patient Isolated Strain (PIS) were selected for the study. The strains were diluted to concentrations of 100 bacteria per milliliter and 1000 bacteria per milliliter. The drugs H: Isoniazid, R: Rifampicin, Z: Pyrazinamide, E: Ethambutol and alcoholic extracts of fruit of Phoenix dectylefera were incorporated in 200 ug/ml and 400 ug/ml. The results suggested that the alcoholic extracts of fruit of Phoenix dectylefera were more active as anti-tubercle agent as compared with the routine anti-tubercle drugs.

Key words: - Anti-tubercle drugs, Ethambutol, Isoniazid, Phoenix dectylefera, Rifampicin, Pyrazinamide.

Introduction

Present study deals in detail about the antibacterial activity of *Phoenix dectylefera* (date palm) on tuberculosis bacteria *Mycobacterium tuberculosis*. It is an obligate aerobe. For this reason, in the classic case of tuberculosis, the *Mycobacterium tuberculosis* complexes are always found in the well-aerated upper lobes of the lungs. The bacterium is a facultative intracellular parasite, usually of macrophages, and as a slow generation time, 15-20 hours, as a physiological characteristic that may contribute to its virulence. Treatment for tuberculosis (TB) depends on the type of tuberculosis, although a long course of antibiotics is most often used. While TB is a serious condition that can be fatal if left untreated, deaths are rare if treatment is completed. The drugs administered for the treatment of tuberculosis includes H: Isoniazid (600 mg), R: Rifampicin (450 mg), Z: Pyrazinamide (1500 mg), E: Ethambutol (1200 mg), S: Streptomycin (750 mg). All these drugs have various side effects and strong need for herbal alternative is needed for treatment. Herbal medicine/material contains more active analogues or active principles also called as natural products such as alkaloids, flavonoids, terpenoids, essential oils, flower absolutes. Herbal medicines have a strong traditional or conceptual base and the potential to be useful as drugs in terms of safety and effectiveness leads for treating different diseases. World Health Organization (WHO) has made an attempt to identify all medicinal plants used globally and listed more than 20,000 species. According to the WHO more than 80% of the world's population realize on traditional herbal medicine for their primary health care. *Phoenix dectylefera* (Date palm) was tested for anti-tubercle activity. These fruits are oblong berries, dark-orange when ripe, up to 50 cm long in the cultivated varieties, their flesh is sacchariferous, and it contains one woody seed.

Material and Methods:-

Collection and authentication of *Phoenix dectylefera* (date palm) (Fruits):

Two media are used to grow *Mycobacterium tuberculosis* Middle brook's agar based medium and Lowenstein-Jensen egg based medium. *Mycobacterium tuberculosis* colonies are small and buff colour when grown on either medium. Both media contain inhibitors to prevent contaminants from out-growing *Mycobacterium tuberculosis*. It takes 4- 6 weeks to get colonies that are visible on either type of media. The human being tried to fight with the

disease and discovered tools and techniques for combating the disease and to overcome the problem.

Fruits of this plant were collected from the local areas of Nagpur region, India. The authentic identification of the plant species were carried out at P.G. Department of Botany, Rashtrasant Tukadoji Maharaj Nagpur University (RTMNU), Nagpur, (M.S.) India and allotted reference no 9185.

Extraction: - About 100 gm. of *Phoenix dectylefera* fruits (without seeds) powder was extracted by 70% ethanol using soxhlet apparatus and was concentrated to dryness extract stored in freeze until use. (Tandon V. *et al*...,2005).

Phytochemical screening of active plant extracts was done by following the standard method of Khandelwal K.R. (2000), for the qualitative analysis of various studies such as alkaloids, coumarins, Saponins, flavonoides and steroids.

Isolation of strains of *Mycobacterium tuberculosis* from Patients: The bacteria were isolated by using Petroffs Method and cultured on freshly prepared L.J Medium for pure culture as per WHO guidelines. The colonies obtained were sub cultured for pure colonies and referred as Patient's Isolated Strains (PIS) of *Mycobacterium tuberculosis* and the standard strain of *Mycobacterium tuberculosis* (SSM) i.e. H37Rv. Each PIS and SSM were sequentially diluted in normal saline up to the 10^3 bacteria/ml, 10^2 bacteria/ml and were cultured on L.J Medium as prescribed by the in WHO manual for the lab testing. Each culture was tested for the positive for AFB Acid Fast Staining. The strains PIS and SSM were tested for the anti tubercle activity for plants extracts.

