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Investigations on Ziziphus Jujuba Seed Extract for Antimicrobial Activity -- A Pilot Study

Miss. Iftesham Mohd. Jalil [1], Muhammad Mujassam [2], Dr. Aatera Anees Ahmad [3]

Mrs. Gayatri Chinchulkar [4], Dr. Naeem Ahmed Shaikh Ibrahim [5], Dr. Jameel Abbas [6]

[1]. Assistant Professor, Dept. of Pharmacognosy, Central India college of Pharmacy, Nagpur.

[2] Associate Professor (HOD), Dept. of Ilmul Saidla, Makaz Unani Medical Collage and Hospital, Kaithapoyile, Kozhikode, Kerala

[3] Associate Professor, Dept. of Tashreehulbadan, Markaz Unani Medical college and Hospital, Kaithapoyile, Kozhikode, Kerala,

[4] Assistant Professor, Dept. of Pharmaceutics, Central India college of Pharmacy, Nagpur

[5] Professor (HOD), Dept. of Ain, Uzn, Anf, Halaq wa Asnan, Markaz Unani Medical college and Hospital, Kaithapoyile, Kozhikode, Kerala,

[6] Associate Professor, Dept. of Pharmaceutics, Kohinoor Institute of Pharmacy, Khuldabad.

Abstract:

The aims of this study were to test the antibacterial activity and chemical composition of Ziziphus jujuba extract. The extract was obtained using 50% aqueous - ethanol extraction solution to extract Ziziphus jujuba seeds. The extract was prepared and evaluated for antimicrobial activity against six bacterial strains by determining minimum inhibitory concentration (MIC). The results revealed that the 50% aqueous ethanol extract is potent in inhibiting bacterial growth of both gram-positive and gram negative bacteria. The chemical composition of fenugreek was analyzed by gas chromatography/mass spectroscopy. The 13-Heptadecyn-1-ol (12.95%), 7-Ethyl- 4-decen-6-one (9.73%), Lineoleoyl chloride (8.54%), Linoleic acid (6.37%), 2,5- Octadecadiynoic acid, methyl ester (5.57%) and Palatinol A (4.81%) were the highest abundant compounds out of total 20 compounds were identified in the Ziziphus jujuba seeds extract. This research work deals with the detailed pharmacognostical evaluation of the crude drug. The physico-chemical and histological parameters presented in this paper may be proposed as parameters to establish authenticity of Ziziphus Jujuba and can possibly help to differentiate the drug from its other species. As there is no pharmacognostical anatomical work on records for this traditionally valued herb, the present study is taken up in the view to lay down the physico-chemical and microscopic standards.

Key words: Ziziphus jujuba, Chemical Composition, Antimicrobial activity.

1. Introduction

The instructions provided in traditional Persian medicine suggest that Iranians have been among the founders of medicine and have had a major role in the development of the science of medicine. Besides, the scientific transfer of traditional medical findings to modern medicine as part of a fully empirical-scientific process is one of the substantially important duties of the heirs of the medical history of Iran. Hence, since medicinal plants have been used by the public for a long time, the number of studies on the traditional applications of plants in the world, especially in the Mediterranean countries, has increased. According to the WHO report, the global sale of medicinal plants is currently about 62 billion dollars, which will increase to 5 trillion dollars by 2050. Therefore, the examination of plants prevalently used in the traditional and classical medicine can be useful. For example, jujube is a plant with a long history of consumption as a fruit and a medicinal plant. Therefore, reviewing the nutritional and pharmacological values and properties of this precious plant is the pivot of this paper.

Scientifically known as Ziziphus jujuba Mill, jujube is a plant in the Rhamnaceae family, which includes 45 genera and 550 species. It grows as a wild plant in tropical and subtropical regions. The height of the jujube trees varies from 2 to 8 m. This plant is also highly drought-tolerant and its fruit is called jujube, which is an edible olive-shaped bright red fruit. This fruit looks like an irregular wrinkled pulp but its exterior surface is smooth and shiny. It has a diameter of 2 mm (the diameter of the fruit core or pulp), and it is crispy and brittle. It has a faint smell and a slightly sweet, mucilaginous, and pleasant taste. It is also available in the fresh, dried, and processed forms around the globe. A plant in the buckthorn family (Rhamnaceae), Z. jujuba Mill is a fruit of the Ziziphus genus that has a pleasant taste and serves as a medicinal plant. This plant, which is the native wild plant of many countries, delivers significant nutritional and medicinal values. It is, however, a native Asian and South European plant that mainly grows in the tropical and subtropical regions. This plant is also known as Ziziphus vulgaris Lam., Rhamnus ziziphus L., Ziziphus sativa Gaertn, and Ziziphus zizyphus (L.) Karsten around the globe. Besides, lageniformis, inermis, jujuba, and spinosa are among the different species of this plant, and Ziziphus mauritiana is another name for Z. jujube Mill. This plant is known as Ennab and Annab in the Arabic and Persian languages, respectively. It is also referred to asbedara, beri , beri, bidara, bor, Chinese date, Chinese jujube, French jujube, kankole, ilantai, ma-tan, masan, onnab, taotau, tsao, and zao. The use of the jujube fruit in traditional medicine has a long history due to some of its pharmacological properties and benefits for blood purification and digestion. It also slows down the process of aging in women. Carbohydrates, sugar, organic acids, proteins, minerals, vitamins, and carotenoids are also abundant in this nutrient-dense fruit.

