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ABSTRACT

Flavonoids are natural antioxidants; that may prevent stress, reduce LDL cholesterol, platelet clump, and ischemic damage. Since the discovery of flavonoids as the significant natural antioxidant, they are known as biological modifiers. They can modify the human's reaction as well as ingredients. They are also instrumental in preventing the oxidative stress and free radical damage. About 25% of prescription drugs are available in the market to treat diseases are derived from nature. Numerous scientists are working with available natural resources to discover new drugs which can be used as medicine to cure or prevent different curable and incurable diseases. The scientific and medical community within the Sultanate of Oman has considered potential natural resources within the Gulf region for purpose to aid medical research. There is an abundant of unexplored plants, marine, and animal sources. Some of them have indicated potential pharmacological activity which can be used to discover new medicines to treat diseases. *Ziziphus jujube* (*Z. jujube*) is a medium size native plant which is available in Oman. It is belongs to Rhamnaceae classification and is traditionally used by the local community for the treatment of joint pain, dandruff, acne, chronic constipation, antiseptic, sedative, hypnotic and cardiac diseases. Previous studies have shown that this particular plant has various active principles which can affect biological activity. In addition, the previous research indicated that the plant extracts and isolated principles also contain significant activity. The plant has several varieties of species globally and one of the most common species is known as *Z. jujube*. Various biological studies have been conducted by scientists on the locally grown selected plant. However, due to lack of unavailable facilities, some of the parameters have not been able to be investigated as of yet. Therefore, the objective of this review is to summarize the previous reported phytopharmacological status of the selected plant species. Also, this review will help to encourage other scientist to continue the work on the selected plant species particularly within the realm of the toxicity and bioactivity. In conclusion, the plant extracts and active principles might be used in the near future as potential drugs to cure different ailments.

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1. Introduction

1.1. Plant description

Nature is the primary sources of medicine for the treatment of different ailments since ancient times. Natural resources found in nature often provide remedies for all kinds of diseases. Scientists are looking for safer drugs that derive from natural sources to treat present diseases worldwide. Increasingly each day, new diseases are discovered that threaten the people's health. Therefore, we must increasingly turn to natural in order to seek a remedy to cure the existing and new diseases. Plants are one of the primary sources for the discovery of new drugs (Asma et al., 2016). The survival flora and fauna diversity depends on environmental and geographical conditions. That why some of the countries contain plenty of plant sources. One of the plants is *Ziziphus jujube* (*Z. jujube*) which has medicinally essential and been used traditionally in different countries to treat various diseases. Plants are distributed all over the world. However, the initial country of origin is still confusing to pinpoint due to the large variety of plant

species. The selected plant related to the research belongs to the Rhamnaceae family (Asma et al., 2016, 2017). *Ziziphus* is classified as part of the *jujube* species. It has about 40 species commonly found throughout the world (Asma et al., 2016). Most of the species are used as medicine particularly in India, China, and other South East Asian countries. It is found in almost all parts of the Asia. Some species of the selected family are also available in Oman. This family's plant contains fruits which are very close to the Vitaceae family (Al-Reza et al., 2009, 2010). The plant has several names. Its botanical name is *Ziziphus jujube*, English name is Jujube fruit, Chinese name is Da Zao and Hong Zoa, and its Indian name is Kul and Borai (Wu et al., 2014). In Oman, it is known as Nabag and Cidr (Vandita et al., 2012). The plant is about 8 to 12 m long with throne branches (Fig. 1). The leaves are green and are arrange alternatively. The flowers are small with greenish and yellowish coloration. The immature fruits are oval with greenish color. However, the fruit turns to red in color when it ripens (Fig. 2). The size of the fruits depends on cultivars. The fruit has a white flesh with a sweet and acidic taste (Kim, 2002; Li et al., 2011; Vandita et al., 2012; Al-Reza et al., 2009, 2010).



Fig. 1. Plant picture.



Fig. 2. Parts of *Ziziphus jujube*.

1.2. Synonyms

The plant is about 8 to 12 m in height. The dry weather is suitable for rapid growth. Therefore, the Gulf countries had plenty of *Z. jujube*. During the summer the selected plant provides shade for various types of livestock. The fruits and leaves have medicinal values and are used traditionally to treat different ailments (Khare, 1995; Kim, 2009). Due to the medicinal importance, the plant is cultivated globally. The most popular synonyms available worldwide are as follows:

1. *Ziziphus jujuba*
2. *Ziziphus celata*
3. *Ziziphus lotus* (L.) Lam.
4. *Ziziphus mauritiana* Lam.
5. *Ziziphus nummularia* (Burm.f.)
6. *Ziziphus obtusifolia*
7. *Ziziphus parryi* Torr.
8. *Ziziphus reticulata* (Vahl) DC.
9. *Ziziphus rignonii*
10. *Ziziphus taylorii* (Britton)

1.3. Taxonomic classification of *Ziziphus jujuba*

Domain: Eukaryota; **Kingdom:** Plantae; **Subkingdom:** Viridiplantae; **Phylum:** Spermatophyta; **Subphylum:** Angiospermae; **Superdivision:** Embryophyta; **Division:** Tracheophyta; **Subdivision:** Spermatophytina; **Class:** Magnoliopsida; **Superorder:** Rosanae; **Order:** Rosales; **Family:** Rhamnaceae; **Genus:** *Ziziphus*; **Species:** *Ziziphus jujuba*.