Fruit of *Phoenix dectylefera* plant was taken and made extracts and counted the percentage of anti-tubercle activity and percentage yield. Different concentration of these plants extracts and different dilutions of different bacterial strains were taken and cultured together. The patient's isolated strains were isolated by Petroff's Method and cultured many times to get pure culture of the *Mycobacterium tuberculosis*. The culture of tubercle bacilli was done on Lowenstein Jensen medium. The routine antibiotics and the extracts of the parts of plants under study were incorporated aseptically during the preparation of Lowenstein Jensen medium. The extracts and the antibiotics were incorporated in definite concentrations of 200ug/ml and 400ug/ml. The *Mycobacterium tuberculosis* bacilli were pre-diluted to 100bacteria/ml and 1000bacteria/ml ascetically and cultured on the Lowenstein Jensen medium with incorporated extracts and antibiotics in different concentrations. In case of PIS (Patient Isolated Strain) it was also observed that the extracts *Phoenix dectylefera* shows maximum activity amongst all

extracts/antibiotics against tubercle bacilli. Ethambutol was overall more active as compared with other antibiotics used in the study. The extracts of *Phoenix dectylefera*, in comparison with Ethambutol, Rifampicine and Isoniazide showed the maximum anti tubercle activity. Both the antibiotics and the extracts showed the maximum activity at dilutions of 100 bacteria/ml. The maximum activity against patient isolated strain of tuberculosis was found in the extracts of Pheonix dactylifera, in comparison with Ethambutol, Rifampicine and Isoniazide. Ethambutol was overall more active as compared with other antibiotics used in the study. At 400 concentrations and 100 dilutions of bacilli the *Phoenix dectylefera* is most active in activity.

Results

Table No. 01:- Percentage yields of Plant extracts.

Name of Plants	**Part Used**	**Percentage yields in gm (w/w)**
Pheonix dactylifera	Fruits	6.9

Table No. 02:- Showing the *phytochemical* components in plant extracts.

S.No	**Plant phytochemical and testing methods**	***Pheonix dactylifera***
1.	**Alkaloids** Mayer's Test Wagner's Test	 + +
2.	**Coumarins** Aromatic Odor Filter paper	 - -
3	**Saponins** Foam Test Hemolytic Test	 + +
4	**Flavonides** Shinoda Test	 +
5	**Steroids** Salkowaski reaction Liberman Bucherd Reaction	 - -

Table No. 03:- Showing proportion of resistant bacilli among standard strain H37Rv at bacterial dilutions of 100 bacteria/ml and extract/antibiotic conc. 200 µg/ml(SSM-100-200) (n=3, Mean ± S.D.)

S.No	**Plant Extracts at conc.200** µg/ml	**No of colonies obtained after 28th days of incubation Mean ± S.D.**	**Proportion of resistant bacilli**
1.	Control	18.0 ± 1.0	--------

2.	*Phoenix dectylefera*	$0^{\#}$	$0^{\#}$
3.	INH (200µg/ml)	4.0 ± 0.70*	0.22
4.	PZA (200µg/ml)	5.0 ± 0.70*	0.277
5.	RIF (200µg/ml)	2.0 ± 0.70*	0.111
6.	ETH (200µg/ml)	1.0 ± 0.0*	0.05

Table No. 04:- Showing proportion of resistant bacilli among standard strain H37Rv at bacterial dilutions of 1000 bacteria/ml and extract/antibiotic conc. 200 µg/ml(SSM-1000-200) (n=3, Mean ± S.D.)

S.No	**Plant Extracts at conc.200** µg/ml	**No of colonies obtained after 28th days of incubation Mean ± S.D.**	**Proportion of resistant bacilli**
1.	Control	36.0 ± 2.0	--------
2.	*Phoenix dectylefera*	$0^{\#}$	$0^{\#}$
3.	INH 200µg/ml	4.0 ± 0.70*	0.111
4.	PZA 200µg/ml	5.0 ± 0.70*	0.138
5.	RIF 200µg/ml	2.0 ± 0.70*	0.055
6.	ETH 200µg/ml	1.0 ± 0.0*	0.0277

Table No. 05:- Showing proportion of resistant bacilli among standard strain H37Rv at bacterial dilutions of 100 bacteria/ml and extract/antibiotic conc. 400 µg/ml (SSM-100-400) (n=3, Mean ± S.D.)