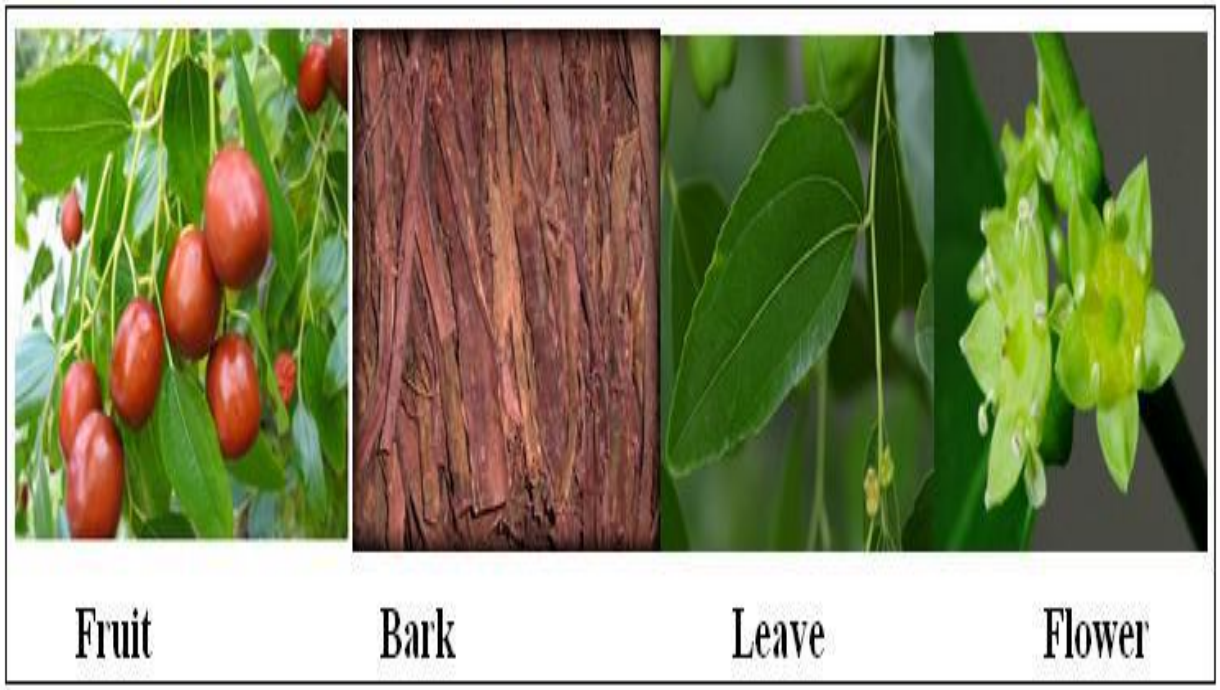

Fig. 1 Ziziphus jujuba Fruit, Bark, Leave, Flowers

Plants are an essential part of human society since the civilization started. Plant materials remain an important resource to combat serious diseases in the world. The traditional medicinal methods, especially the use of medicinal plants, still play a vital role to cover the basic health needs in the developing countries. The medicinal value of these plants lies in some chemical active substances that produce a definite physiological action on the human body. In the last decades, various plant extracts have been the focus of great interest from researchers because they represent natural resources of new antibacterial agents with possibly novel mechanisms of action. The potential use of these products as an alternative for the treatment of several infectious diseases has been extensively screened. They are effective in the treatment of infectious diseases while simultaneously mitigating many of the side effects that are often associated with synthetic antimicrobials. Therefore, it is of great interest to carry out a screening of these plants in order to validate their use in folk medicine and to reveal the active principle by isolation and characterisation of their constituents. Systematic screening of them may result in the discovery of novel active compounds.

The Ziziphus species (Rhamnaceae family) are considered to be multi-purpose plants and have been used as foods, folklore medicines, the environmental protection plants, etc. Ziziphus jujuba Mill. (Rhamnaceae) mainly distribute in the tropical and subtropical regions of Asia and have been employed as essential oriental medicine for thousands of years. Different parts of the plant could be used as remedies in insomnia, fever, diarrhoea, wounds and ulcer, in which the fruits were claimed to be beneficial to purify the blood and aid digestion. Also it has been widely distributed in northern China. Its fruits and seeds are usually applied in traditional medicine (TCM) for the treatment of various diseases, such as anorexia, lassitude, insomnia, anxiety, etc., and many studies about their chemical constituents as well as pharmacology activities have been reported. A lot of extraction methods and analytical methods such as spectrophotometry, high performance liquid chromatography, capillary electrophoresis, gas chromatography (GC) with flame ionization detection (FID), gas chromatography–mass spectrometry (GC–MS) are developed for plant

active compounds study. The combination of an ideal separation technique (GC) with the best identification technique (MS) made GC/MS an ideal technique for qualitative and quantitative for volatile and semi-volatile compounds. In addition, the use of a proper extraction method is needed.

