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Short Review

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A Review of Phytochemistry and Meidicnal Properties of Jujube (Ziziphus vulgaris L.)

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Abstract

Iran has a great wealth of various naturally occurring medicinal plants which have great potential pharmacological activities. Ziziphus vulgaris known as Jujube is one of these plants. For a long time Z. vulgaris has been used in alternative medicine as anti-hyperglycemic, anti-hyperlipidemia and anti- hypertension. Z. vulgaris has recently been shown to have antibacterial, antioxidant, anti-hyperglycemic, antihyperlipidemic and sedative activities. Flavonoids, alkaloids and saponins are the main phytochemicals which are reported from this plant. Considering the easy collection of the plant, its wide distribution in warm-temperate regions, and remarkable biological activities, this plant is used as both medicine and food in some parts of the world including Iran. This paper reviews the botany, traditional uses, phytochemistry, and pharmacology of this medicinal plant.

Keywords: Ziziphus vulgaris, Rhamnaceae, Pharmacology, Phytochemistry

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1. Introduction

Affordability and accessibility of the medicinal plants have made them as an important part of many people's life all over the world. The medicinal plants selection is a conscious process, which has led to an enormous number of medicinal plants being consumed in many cultures in the world (Heinrich et al., 2004). According to the World Health Organization (WHO), due to the poverty and lack of access to modern medicines, about 65-80% of the world's population in developing countries depends on plants for their primary health care (Calixto, 2005). Regarding the lack of safe and modern drugs, evaluation of active and effective plants for treating illnesses such as diabetes has been recommended by WHO (Kim et al., 2007). It is estimated that close to 25% of the active compounds in currently prescribed synthetic drugs were first identified in natural sources especially in plant (Halerstein, 2005).

Commonly known as Jujube, Ziziphus vulgaris L., is a deciduous tree, native to the warm-temperate and subtropical regions including North Africa, South Europe, Mediterranean, South and East of Asia and Middle East (Salehi Surmaghi, 2010). It belongs to Rhamnaceae family in the order of Rosales that contains about 60 genera and more than 850 species. The genus Ziziphus consists of approximately 40 species of spiny shrubs and small trees throughout the world. Z. vulgaris has been among the key plants of the Iranian traditional medicine since ancient times and is indigenous and naturalized throughout Iran (Solati and Soleimani, 2010). It has been known as "Annaab" in Iran and is wildly distributed in eastern, south, north-eastern and central parts of Iran (Salehi Surmaghi, 2010).

Z. vulgaris is a deciduous tree up to 12 m in height. It grows mostly in tropical forests, however, it has as well been found in stubbles, pastures, in the coastal ranges, tropical mountain areas and interior in wet areas to dry regions. The leaves are alternate, entire, with three prominent basal veins, and 2-7 cm long. Some species are deciduous while others evergreen. The flowers are small, inconspicuous yellow-green. The fruit is an edible drupe, yellow-brown, red, or black, globose or oblong, 1-5 cm long, often very sweet and sugary, reminiscent of a date in texture and flavor (Zargari, 1988).

For a long time, in folklore medicine, Z. vulgaris has been used for the treatment of some illnesses, such as digestive disorders, weakness, liver complaints, obesity, urinary disorders, diabetes, skin infections, fever, diarrhea and insomnia (Steiner, 1986; Scartezzini and Speroni, 2000). The seeds of Z. vulgaris (Sanjoin in Korean) are reputed to be the most important herbal drug for the treatment of insomnia as a sedative and nerve tonic in Chinese medicine. The fruits (fresh or dried) are used in Iranian traditional medicine to treat diabetes, colds and coughs (Han et al., 1990; Han and Park, 1987). These fruits are also used in Chinese and Korean traditional medicine, where they are believed to alleviate stress (Mill, 2009). Flavonoids, alkaloids, triterpenoids and saponins are the compounds most widely studied (Han et al., 1989).