S. No.	**Plant Extracts at conc.400 µg/ml**	**No of colonies obtained after 28th days of incubation Mean ± S.D.**	**Proportion of resistant bacilli**
1.	Control	18.0 ± 1.0	--------
2.	*Phoenix dectylefera*	1.0 ± 0.70*	0.0625
3.	INH 400µg/ml	5.0 ± 1.0*****	0.277
4.	PZA 400µg/ml	4.0 ± 0.70*****	0.22
5.	RIF 400µg/ml	3.0 ± 1.41*****	0.166
6.	ETH 400µg/ml	4.0 ± 1.0*****	0.22

Table No.06:- Showing proportion of resistant bacilli among standard strain H37Rv at bacterial dilutions of 1000 bacteria/ml and extract/antibiotic conc. 400 µg/ml (SSM-1000-400) (n=3, Mean ± S.D.)

S.No	**Plant Extracts at conc.400 µg/ml**	**No of colonies obtained after 28th days of incubation Mean ± S.D.**	**Proportion of resistant bacilli**

1.	Control	36.0 ± 2.0	--------
2.	*Phoenix dectylefera*	1.0 ± 0.70*	0.0625
3.	INH 400µg/ml	8.0 ± 0.70****	0.22
4.	PZA 400µg/ml	11.0 ± 0.70****	0.305
5.	RIF 400µg/ml	3.0 ± 1.41****	0.277
6.	ETH 400µg/ml	4.0 ± 1.0****	0.111

Table No. 07:- Showing proportion of resistant bacilli among Patient Isolated Strain (PIS) at bacterial dilutions of 100 bacteria/ml and extract/antibiotic conc. 400 µg/ml (PIS-100-400) (n=3, Mean ± S.D.)

S.No	Plant Extracts at conc.200 µg/ml	No of colonies obtained after 28th days of incubation Mean ± S.D.	Proportion of resistant bacilli
1.	Control	36.0 ± 2.0	--------
2.	*Phoenix dectylefera*	1.0 ± 0.70*	0.0625
3.	INH 400µg/ml	8.0 ± 0.70****	0.22
4.	PZA 400µg/ml	11.0 ± 0.70****	0.305
5.	RIF 400µg/ml	3.0 ± 1.41****	0.277
6.	ETH 400µg/ml	4.0 ± 1.0****	0.111

Table No. 08:- Showing proportion of resistant bacilli among Patient Isolated Strain (PIS) at bacterial dilutions of 1000 bacteria/ml and extract/antibiotic conc. 200 µg/ml(PIS-1000-200) (n=3, Mean ± S.D.)

S.No	Plant Extracts at conc.200 µg/ml	No of colonies obtained after 28th days of incubation Mean ± S.D.	Proportion of resistant bacilli
1.	Control	36.0 ± 2.0	--------
2.	*Phoenix dectylefera*	1.0 ± 0.70*	0.0625
3.	INH 200µg/ml	8.0 ± 0.70****	0.222
4.	PZA 200µg/ml	6.0 ± 0.70****	0.166
5.	RIF 200µg/ml	4.0 ± 1.41****	0.111
6.	ETH 200µg/ml	2.0 ± 1.0****	0.055

Table No.09:- Showing proportion of resistant bacilli among Patient Isolated Strain (PIS) at bacterial dilutions of 100 bacteria/ml and extract/antibiotic conc. 400 µg/ml(PIS-100-400) (n=3, Mean ± S.D.)

S.No	Plant Extracts at conc.400 µg/ml	No of colonies obtained after 28th days of incubation Mean ± S.D.	Proportion of resistant bacilli

1.	Control	16.0 ± 0.67	--------
2.	*Phoenix dectylefera*	1.0 ± 0.70*	0.0625
3.	INH 400µg/ml	11.0 ± 0.70*	0.6875
4.	PZA 400µg/ml	9.0 ± 1.0*	0.5625
5.	RIF 400µg/ml	5.0 ± 1.0*	0.3125
6.	ETH 400µg/ml	3.0 ± 1.41*	0.1875

Table No. 10:- Showing proportion of resistant bacilli among Patient Isolated Strain (PIS) at bacterial dilutions of 1000 bacteria/ml and extract/antibiotic conc. 400 µg/ml (PIS-1000-400) (n=3, Mean ± S.D.)

S.No	Plant Extracts at conc.400 µg/ml	No of colonies obtained after 28th days of incubation Mean ± S.D.	Proportion of resistant bacilli
1.	Control	16.0 ± 0.67	--------
2.	*Phoenix dectylefera*	3.0 ± 1.41	0.1875
3.	INH 400µg/ml	12.0 ± 0.70	0.75
4.	PZA 400µg/ml	10.0 ± 0.70	0.625
5.	RIF 400µg/ml	8.0 ± 0.70	0.5
6.	ETH 400µg/ml	5.0 ± 1.0	0.3125

Table 03-10
***Significant at level of p<0.05 when compared with respective control levels.**
#No growth and hence no SD
(Statistical analysis was done by one-way ANOVA followed by Tukey's Multiple Comparison Test EPI info V3.3.2.)
INH-Isoniazide, RIF-Rifampicine, PZA-Parazimide, ETH-Ethambutol, SSM- standard strain H37Rv

Conclusion and Discussion

The date palm, native to North Africa has been extensively cultivated here as well as in Arabia and as far as the Persian Gulf, where it features as the characteristic vegetation of oases. Moreover it is grown over the Canary Islands, in the northern Mediterranean and in the south of the United States.