This study aimed to evaluate the antimicrobial activity of Z. jujuba extracts and identify the active compounds of Z. jujuba seeds extract. To our knowledge this is first report on the study of antimicrobial components extracted from Z. jujuba seeds against the clinical Pathogens action. The assessment might provide a basis for searching the potent active compounds for the antimicrobial related search and improve the therapeutic application of Ziziphus species.

2. Antimicrobial Activity

The therapeutic properties of Z. jujuba, as a medicinal plant, have been proven through research, and there have been reports of the positive antibacterial effects of jujube essential oils in different studies on its antimicrobial properties. Therefore, jujube essential oils have antimicrobial properties while different parts of this plant such as its leaves deliver therapeutic values. In fact, jujube fruit owes its biological properties to its antibacterial and antifungal effects. For example, the crude extract of jujube fruit had a positive antimicrobial effect on the gram-negative and gram-positive bacteria and fungi in a study, demonstrating the greater antimicrobial properties of this fruit than the conventional antibiotics such as vancomycin. Therefore, this study proved the antimicrobial effect of jujube extract on fungi and the gram-positive and gram-negative bacteria and demonstrated its effectiveness in treating infectious diseases especially pediatric infections.

Study was undertaken to ensure the antimicrobial efficiency of crude seed extract of Z. jujuba. The result revealed that the seed of Z. jujuba have effective antimicrobial activity particularly against Salmonella and staphylococcus aureus infections. The crude methanol extract of Z. jujube plant showed modest activity against P. aeruginosa, B. pumalis and E. aerogens and low against S. typhi, S. epidermidis, S. pneumoniae, S. aureus and K. pneumoniae.

In consequences to Abd-Alrahman et al., conducted study to assess the antimicrobial activity of ethanol extract of Z. jujuba seeds against six bacterial strains by determining minimum inhibitory concentration (MIC) and analyzed their content by using chromatographic techniques to recognize the principal bioactive phytochemicals. Additional, GC/MS analysis of ethanol extract of Ziziphus jujuba seed revealed the subsistence of 20 component, major components were 13-Heptadecyn-1-ol (12.95%), 7-Ethyl-4-decen-6- one (9.73%), Lineoleoyl chloride (8.54%), Linoleic acid (6.37%), 2,5-Octadecadiynoic acid, methyl ester (5.57%) and Palatinol A (4.81%). The results indicated that the ethanolic extract of Z. jujuba seed contains a many bioactive components that could have advantage offer a platform of using Z.jujuba seed as herbal alternative for the current synthetic antimicrobial agents.

Acute Toxicity Studies of Z. jujube

Z. jujube Extract	**LD50**
Methanolic root extract	447.21 mg/kg (ip) in mice
Ethanol and ethyl acetate extract(Endocarp)	1200.24 mg/kg in rat
Ethanolic root extract	450 mg/kg (ip)
Alkaloidal fraction(root)	400mg/Kg(ip)

3. MATERIALSAND METHODS

Preparation of extracts

The Fresh Ziziphus seeds, was purchased from a local Market of Nagpur. The collected Ziziphus Jujuba seed was washed with tap water. The seeds were crushed into small pieces and air-dried thoroughly under shade for 1 month to avoid direct loss of phyto-constituents from sunlight. The shade dried materials were powdered using the pulverize and sieved up to 80 meshes. It was then homogenized to fine powder and stored in air-tight container for furthers analysis. Collected moderately coarse plant powder of Ziziphus Jujuba was used for the preparation of various extracts. The seed powder of the Ziziphus Jujuba was extracted with petroleum ether, methanol and water using as solvent respectively by continuous hot extraction. The residue was evaporated by filtration through Whatmann No. 1 filter paper and the aqueous extract was concentrated used on a Rotary evaporator to get solid yield extract.

Sr. No.	Plant name	Solvents for extraction
1	Ziziphus Jujuba	Petroleum ether
2	Ziziphus Jujuba	Methanol
3	Ziziphus Jujuba	Water