From currently available pharmaceutical studies, additional pharmaceutical applications of Z. vulgaris include antifungal, antibacterial, antiulcer, anti-inflammatory, sedative and antiseptic (Jiang et al., 2007; Mahajan & Chopda, 2009) hypnotic, tranquilizing, sedative, analgesic, anti-inflammatory, antiarrhythmic and hypotensive (Han et al., 1989) activities.

To date, no review and systemic analysis of chemistry, pharmacology and clinical properties of Z. vulgaris has been reported. To help filling this gap, we prompted to provide the currently available information on traditional and local knowledge, ethno biological and ethno medicinal issues, identification of pharmacologically important molecules and pharmacological studies on this useful plant. The aim of this paper is to introduce

Z. vulgaris as a potent medicinal plant by highlighting its traditional applications as well as the recent findings for novel pharmacological and clinical applications.

2. Review

The data presented in this paper were collected using extensive scientific data from encyclopedia books, journals articles, and scientific biomedical databases including Pubmed, Scopus and Google Scholar.

Phytochemical Contents

A survey of the literature revealed that a number of cyclopeptide and isoquinoline alkaloids flavonoids, terpenoids and their glycosides have been found to occur in various amounts in most Ziziphus species. The leaves of these plants contain betulic and ceanothic acids, various flavonoids, saponins, erols, and triterpenes (Ali and Hamed, 2006; Glombitza et al., 1994).

Some phytochemical papers described the isolation of saponin compounds, Jujuboside A and B and flavonoid components and flavone-C-glycosides such as swertisin, spinosin, 6-sinapoylspinosin, 6-feruloylspinosin and ρ-coumaroylspinosin from Z. vulgaris seeds as the active principles for some pharmacologic activities (Han et al., 1989; Shin et al., 1982).

Sanjoinine A (frangufoline), B, D, F, G1 and Sanjoinenine were cyclopeptide alkaloids also isolated from the seeds. Other compounds were identified to be nuciferine, nornuciferine, norisocorydine, N-methylasimilobine and caaverine which were included as alkaloids of aporphine series. Sanjoinine-K was identified as Coclaurine, a benzylisoquinoline alkaloid (Figure 1) (Han et al., 1989). A steroid triterpene, botulin, was also characterized in the seeds (Figure 5) (Patocka, 2003).

Ziziphusine, a new quarternary aporphine alkaloid was also identified in the seeds (Han et al., 1989).

3-O-[(2-O-α-D-fucopyranosyl-3-O-β-D-glucopyranosyl)-α-L-arabinopyranosyl]-jajubogenin is the major saponin glycoside isolated from Z. vulgaris leaves and stems (Ikram et al., 1981). Mucilage, vitamin C, proteins, sugar and ziziphique acid are found in Z. vulgaris fruits (Salehi Surmaghi, 2010). This acid accompanying with a tannin named ziziphotannique acid were characterized in Z. vulgaris bark (Salehi Surmaghi, 2010).

