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Mini review:

SEDATIVE AND HYPNOTIC EFFECTS OF IRANIAN TRADITIONAL MEDICINAL HERBS USED FOR TREATMENT OF INSOMNIA

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ABSTRACT

For tens of centuries, plants have been highly valued and regularly used as medicine amongst the masses. Insomnia, a loss of sleep, is mostly treated by synthetic sleeping tablets these days. However, questions have been raised about the safety of prolonged use of artificial sedatives due to their deleterious side effects such as physical dependence. In recent years, there has been an increasing propensity to preclude insomnia by herbal medicines throughout the world. Many herbs have a lengthy background in terms of insomnia treatment in Iran. This paper gives an account of previously published research on sedative and hypnotic effects of medicinal herbs used for treatment of insomnia in Iranian traditional medicine.

Keywords: Iranian medicinal herbs, Iranian traditional medicine, insomnia, sedative effect, hypnotic effect

INTRODUCTION

Nowadays, insomnia has been a conspicuous problem or disease in our restless society. It has been reported that 10 to 20 percent of adults across cultures suffer from chronic insomnia (Lamberg, 2005). Insomnia is often defined by sleeping problems. People who suffer from insomnia may encounter difficulty of getting to sleep or staying asleep, or having non-refreshing sleep, to some degree. The poor quality of sleep is naturally followed by functional impairment while awake (Scott et al., 2011). Insomnia is secondary to other conditions. Indeed, it may stem from life events, mental disorders, pain, hormone shift and alcohol usage, to name but a few. Insomnia can be treated by synthetic medicines. Some insomniacs rely on sleeping tablets such as benzodiazepines and newer nonbenzodiazepines to get rest (Smith and Tett, 2010; Richey and Krystal, 2011). Despite clinical success, these medicines have a number of problems in use. Apart from daytime fatigue and cognitive impairment as side effects of these sedatives (Zlott and Byrne, 2010; Hendler et al., 1980), they may engender physical dependence (Blais and Petit, 1990). On the other hand, insomnia can be treated by herbal remedies. Some insomniacs are inclined to take medicinal plants owing to low frequency of side effects. Several medicinal herbs have been used throughout the world (Wing, 2001). Moreover, the usage of herbal medicines has come to Iranian people since ancient times and apparently still serves a key role

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in the arsenal of medicines in modern medicine. In fact, various climates in Iran exert a crucial role in distribution of plants used in traditional medicine. To date, several reviews have been published with respect to hypnotic impacts of herbal remedies throughout the world (Kim et al., 2011; LaFrance et al., 2000). We previously published a review on Persian herbal medicines with anxiolytic properties (Rabbani et al., 2011). Nonetheless, a comprehensive review has been absent with regard to hypnotic effects of herbs used in Iranian traditional medicine. Therefore, this paper reviews the literature pertaining to medicinal herbs used for treatment of insomnia in Iran.

Coriandrum sativum

Coriandrum sativum is an herb which is currently cultivated in Iran. It is popularly referred as Geshniz in Persian. In addition to the extensive use of *Coriander* leaves in Iranian recipes, various parts of this plant such as seed, leaf, flower and fruit have been used in Iranian traditional medicine (Pathak Nimish et al., 2011). Emamghoreishi et al. (2005) reported that *coriander* seeds led to a decrease in spontaneous activity in mice and therefore exhibited a sedative effect. Thereafter, Emamghoreishi and Heidari-Hamedani (2006) investigated the hypnotic and sedative activities of aqueous or hydro-alcoholic extracts and essential oil of *coriander* seeds in male albino mice by means of pentobarbital-induced sleeping time test and Animex activity meter. Aqueous extract with doses of 200, 400 and 600 mg/kg, hydro-alcoholic extract with doses of 400 and 600 mg/kg, and essential oil with a dose of 600 mg/kg were found to increase pentobarbital-induced sleeping time. It was also demonstrated that aqueous extract at doses of 50, 100 and 500 mg/kg significantly declined spontaneous locomotor activity. They pointed out that although the extracts and essential oil of *coriander* seeds exerted sedative and hypnotic influence, aqueous extract was assumed to be mainly responsible for the hypnotic effect.