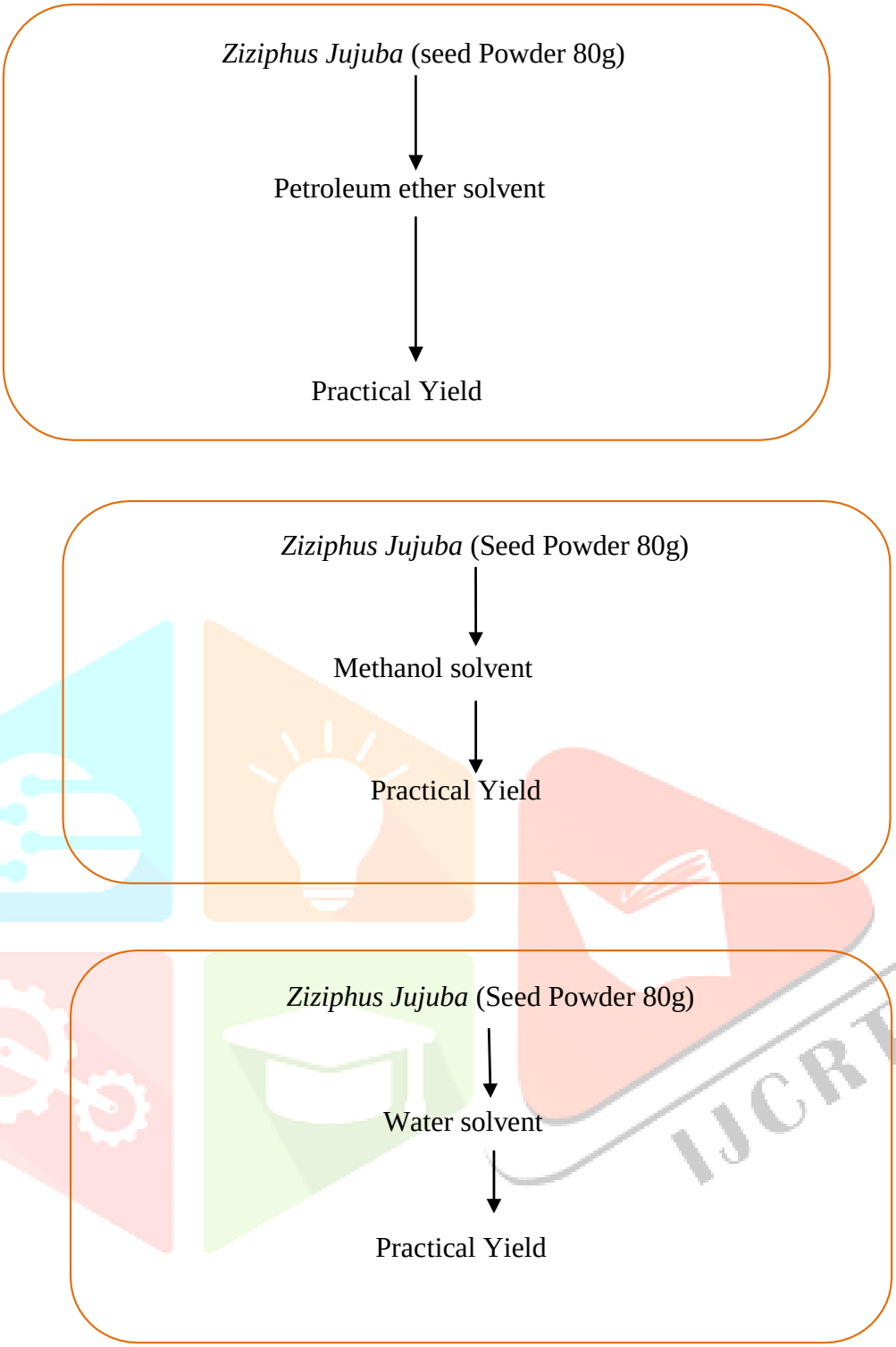

Fig. 2 Extraction protocol of selected Seed of Plant

4.Preliminary Phytochemical Screening

Preliminary screening of phytochemicals is a valuable step, in the detection of the bioactive principles present in medicinal plants and subsequently may lead to drug discovery and development. It refers to the extraction, screening and identification of the medicinally active substances found in plants. The preliminary phytochemical screening of the ethyl acetate, methanol and water extracts of plant powder of Ziziphus jujuba was carried out using standard laboratory procedures to detect the presence of different secondary metabolites such as alkaloids, flavonoids, saponins, tannins, steroid glycosides, phenols, coumarins, reducing sugars, protein, fixed oils and fats.

Following phytochemical tests of plant extracts were performed.

A. Test for Alkaloids:

0.5g of each extract was stirred with 5mL of 1% aqueous Hydrochloric acid on a steam bath. 1mL each of the filtrate was treated, and then it was treated separately with a few drops of Dragandroff's reagents, Meyer's reagent and Wagner's reagents. End colour was noted.

B. Test for Cardiac Glycosides (Keller-Killiani test):

0.5g of each extract was dissolved in 3mL of Ferric chloride in glacial acetic acid and leave for a minute. 15mL of concentrated sulphuric acid was added with the aid of pipette, so that it runs down the side of the test tube.

C. Test for Flavonoids

1mL of each extract was dissolved in 2mL of sodium hydroxide solution. The appearance of a yellow solution which disappeared on addition of Hydrochloric acid indicates the presence of flavonoids.

D. Test for Saponins:

10mL of distilled water was added to 0.5mL of each extract. Shake the content vigorously with the test tube for 2 minutes. The presence of frothing or bubbling indicates the presence of saponins.

E. Test for Steroids:

5 drops of concentrated sulphuric acid was added to 1mL of the extract. A reddish brown colour indicates the presence of steroids.

F. Test for Tannins (Ferric chloride Test):

A little portion of extract was diluted with water in the ratio of 1:4 and few drop of 10% Ferric chloride solution was added, end colour was noted which indicated presence of tannins.