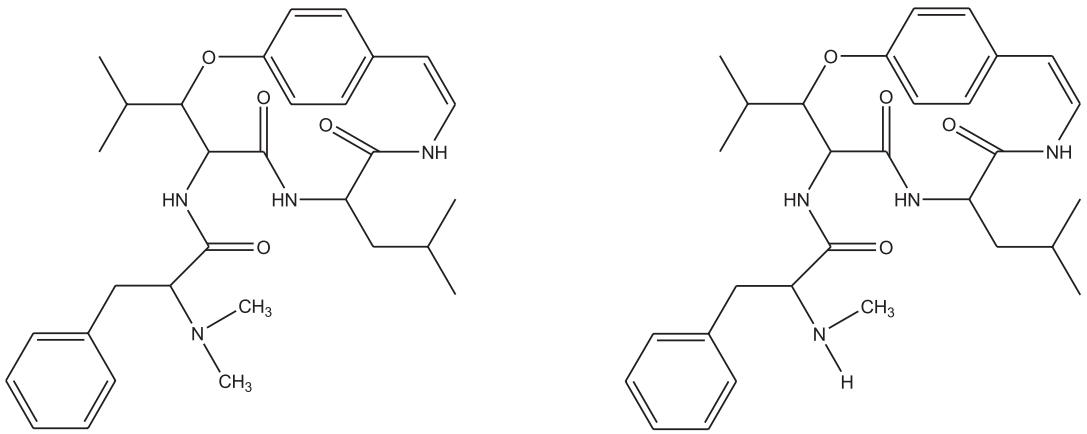
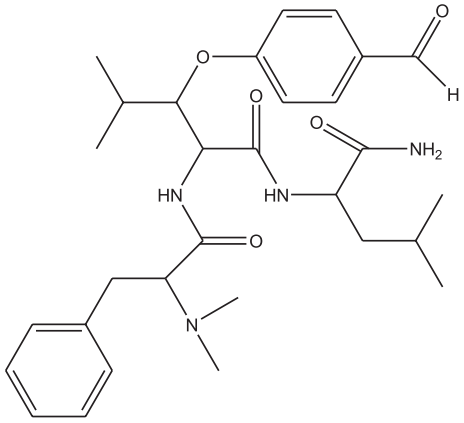


Figure 1. Structures of: A= Sanjoinine A, B= Sanjoinine B



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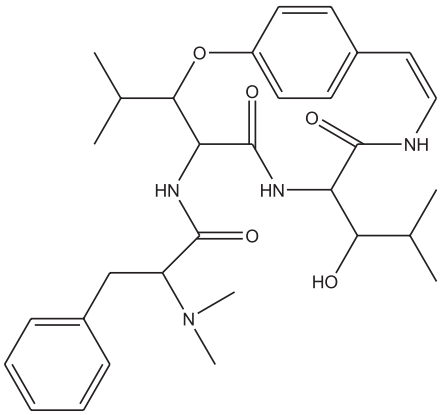

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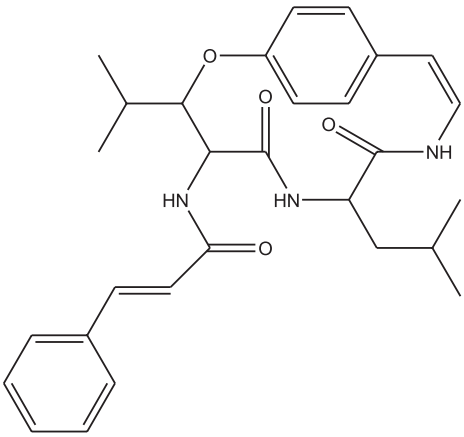

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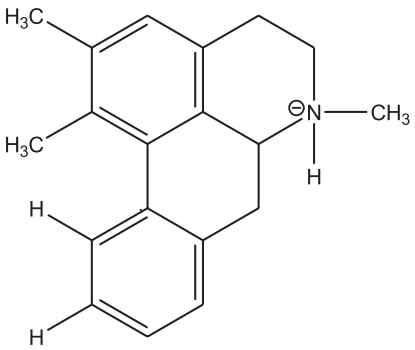

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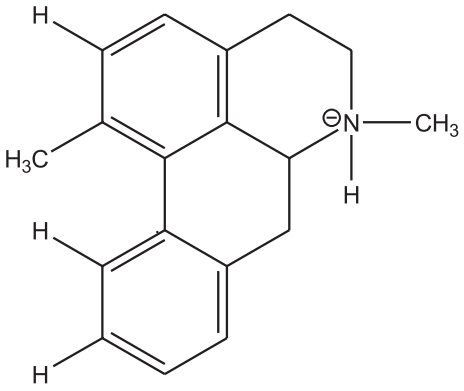