The different parts of this plant is majorly used in conventional medicine for treatment of various disorders like memory instability, fever, pain, stammering , nervous disorders (Nadkarni K.M.1976).

FatmahH (2013) discussed on Effect of Tempeh Dates Biscuits on Nutritional Status of Preschool Children with Tuberculosis.

Antifungal activity of water, acetone and methanol extracts of leaves and pits of *Phoenix dectylefera* Linn. were evaluated against several pathogenic fungi by Bokhari NA *et al.* in

2005. Except water extract acetone and methanol extracts showed varying degree of growth inhibitors against Fusarium oxysporum, Fusarium species and Fusarium solani. Anti-hyperlipedemic Activity Coronary heart disease is related to decrease in the concentrations of high density lipoprotein cholesterol (HDL) and increase of low density lipoprotein cholesterol(LDL). Saleh F A (2013)and Al miaman (2005) have reported that feeding of defatted date seed flour containing diet at 1.5%, 2.5%, and 5.2% to rats reduced the plasma triglycerides, total cholesterol and low density liporoteins. Anti-ulcer activity Pre-treatment with date fruit ethanolic and aqueous extracts at a dose of 4 ml/kg for 14 days markedly ameliorated the ulcer index, histological indices such as necrosis, haemorrhage, congestion and oedema in stomach sections and biochemical levels of some enzymes such as gastrin in plasma and mucin and histamine in gastric mucosa of ethanol-induced gastric ulceration in rats.(Al- Qarawi A, *et al.*2005) This support to the local folk medicinal claim that dates may be useful to humans with ulcers.

The polysaccharides (glucans) prepared from the date fruits exhibited a dose dependant anticancer activity with an optimum activity at a dose of 1 mg/kg in tumour induced by subcutaneously transplanting allogenic solid Sarcoma-180 tumor cells into the right side of female CD1 mice. (Ishurda O, *et al.* 2005)

This research validated the traditional claim of date fruits to be used against various kinds of tumors. Anti-diarrhoeal Activity: Aqueous extract of *Phoenix dectylefera* L at doses of 3, 6 and 12 mg/kg produced a statistically significant reduction in both castor oil induced intestinal transit and frequency of diarrhoea in rat (Abdulla Y, Al –Taher,2008). These properties may explain the rational for the effective use of the plant as an anti-diarrhoeal agent in traditional medicine. Effect on gastrointestinal transit Water and ethanolic extracts from date flesh and date pits at doses of 0.01, 0.02 and 0.04 ml/kg showed a dose dependant increase in the gastrointestinal transit time. While water extract from dialyzed date flesh extract induced a dose-dependent decrease the gastrointestinal transit time. (Al-Qarawi AA, *et al.*2003) The possible reason for this may be the method based extraction of pirticular component which could be valuable towards respective clinical conditions. Effect on reproductive system Oral administration of date palm fruit suspensions at doses of 120 and 240 mg/kg improved the sperm count, motility, morphology, and DNA quality with a concomitant increase in the weights of testis and epididymis. (Bahmanpour S, *et al.* 2006) Hepatoprotective activity: Pre and post treatment with aqueous extract of date flesh or pits significantly reduced CCl4 induced elevation in plasma activities of aspartate