G. Test for Terpenoids

2.0 ml of chloroform was added with the 5 ml aqueous plant extract and evaporated on the water path and then boiled with 3 ml of H_2SO_4 concentrated. A grey color formed which showed the entity of terpenoids.

Physicochemical parameters were determined as per guidelines of WHO, air dried coarse powdered sample of Ziziphus jujuba were subjected for determination of physicochemical parameters such as pH, foreign organic matter, methanol soluble extractives, water soluble extractives, total ash content, acid insoluble ash, water soluble ash, loss on drying and % moisture content were determined. The Average physicochemical parameters of the Ziziphus jujuba course powder are tabulated in table **5. Extraction of plant Drug**

The plant leaves powder of the Ziziphus jujuba was extracted with ethyl acetate, methanol and water using as solvent respectively. The solvent was removed and practical yield was found and recorded. The findings were tabulated in table.

Preliminary Phytochemical Screening

The preliminary phytochemical screening of the ethyl acetate, methanol and water extracts of plant powder of Ziziphus Jujuba were carried out using standard laboratory procedures to detect the presence of different secondary metabolites. All the findings were recorded in table 5.3, 5.4, 5.5.

Table: 1 Physicochemical Parameters of Ziziphus Jujuba plant Seeds

Sr. No.	Parameters	Values
1	Total ash value	4.20±1.25
2	Water soluble ash	1.20±0.10
3	Acid insoluble ash	1.45±0.40
4	Sulphated ash	1.70±0.10

Table: 2 Extractive values of Ziziphus Jujuba Seeds

Solvent	Yield (g)	% Yield
Petroleum ether	8.2g	10.25%
Methanol	13.5g	16.87%
Water	11.0g	13.75%

Table: 3 Preliminary phytochemical screening of petroleum ether extract of Ziziphus jujuba Seeds

Sr. No.	Phyto constituents	Petroleum ether extract
1.	Alkaloids	Negative
2.	Glycosides	**Positive**
3.	Flavonoids	Negative
4.	Saponins	Negative
5.	Steroids	**Positive**
6.	Tannins	Negative
7.	Terpenoids	Negative

Table: 4 Preliminary phytochemical screening of methanol extract of Ziziphus jujuba Seeds

Sr. No.	Phyto constituents	Methanol extract
1.	Alkaloids	Negative
2.	Glycosides	Negative
3.	Flavonoids	**Positive**
4.	Saponins	Negative
5.	Steroids	Negative
6.	Tannins	**Positive**
7.	Terpenoids	**Positive**

Table: 5 Preliminary Phytochemical screening of aqueous extract of Ziziphus jujuba Seeds

Sr. No.	Phyto constituents	Aqueous Extract
1.	Alkaloids	Negative
2.	Glycosides	Negative
3.	Flavonoids	**Positive**
4.	Saponins	**Positive**
5.	Steroids	Negative
6.	Tannins	**Positive**
7.	Terpenoids	**Positive**

6. Analysis and identification of compounds

The chemical composition of fenugreek extract was identified according to Chemical identification of components was assigned by matching their mass spectra with Wiley and NIST library data, standards of the main components and comparing their Kovats Retention Indices (KRI) with reference libraries and from the literature. The component concentration was obtained by semi-quantification by peak area integration from GC peaks and by applying the correction factors.

7. Microorganisms

Six bacterial strains used in this study, including Bacillus cereus, Staphylococcus aureus as Gram positive bacterium. Escherichia coli, Pseudomonas aeruginosa, Klebsiella peunomonia and Listeria monocytogenes as Gram negative bacterium. These bacteria were obtained from the Rajiv Gandhi, Biotechnology Centre, Nagpur University, and Nagpur. Nutrient Broth and Nutrient Agar medium all these Medias were purchased from Hi-media. The tests were run intriplicate. Petri plates (23x23 mm) were prepared

with Trypticase soy agar and an adequate amount of inoculum was flooded onto each plate, excess inoculum was removed and the plates were dried for 30 min at 37°C. Holes (6 mm diameter) were made in the inoculated agar and filled with samples of plant extracts, plates were incubated for 24 h at 37°C. Inhibition zones when present were measured in millimeter.

8. Antimicrobial activity assay

The Antimicrobial activities were determined by Kirby Bauer Disc diffusion method described by Bauer et al. 1966. The extracts were prepared and the sterile blotting paper disc (5 mm) was soaked in the diluted extract in two different final concentrations (50 µl and 100 µ l/disc). The prepared disc were dried in controlled temperature (at 37 ºC overnight) to remove excess of solvent and used for study.

Determination of Minimum Inhibitory Concentrations (MIC)The antimicrobial activity of the Ziziphus jujuba extract, that shows antimicrobial activity, were determined using micro dilution broth method as described by Brantner and Grein, 1994. Different antibiotics [Ampicillin, amikacin, gentamicin, kanamycin, and tetracycline (10–32 □g/ ml)] were used as reference standards (CLSI, 2011). The Ziziphus jujuba extract solution was prepared to obtain final concentrations of 0.25-2.0 mg/ ml for antibacterial testing. One microliter of an overnight culture of each bacterial strain, containing approximately 10^4 CFU, was applied onto a 96-well microliter plate in the presence of MHB. The microliter plates were incubated at 35°C for 18 h. Observations were performed at least in replicate and results were expressed as the lowest concentration of plant extracts that produced a complete suppression of colony growth, MIC.