1.4. Vernacular names

Ziziphus jujube (Botanical); Jujube fruit (English), Ennab, Nabec and Zenzeli (Brabic); Da Zao and Hong Zoa (Chenise), Kul and Borai (Bangali); Nabag and Cidr (Oman); Gemeine Jujube (German); Ber and bor (Pakistan); Zi (Myanmar); Jujubenboom (Netherlands); Giuggiolo and sisifo (Italy); Rajabadari (Sanskrit); Bogori (Assamese); Bordi (Gujarati); Ber (Hindi); Bor (Marathi); Badaram, (Malayalam); Bogari (Kannada); Vadari (Tamil); Renu (Telugu); Ber (Urdu); Jangri (Sindhi).

1.5. Distribution of plant

The literature review of previous research showed that the plant originates from Africa and from Australia (Vandita et al., 2012). However, the selected plant is widely available in most tropical countries including the Arabian Peninsula (Vandita et al., 2012; Al-Reza et al., 2009, 2010). The plant is also commonly found in Malaysia, India, Bangladesh, Pakistan, Nepal, and Thailand (Erenmemisoglu et al., 1995; Khare, 1995). Most of the genus are available in Indonesia and Malaysia. The *Zizyphus jujuba*, *Ziziphus glaberata*, *Ziziphus mauritiana*, and *Ziziphus rugosa* are the medicinally most important species of this genus (Bashir et al., 2011). The selected plant grows faster than other species. The fruit is sweet, and its taste is similar to a combination of dates and apples (Kim, 2002; Li et al., 2011; Vandita et al., 2012; Al-Reza et al., 2009, 2010).

1.6. Medicinal usage

Traditionally, the selected plant along with other sub-species is used to treat different ailments (Kim, 2002; Li et al., 2011; Vandita

et al., 2012). Current research indicates that almost all parts and its extracts showed significant pharmacological activity and frequently used as an alternative medicine to treat a range ailments and disorders. In India, the roots of *Z. nummularia* species in Ayurveda system is used to treat coughs, nausea, and headache. The bark of the same species is used to treat chronic dysentery and diarrhea (Kirtikar and Basu, 1994). The leaves boiled in water is also used to clean corpse prior to burials. In addition, the leaves can be used to reduce the weight and combat obesity. The fruits are the main ingredient which are traditionally used as a digestible, tonic, aphrodisiac, and laxative to treat nausea, burn, sensations, thirst, tuberculosis and blood bone diseases (Bashir et al., 2011; Erenmemisoglu et al., 1995; Khare, 1995; Kim, 2009). The seed extracts of the selected species can be used to treat eye inflammation and leucorrhoea (Wu et al., 2014). Some of the Indian ethnic communities use the fruits to treat fever, diabetics, and vomiting. In India, traditionally the leaves and bark powdered are used as dressing materials to treat wounds (Bashir et al., 2011;

Erenmemisoglu et al., 1995; Khare, 1995; Kim, 2009). In addition, the fresh leaves of this species can be used to treat a wounds and urinary infections (Bashir et al., 2011; Erenmemisoglu et al., 1995; Khare, 1995; Kim, 2009). When boiled in water it can be used to treat smallpox and chickenpox (Bashir et al., 2011; Erenmemisoglu et al., 1995; Khare, 1995; Kim, 2009). However, the Omani community, primarily use the plant as an antifungal agent, cardiotoxic, and an antiseptic agent to treat swollen especially joint, acne, shampoo, burns, acute constipation and diarrhea (Asma et al., 2016, 2017). Elsewhere, the selected plant species has been used as an antifertility, antihypotensive, sedative, hypnotic, cardiac tonic, antioxidant, antimicrobial, and immune modulator to treat different ailments (Souleles and Shammam, 1998; Jeong et al., 2004; Khare, 1995; Peng and Zhu, 2001; Jiang et al., 2007). Previous several studies showed that the selected plant from Chinese and Korean ethnic communities have been used it as an antifungal, antibacterial, antioxidant, antiulcer, anti-stress, hypnotic, anti-inflammatory and sedative effect to treat several diseases



Fig. 3. Preparation of different polarity of extracts.

such as joint pain, acne, shampoo, severer burns, acute constipation, GIT problem, various forms of inflammation, cardiovascular diseases, urine infections, liver diseases and chronic diarrhea (Kim, 2002; Souleles and Shamma, 1998; Ziping et al., 2009; Al-Reza et al., 2009, 2010; Jiang et al., 2007).