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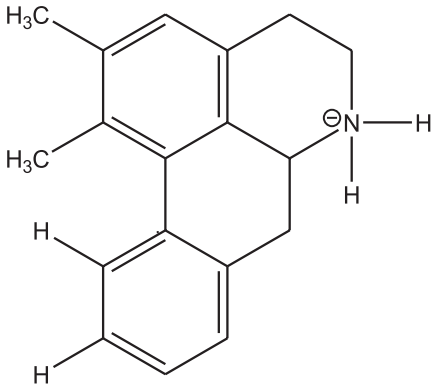

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Figure 2. Structures of: C= Sanjoinine G2, D= Sanjoinine F, E= Sanjoinenine, F= Nuciferine, G= G-methylasimilobine, H= Nornuciferine

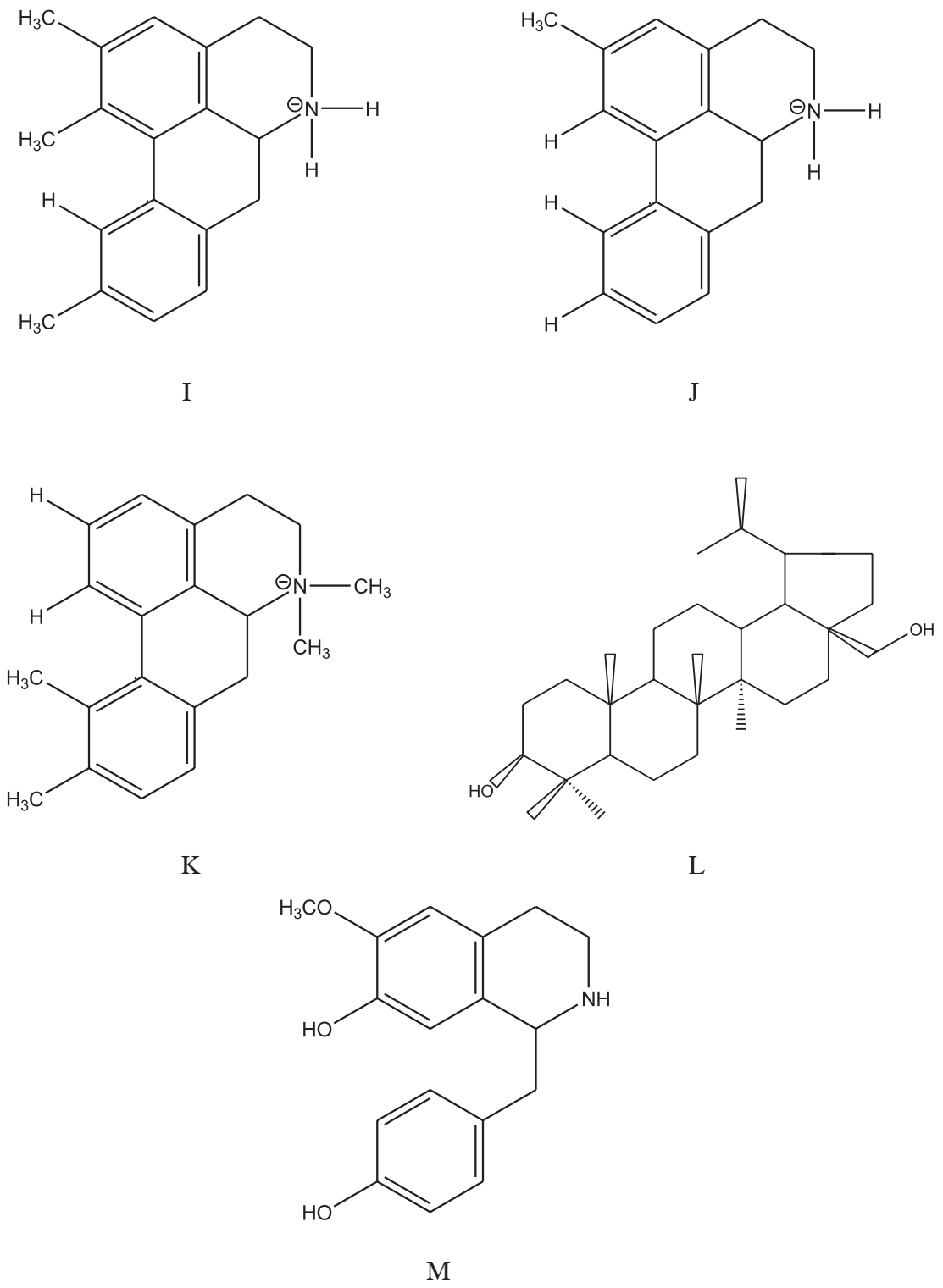

Figure 3. Structures of: I= Norisocorydine, J= Caaverine, K= Ziziphusine, L= Betulin, M= Coclaurine from Z. vulgaris.

Ziziphin is a compound contained in the leaves that temporary anesthetizes the taste after chewing (Salehi Surmaghi, 2010).

Pharmacological Properties

Various studies have revealed the different pharmacological potentials of Z. vulgaris in a range of in vitro and in vivo test models. In particular The aerial parts of the plant, has been demonstrated to possess antihyperglycemic, antihyperlipidemic, antioxidant and sedative activities at different doses/concentrations. These have been described in greater detail in the following subsections.

Antihyperglycemic and Antihyperlipidemic Effects

Aqueous extract of Z. vulgaris fruits produced significant hypoglycemic effects in streptozocin-induced diabetic rats. A continuous treatment with the extract (0.25, 0.5, 1, 1.5 and 2 g/kg) for a period of 14 days resulted in a significant decrease in the blood glucose, but there were no significant changes in the insulin levels of diabetic rats.

Z. vulgaris aqueous extract demonstrated hypoglycemic effect by acting on glucose homeostasis in an extra-pancreatic way (Solati and Soleimani, 2010).

Improvement of liver function and a subsequent increase in the uptake of blood glucose and its utilization might be other mechanisms of action of Z. vulgaris (Vetrichelvan and Jegadeesan, 2002; Joy and Kuttan, 1999).

Another possible interpretation depends on the glucagon-lowering effect of saponin glycoside. Steroid saponin glycosides have been reported to significantly decrease plasma glucose, glucagon and cholesterol values in diabetic dogs (Al-Habori and Raman, 1998; Madar et al., 1988).