9. Results and Discussion

With the increase in the incidence of resistance to antibiotics, alternative natural products of plants could be of interest. Some plant extracts and phytochemicals are known to have antimicrobial properties, which could be of great importance in the therapeutic treatments. In the last years, various studies have been conducted in different countries, demonstrating the efficacy of 89.25µg/ml. The poor activity of the 50 % ethanol/water extract against most bacterial strains investigated in this study is in agreement with previous reports. This could be due to theinsolubility of the active compounds in water or the hot water could have caused denaturation of the active compounds. It is also observed from the results that the ethanol/water extract had wide antibacterial activity against both gram positive and gram negative bacteria S. aureus and S. typhi, respectively. The activity of the extracts against the Gram negative bacteria is noteworthy as these bacteria are known to exhibit high degree of resistance to conventional antibiotics. The few variations in results between the disc diffusion and MIC results can be due to the different susceptibility of the bacterium to the plant extract, the rate of growth of bacteria, solvents used to extract the plant compounds and the rate of seeds extract diffusion.

Table: 6 Proximate Composition (%) of *Ziziphus jujuba* seeds extract

Sr. No.	Component	Seeds
1	Moisture (%)	87.5
2	Total Soild	12.32
3	Ash	5.2
4	Carbohydrate %	16.45
5	Protein	3.31
6	Lipid	1.3
7	Total sugar %	15.9

Table: 7 Mean inhibition zone diameter (mm) of 50% aqueous-ethanol of *Ziziphus jujuba* on tested microorganisms by disc diffusion method with respect to various concentrations in µg/ml

Sr. No.	Bacteria	50 % Eth / H_2O Extract		
		50	250	1000
2	Bacillus cereus	7.0	6.0	13.0
3	Staphylococcus aureus	---	---	10.0
4	Escherichia coli	6.0	8.0	17.5
5	Pseudomonas aeruginosa	---	---	---
6	Klebsiella pneumonia	---	9.0	17.0
7	Listeria monocytogenes	---	7.0	16.5

Table: 8 Minimal inhibitory concentration (MIC) of 50% ethanolic extract of *Ziziphus jujuba* seeds against different strains (µg/ml)

Sr. No.	Bacteria	Minimum Inhibitory Concentration(MIC)
2	Bacillus cereus	72.5
3	Staphylococcus aureus	41.25
4	Escherichia coli	52.5
5	Pseudomonas aeruginosa	89.25
6	Klebsiella pneumonia	42.5
7	Listeria monocytogenes	51.25

A side from concerns with food quality degradation, these microorganisms may be causal agents of intestinal infections in humans. According to the values of microbial growth rate in the presence of different extract concentrations, Ziziphus jujuba extract was presented antimicrobial capacity following the order: E. coli ~Ps. Aeruginosa> B. cereus ~K. pneumonia> S. aureus> E. coli and Ps. aeruginosa (Gram- negative)

were the most sensitive microorganisms even at lower concentration. Pseudomonas aeruginosa was the most resistant microorganism even at higher concentration. The MIC as low as □g mL^{-1} of a semi- purified fraction against gram negative and positive bacteria is suggestive of good antibacterial potential of the compounds of Ziziphus jujuba. Hence Ziziphus jujuba may yield potential molecules in the treatment of infections caused by pathogenic bacteria which have developed resistance against the known antibiotics.

10. Chemical composition of Ziziphus jujuba seeds extract

Figure 1 presented the typical GC/MS chromatogram of a total of 20 compounds were recorded in solvent extracts as indicated in Table. Most of these identified compounds are playing a role in the biological activity of natural extracts. Some of these compounds are reported for the first time in Ziziphus jujuba seeds. The major compounds characterized were 13-Heptadecyn-1- ol (12.95%), 7-Ethyl-4-decen-6-one (9.73%), Lineoleoyl chloride (8.54%), Linoleic acid (6.37%)2,5-Octadecadiynoic acid, methyl ester (5.57%), Palatinol A (4.81%). The structure of the highest compounds were identified in Ziziphus jujuba seeds extract given in Table 4 and figure 2.13-Heptadecyn-1-ol (12.95%), is phenolic compound and one of the major flavour compounds. phenolic compounds were found to inhibit the cell growth and fermentation and used as antioxidant. Furthermore, its derivatives have also been used for therapeutic purposes. For instance, Hydroxymethyl furfural is a potential candidate for treating sickle cell anemia[11]. Lineoleoyl chloride, has been found to possess many interesting pharmacological and physiological activities, such as anti-inflammatory effects. Lineoleoyl chloride results from the hydrolysis degradation of Linoleic acid during extraction. 7-Ethyl-4-decen-6-one (9.73%), Lineoleoyl chloride (8.54%), Linoleic acid (6.37%), 2, 5-Octadecadiynoic acid, methyl ester (5.57%) also play a role in the activity of Ziziphus seeds extracts. While for the first time we identified Palatinol A (4.81%) in Ziziphus seeds extracts. Ziziphus jujuba seeds extract were found to contain small amounts of other compounds, this in line with other investigators.