1.7. Chemical ingredients

The selected plant species contain different groups of compounds such as tannin, saponins, flavonoids, terpenoids, phenolic compounds cardiac glycoside, alkaloids, amino acids, sugar, protein, fats, calcium, potassium, phosphate and high concentration of iron (Vandita et al., 2012; Asma et al., 2016; Elaloui et al., 2015, 2017). In addition, the plant pulp contains vitamin A, B and C, carbohydrate, calcium, phosphorus, iron, β -carotene, γ -thiamine, linoleic acid, oleic acid and riboflavin (Kim, 2002; Li et al., 2011; Vandita et al., 2012; Al-Reza et al., 2009, 2010). It also contains moisture and pale yellowish oil. The fruits contain high amounts of vitamin A, B, and C along with vitamin B1 and B12 (Kim, 2002; Li et al., 2011; Vandita et al., 2012; Sajida et al., 2017). According to FAO and WHO, one fruit is enough to fulfill daily dietary requirement of different types of vitamins (Tomoda et al., 1985). However, the Omani *Ziziphus* fruits are known to be of high quality. The previous study showed that the plant contains about 79 chemical compounds. About 56 chemical compounds were isolated and characterized from the different parts of the selected plant (Kim, 2002; Li et al., 2011; Vandita et al., 2012; Al-Reza et al., 2009, 2010; Fatma et al., 2014).

1.8. Extraction

The scientists were collected leaves and fruits samples from their suitable places and washed and dried under different conditions. The fruits samples were sliced by a knife before drying. The samples were grounded into coarse powder. The samples were extracted from the powder with different solvents by using either hot or cold extraction methods. After completion extraction, the solvent was evaporated. Some authors, the extracts of leaves and fruits were dissolved in water and then transferred into the separatory funnel (Fig. 3). Then fractionation by various solvent with increasing polarity. Finally, the solvent was evaporated from each polarity of extract. The fractionated all polarity extracts were used for pharmacological and toxicological studies by the modified established assay (Asma et al., 2016, 2017).

2. Pharmacological activities

According to the literature, the *Z. jujube* species is considered as a medicinal plant, and it is used traditionally to treat different diseases. Omani people have traditionally used it to cure different diseases. Due to its customary use, the selected plant species was targeted to evaluate their different pharmacological and toxicological activities by the modified assay. Previous studies on the selected indigenous species showed that all polarity extracts from the leaves and fruits give significant pharmacological and toxicological activities (Vandita et al., 2012; Al-Reza et al., 2009, 2010; Fatma et al., 2014; Sajida et al., 2017). Our conclusion showed that the activity of the prepared extracts from the leaves and fruits depends on the active ingredients as well as the polarity of the ingredients (Asma et al., 2016, 2017). Also, the previous study showed that the extracts of different polarity give potentially different pharmacological and toxicological activities (Souleles and Shamma, 1998; Jeong et al., 2004; Khare, 1995; Peng and Zhu, 2001; Sajida et al., 2017).

2.1. Antioxidant activity

The prepared different polarity leaves and fruits extracts were used to determine their antioxidant activity by modified free radical scavenging method (Asma et al., 2016, 2017; Kamiloglu et al., 2009; Li et al., 2011). The extracts from edible fruits of the selected local species showed maximum antioxidant activity against free radical scavenging assay compare to other countries species. The maximum scavenging activity was obtained in chloroform extract, and minimum scavenging activity was in methanol. Our result indicated that the polarity of the extract is decreasing with increasing the scavenging activity. Therefore, the less polar extract contains the maximum antioxidant compound which can participate directly to the scavenging activity. The current research experimental results are not align with previous literature results; which were reported earlier on the same species by differing authors (Kamiloglu et al., 2009; Li et al., 2011; Vandita et al., 2012; Al-Reza et al., 2009; Fatma et al., 2014; Elaloui et al., 2015, 2017). It could be due to the preparation of extract or weather, rainfall, temperature and harvesting procedure.