aminotransferase (AST), alanine aminotransferase (ALT), Alkaline phosphatase (ALP) enzymes and bilirubin concentration and ameliorated morphological and histological liver damage in rats. This study suggests that CCl4-induced liver damage in rats can be reversed by treatment of extracts from date flesh or pits. Moreover it can also be used prophylactically as a dynamic liver support GT (Al-Qarawi AA, *et al.*2004), enzymes and plasma concentration of bilirubin but also exhibited an enormous increase in the reduced serum levels of testosterone, alpha fetoprotein (AFP) and glucose in the thioacetamide induced chirrotic rats. The extracts also showed significant reduction in oxidative stress evidenced by significant rise in the hepatic malonaldehyde (MDA) levels and decline in hepatic glutathione levels by normalising them. In another study the date flesh or pit extracts not only normalised the elevated plasma activities of AST, ALT, ALP, lactate dehydrogenase (LDH). H.A. Abdelrahman *et al*. in 2012 also studied the protective effect of dates (*Phoenix dectylefera*) on carbon tetrachloride induced hepatotoxicity in Dogs. Antioxidant activity: *Phytochemical* from fruits have been shown to possess significant antioxidant capacities that may be associated with lower incidence and lower mortality rates of degenerative diseases in human (Javanmardi J, *et al.*2008). Various *in vitro* and *in vivo* antioxidant activites have been carried out on various extracts of different parts of Phoenix dectylefera. Studies conducted on antioxidant activity and phenolic content of various fruits of *Phoenix dectylefera* cultivated in Iran, Algeria and Bahrain demonstrated a linear relationship between antioxidant activity and the total phenolic content (TPC) of date fruit extract(Allaith, Abdul AA, 2005). Aqueous date extract was found to inhibit significantly the lipid peroxidation and protein oxidation and also exhibited a potent superoxide and hydroxyl radical scavenging activity in a dose-dependent manner in an in vitro study (Dammak I *et al.* 2007). Methanolic extract of *Phoenix dectylefera* seeds showed a significant increase in plasma levels of vitamin C, E and A, β-carotene and significant decrease in the elevated MDA levels due to the lipid peroxidation in adjuvant arthritis in rats. (Mohamed DA *et al.*2004) These findings suggests its possible use in diseases such as scurvy, ataxia and night blindness caused due to the deficiency of vitamins C, E and A respectively. Date seed oil was found to limit oxidative injuries induced by hydrogen peroxide in human skin organ culture which confirmed the potent free radical scavenging activity of the plant(Dammak I *et al.*2007). Studies indicate that the aqueous extracts of dates have potent antioxidant activity (Mansouri *et al*.2005). The antioxidant activity is attributed to the wide range of phenolic compounds in dates including p-coumaric, ferulic and sinapic acids, flavonoids and procyanidins (Gu *et*

*al.*2003 and Al-Farsi *et al.*2005). The anti bacterial study on *Phoenix dectylefera* carried out by Ramesa Shafi Bhat *et al.* and Saleh FA, *et al*. observed the extracts of fruit showed the antibacterial activity against the human pathogen such as S.aureus, S. pyogenes, B.subtillis ,E. coli and P. aeruginosa and Staphylococcus saprophyticus (Ramesa Shafi Bhat *et al.*2012, Saleh FA).

The fruits of *Phoenix dectylefera* contain different chemical compounds such as saturated and unsaturated fatty acids, Zinc (Zn), Cadmium (Cd), Calcium (Ca), and potassium (K). Saturated fatty acids include stearic and palmitic acid and unsaturated fatty Acids contain linoleic and oleic acids which could inhibit 5 -α reeducates enzyme (Shariati *et al*... 2008). Also, dates contain at least six vitamins including a small amount of vitamin C, and vitamins B1 (thiamine), B2 (riboflavin), nicotinic acid (niacin) and itamin A (Al-Shahib and Marshall,1993).

Dates contain a high percentage of carbohydrate (total sugars, 44-88%), protein (2.3-5.6%), fat (0.2-9.3%), essential salts and minerals, vitamins and an elevated proportion of dietary fiber (6.4-11.5%) (El Hadrami *et al.* 2009). They also contain oil in the flesh (0.2-0.5%) and the seed (7.7-9.7%). The seed represents 5.6-14.2% of the entire fruit weight. Dates are very rich in vitamins, especially β-carotene (vitamin A), thiamine (B1), riboflavin (B2), niacin, ascorbic acid (C) and folic acid (folacin) (El Hadrami, 2009). Some of these vitamins provide 10-50% of the daily recommended intake of an adult. Ripe fruits were reported to contain a substantial amount of carotenoids including lutein and various forms of β-carotene and minor carotenoids. The contents vary with the cultivar and stage of ripeness, with the total content of carotenoids decreasing towards the final ripening stages and in storage.

Plant wise anti tubercle action is studied and found that the *Pheonix dactylifera* having the best anti-microbial activity against the PIS and SSM. The activity may be due to the presence of ample quantities of Alkaloids, Vitamin C, Saponins and Flavonoids. The data present in the tables 3-10 with focus on the calculation of the proportion of resistant bacilli. The proportion was found varying in herbal extracts and at lower side when compare with the routine antibiotics.

The possible underlying cause of anti-tubercle activity in *Phoenix dectylefera* may be due to the presence of the phytochemical like phenolics, sterols, carotenoids, anthocyanins, procyanidins and flavonoids. These phytochemicals also contribute to the nutritional and organoleptic properties of the fruits. (Ahmad Ateeq *et al.*2013).

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