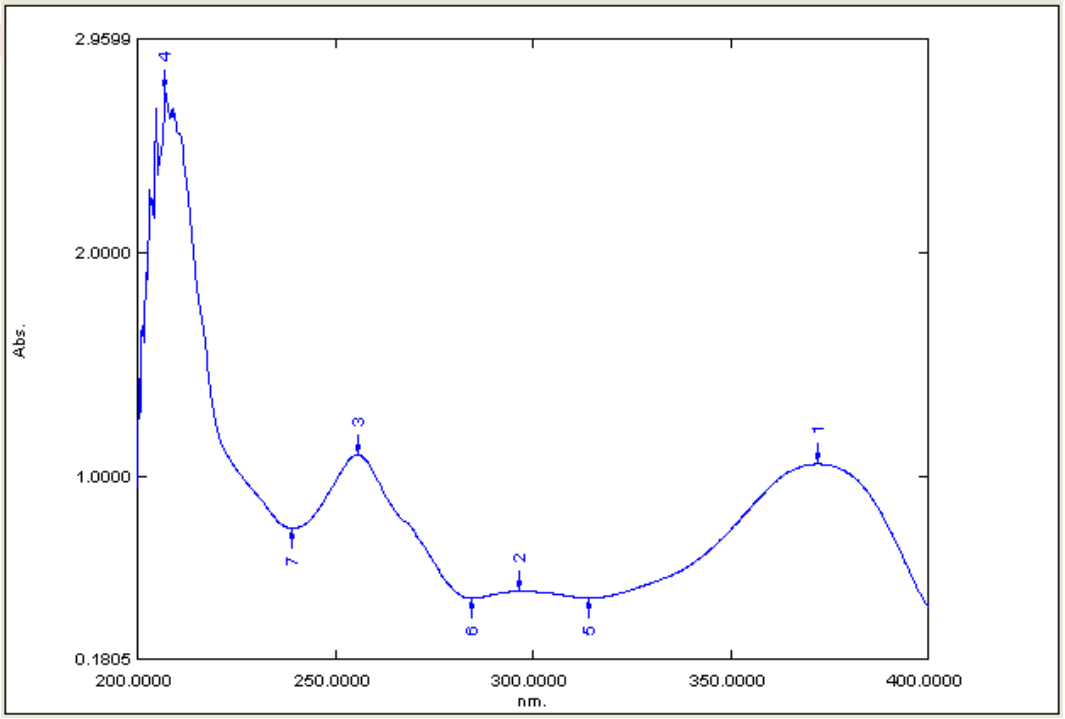

Fig. 3 Estimation of Palatinol A contents of Ziziphus jujuba seeds extract

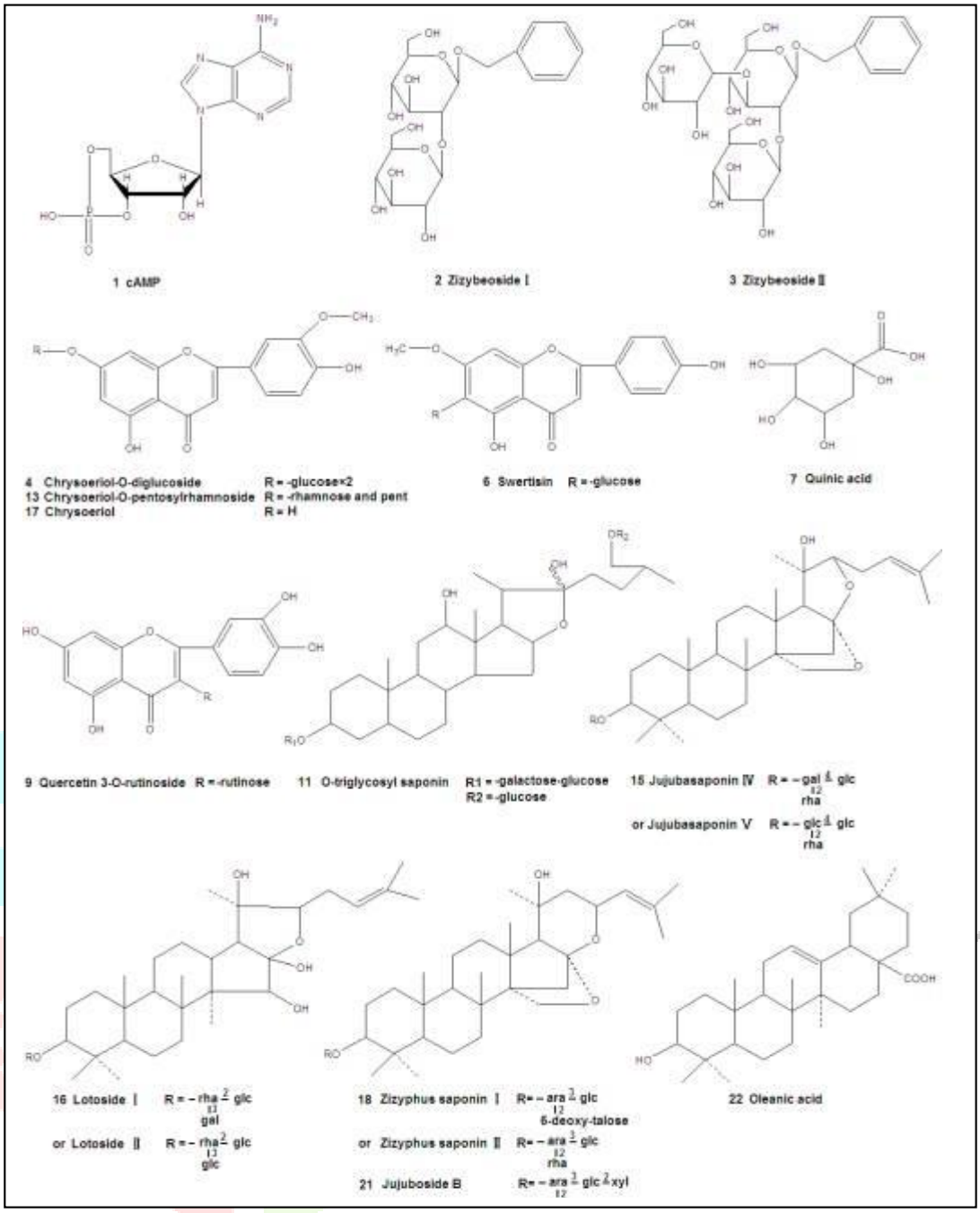

Fig. 4 Chemical constituents and structure of Ziziphus Jujuba

Fig. 5

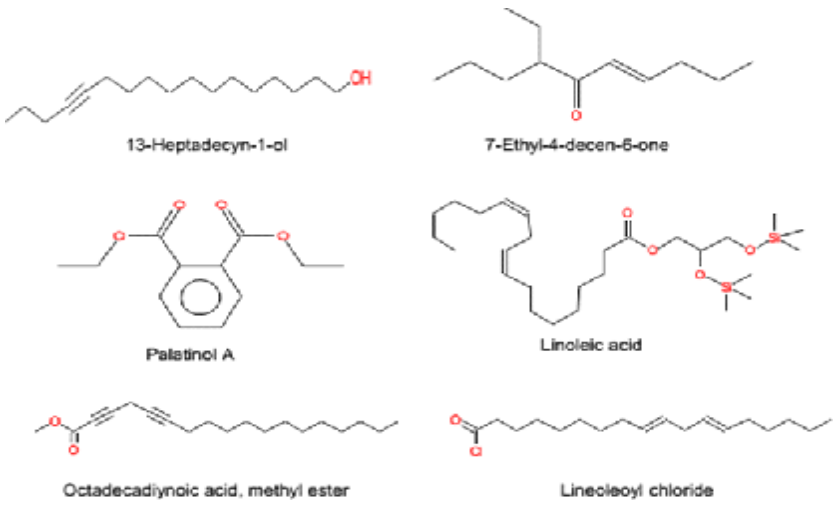

Fig. 2. Chemical structure of the highest abundant compounds were identified in the Ziziphus jujuba seeds

extract. 13-Heptadecyn-1-ol (12.95), 7-Ethyl-4-decen-6-one (9.73), Lineoleoyl chloride (8.54), Linoleic acid (6.37), 2,5-Octadecadiynoic acid, methyl ester (5.57), Palatinol A (4.81)

CONCLUSION

In conclusion, our study was one of very few studies have confirmed that the antimicrobial activity of Ziziphus jujuba seeds extract against certain microorganisms. Results of this study showed that the have found for the first time that Ziziphus jujuba extracts are effective in inhibiting the growth of Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumonia and Listeria monocytogenes. Remarkably, they elicited no effects on immortalized normal human foreskin fibroblasts cells and nonmalignant epithelial breast cells. Triterpenic acids resulted the bioactive compounds present in the most effective extracts (ZE2 and ZE4). Our data provide a strong rational base for the use in Traditional Chinese Medicine of Ziziphus extracts in the treatment of cancers. Moreover, our results highlight that Ziziphus jujuba are valuable fruits rich in bioactive compounds with potential human health benefits. More experiments are in progress to understand the molecular targets and pathways affected by Ziziphus jujuba.

According to our findings, the traditional Persian medical texts present instructions on different types of medicinal plants including jujube. Therefore, it is possible to achieve economic, social, and mental efficiency by comparing these books to the new sciences and conducting research in this subject area. For instance, jujube is a well-known medicinal plant with various nutritional values and pharmacological properties. There is no report of the toxicity or serious side effects of the oral intake of jujube. This fruit has a pleasant taste and is good for the human body. It has been recommended in several centuries in the old and recent Persian references. Besides, its pharmacological properties, phytochemical compounds, and pharmacological reports reflect its importance.

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