2.2. Antimicrobial activity

The determination of antimicrobial activity of the various prepared extracts was done by modified agar gel assay (Asma et al., 2017). The clinically isolated Gram (+ and –) bacterial strains used in the present experiment were collected from a local hospital. All extracts at each concentration give notable antimicrobial potency against selected applied Gram (+ and –) bacterial strains. The hexane extract showed the maximum potency against the applied clinically isolated bacterial strains within the range of 0–15 mm. However, the polar extracts at each concentration showed the activity within the range of 0–9 mm (Asma et al., 2017). The range of inhibition zone entirely depends on the chemical ingredients in the respective extract. That means, the hexane extract both the leaves and fruits contains the maximum number/concentration of bioactive compounds which is directly or indirectly influence the inhibition zone. Our results are not aligned with the published results reported by the other authors (Peng and Zhu, 2001; Bashir et al., 2011). The difference in results due to the preparation of extract. Our extraction procedure is entirely different from others. In addition, the assay, dose of extract and bacterial strains used for the determination of antimicrobial activity are also entirely different. Not only is these differences, the climate of Oman not the same. Therefore, our experimental results are reversed compared with the other reported values (Peng and Zhu, 2001; Bashir et al., 2011).

2.3. Cytotoxic activity

Brine shrimp lethality assay was to determine the cytotoxic activity of the prepared different polarity extracts of the selected endemic *Z. jujube* (Asma et al., 2016). Artificial seawater DMSO and hatch shrimp were used to determine the cytotoxic activity of the prepared extracts. Six different polarities of locally grown *Z. jujube* extracts were used for this experiment. The highest toxicity activity was found in the butanol leaves extract, and the lowest activity was found in the chloroform leaves extract. However, in the fruits, the highest activity was found in ethyl acetate, and the lowest was in water extract. The toxicity of the extracts depends on the toxic ingredients present in the extract. That means, more toxic ingredients, as well as the concentration of toxic ingredients, were interfered to increase the toxicity of the extracts. Similar cytotoxic activity results were found and reported by other authors on the same species from other countries (Hoshyar et al., 2015; Reyhane et al., 2015; Fatma et al., 2014). Even though, the harvesting of the selected plant samples, the extraction procedure, and

geographical condition are not the same. It could be due the toxic compounds is stable and completely soluble in the ethyl acetate solvent.

3. Total phenols

Modified Folin-Ciocalteu reagent (FCR) assay was used for the determination of total phenols of prepared different polarity both fruits and leaves extracts from the selected plant. The gallic acid was used as a standard, and the total amount of phenols was calculated from regradation equation from the gallic acid standard curve. The ethyl acetate extract showed the maximum total phenols content in both fruits and leaves extracts. However, the water extracts from both fruits and leaves showed the minimum amount of total phenols (Asma et al., 2016). The other prepared extracts also showed the considerable amount of total phenols. The literature search reveals that some previous report published elsewhere were not wholly supported by our results (Fatma et al., 2014; Elaloui et al., 2017). Previous report also showed that significant number of polyphenolic compounds are present in the extract of the selected plant (Elaloui et al., 2015). In general, the phenols compounds are recently used as a medicine for the treatment of various diseases (Fatma et al., 2014). Therefore, the extracts which contain the maximum amount of total phenols could be used as medicine to treat various diseases.

3.1. Total flavonoids

A modified colorimetric assay was used for the determination of total flavonoids of the variously prepared polarity of extracts of fruits and leaves. The standard quercetin was used for the calculation of total flavonoids (Asma et al., 2016). The chloroform extract showed the maximum total flavonoids in both leaves and fruits samples. However, the hexane leaves extract showed the minimum amount of total flavonoids, and the methanol fruits extract showed the minimum amount of total flavonoids. The remaining fruits and leaves extracts also showed the notable amount of total flavonoids. Our results are entirely aligned with other results which are published earlier (Aye et al., 2013; Fatma et al., 2014; Jiang et al., 2007). More recently, most of the polyphenols compounds are using as medicine to treat various diseases. The extracts from the leaves and fruits which contain the maximum amount of total flavonoids could be used as medicine to treat a host of ailments.

4. Conclusion

According to the literature, the selected plant species showed significant medicinal values which are used traditionally to treat different diseases for centuries. The *Z. jujube* is available in Oman and the local community traditionally used it to treat swollen joints, acne, shampoo, burns, acute constipation and diarrhea (Asma et al., 2016). About 79 bioactive ingredients present in the selected plant among them 54 bioactive compounds are isolated. All the bioactive ingredients were isolated from the fruits and leaves and showed several pharmacological activities. The prepared fresh, dry fruit, leaves, and their paste also showed significant activity against antifungal, antibacterial, antioxidant, antiulcer, anti-stress, anti-inflammatory and sedative effect. Therefore, the investigation is focused on the selected plant species for the discovery of the new medicines to treat different diseases. Our present review aims to identify the present status of the phytochemical and pharmacological activities of the locally grown *Z. jujube*. The current research would support further research initiatives in the future to further isolate new drugs that would benefit the pharmaceutical, agrochemical, and cosmetics industries.

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