Continuous treatment with Z. vulgaris fruits produced a significant decrease in the blood triglycerides and LDL-cholesterol level. Inulin is a polymer of fructose with b-(2-1) glycosidic linkages, and it is present in the Ziziphus species (Xue et al., 2006). As it is water-soluble, thereby not being hydrolyzed by human digestive enzymes, it behaves such as a soluble fiber and possesses a hypolipidemic effect (Lairon, 1996).

During extract treatment, there was no significant change in the activation of these enzymes, and the extract was found to be non-toxic to the mammalian system (Solati and Soleimani, 2010).

Antioxidant Activity

Free radicals especially reactive oxygen species can produce several disorders by damaging biomolecules like Deoxyribonucleic Acid (DNA), proteins, and membrane lipids. Lipid peroxidation in Low-Density Lipoprotein (LDL) and membranes of hepatocytes are involved in atherosclerosis and liver disease respectively. Non-enzymatic glycosylation of proteins is involved in complications of diabetes (Foroughinia et al., 2011). An antioxidant is defined as 'any substance that, when present at low concentrations compared to those of an oxidizable substrate, significantly delays or prevents oxidation of that substrate' (Rhee et al., 2009; Wiseman et al., 1997; Mates et al., 1999). Antioxidants are of interest to biologists and clinicians because they help to protect the human body against injuries induced by reactive free radicals generated in atherosclerosis, ischemic heart disease, cancer, Alzheimer's disease, Parkinson's disease and even in aging process (Aruoma, 2003; Hemati et al., 2010). There is much evidence on the efficient anti-oxidative activity of natural products and their derivatives, thereby, their association with to anti-cancer, hypolipidemic, anti-aging and anti-inflammatory activities (Rhee et al., 2009; Wiseman et al., 1997; Hogg, 1998; Mates et al., 1999; Aruoma, 2003; Cho et al., 2006). Anti-oxidative capabilities of Z. vulgaris were evaluated by determining its effect on cell membrane of hepatocytes and red blood cell hemolysis (Foroughinia et al., 2011).

The inhibitory effects of Z. vulgaris ethanolic

and aqueous extracts on hemolysis of RBC were 67% at a concentration of 10 μg/ml. The results showed that the fruits of this plant may have an antioxidant effect and can be probably used as an antioxidant and food supplement in diabetic and liver disease patients, and also in individuals susceptible to atherosclerosis. In addition, it may exert protective effects against some complications of diabetes (Foroughinia et al., 2011).

Sedative Properties

The alkaloids isolated from Z. vulgaris seeds have shown sedative activity by measuring the hexobarbital induced sleeping time (Han et al., 1989). Oral administration of methanol extract of the seeds (1g/kg) prolonged the hexobarbital induced sleeping time by more than 67%. Sanjoinine A and nuciferine showed strong sedative activity. Nuciferine has been already reported as having major tranquilizing characteristics. The sedative activity of sanjoinine-A at dose of 3 mg/kg was potent enough to indicate that such cyclopeptide alkaloids can be effective components in the seeds and this was the first finding of sedative activity in cyclopeptide alkaloids (Han et al., 1989).

Actually all the alkaloids of Z. vulgaris seeds exist as a mixture in a certain ratio, hence some drug interactions such as additively, synergistic or counteracting interaction could be postulated. In order to clarify these possibilities, sanjoinine A was co-administered with nuciferine. There was additively between sanjoinine A and nuciferine.

Butanol fraction of the seeds has also shown potent sedative activity. Some papers described the sedative activity of flavonoids or saponins which constitute the major part of this fraction. In fact the butanol fraction contains also small amount of aporphine alkaloids such as caaverine and N-methylasimilobine and norisocorydine as minor components impurity which are very difficult to separate by solvent partition due to the formation of salt with flavonoids. It is very likely that some part of the sedative activity of this fraction may be attributed to the presence of these minor alkaloids (Han et al., 1989).

3. Conclusion

This paper reviewed the relevant literature to congregate the botanical, ethnobotanical, phytochemical, and pharmacological information on Z. vulgaris. Previous studies have demonstrated various pharmacological activities of Z. vulgaris. However, detail and careful analysis of the reported data leads us to conclude that the only promising antioxidant and sedative activities of the plant are related to antihyperglycemic, antihyperlipidemic. Despite that there are many diseases for which the plant finds use as a medicine, few studies has assessed its therapeutic efficacy. Regarding the wide medicinal uses of Z. vulgaris in Asian, Iranian and Arabic folklores as described in ethnobotanical surveys, it is necessary to conduct more clinical and pharmacological studies at molecular level to investigate untapped potential of this plant. For this reason, extensive pharmacological and chemical experiments, together with human metabolism, will be a focus for future studies. Recent increase in interest on herbal medicines accompanied by increased laboratory investigation into the pharmacological properties of the bioactive ingredients and their ability to treat various diseases has contributed to numerous drugs/herbal extracts entering the international market. As the recent information shows, it is also possible that saponins and alkaloids might be useful in the development of new drugs to treat antihyperglycemic and antihyperlipidemic. However, clinicians should remain alert until more definitive studies demonstrate the safety, efficacy and quality of the compound. Last but not the least, this paper emphasizes the potential of Z. vulgaris to be employed in the development of new therapeutic drugs and

provide the basis for future research on the application of transitional medicinal plants.

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