Rosa damascene

Rosa damascene is cultivated in central Iran and known as Gole Sorkh. It is an erect shrub that grows about 1 to 2 meters with colorful and large flowers. In Iranian traditional medicine, flowers, petals and hips are administered to treat insomnia. It was shown that not only did *R. damascene* inhibit the reactivity of the hypothalamus and pituitary systems in rats, but also it suppressed the activity of the central nervous system (Libster, 2002). Rakhshandah and Hosseini (2006) examined the hypnotic effect of ethanolic, aqueous and chloroformic extracts of *R. damascene* by means of pentobarbital-induced sleeping time test (30 mg/kg, i.p.) in mice and demonstrated that this herb can relive insomnia. Intraperitoneal doses of 500 and 1000 mg/kg of ethanolic and aqueous extracts were demonstrated to produce hypnotic effect which was comparable to diazepam. The hypnotic effect of aqueous extract was induced dose dependently, notwithstanding the maximum effect of this extract at the dose of 500 mg/kg. Chloroformic extract-treated mice did not show any hypnotic effect. In another study, hypnotic effect of *R. damascene* extract and fractions (ethanol extract, N-butanol fraction, ethyl acetate fraction, aqueous fraction) was assessed based on prolongation of pentobarbital (diazepam)-induced sleeping time in mice (Rakhshandah et al. 2007). They found that ethanol extract and fractions of *R. damascena* at doses of 250 and 500 mg/kg increased the sleeping time in mice. Aqueous fraction of *R. damascene* had the minimum hypnotic influence. However, ethyl acetate fraction showed maximum hypnotic influence at a dose of 500 mg/kg.

To date, no single study has covered the mechanism in which *R. damascene* extract or fractions produce their hypnotic effect. Nevertheless, Noguerira and Vassilieff studied the hypnotic effect of the other geniuses of Rosaceae family, that is, *Rubus*

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brasiliensis and suggested that a benzodiazepine-like principle in hexanic fraction of this herb induced the hypnotic effect through GABAa system (Nogueira and Vassilieff, 2000).

Crocus sativus

Saffron stigma (*Crocus sativus*), is the world's most expensive herb. It is cultivated in north east of Iran and called as Zafaran in Persian. Saffron, a spice derived from the flower of the saffron crocus, is found almost in every kitchen in Iran. Additionally, Saffron stigma has traditionally been administered in order to prevent insomnia. Sedative and hypnotic effects of Saffron aqueous extract and its constituents, crocin and safranal formed the central focus of a study by Hosseinzadeh and Noraei (2009) in which the authors found that Saffron aqueous extract and Safranal showed sedative and hypnotic effects. They administered agents intraperitoneally to mice before tests of sodium pentobarbital-induced sleeping time (30 mg/kg) and locomotor activity (open field test). It was then mentioned that the decline in locomotor activity caused by aqueous extract was dose dependent, and Saffron only with a dose of 0.56 g/kg prolonged the total sleeping time in the hypnotic test. Crocin was identified to have no anxiolytic, hypnotic or myorelaxation effects. Safranal was shown to increase the total sleeping time dose dependently. However, at lower doses (0.05 and 0.15 mL/kg), it decreased some parameters of locomotion activity. It was also demonstrated that Safranal had no effects on motor coordination.

Salvia leriifolia

Salvia leriifolia, which is known as Noruzak, is endemic to Khorasan province of Iran. It has traditionally been used for its various health benefits. It is generally thought that it can relive pain, decrease blood sugar and treat inflammation and insomnia. Hosseinzadeh and Hassan Zadeh (2001) investigated sedative and hypnotic effects of extract of *S. leriifolia* on mice by means of thiopental-hypnosis test. Aqueous decoction extract at intraperitoneal doses of 1.15 and 1.57 g/kg was shown to slightly increase the total sleeping time up to 20.58 minutes versus 63.67 minutes in diazepam (3 mg/kg). Relaxation of skeletal muscles was also assessed by traction test. An intraperitoneal treatment of the extract (0.29-2.87 mg/kg) caused relaxation in muscles; even so, muscle relaxation induced by the extract with a low dose of 0.29 mg/kg was found to be as effective as relaxation produced by diazepam (1 mg/kg). In another study, preliminary phytochemical test showed that the extract was composed of low amount of flavonoid, but enriched with tannin and saponin (Hosseinzadeh and Hassan Zadeh, 2001). Nevertheless, the mechanism in which they produce effect has not been well characterized.

Salvia reuterana

Salvia reuterana, which is commonly known as Mariam Goli Esfahani in Iran, has been mostly found in highlands of center of Iran. The aerial parts of this herb have been used in Iranian traditional medicine owing to its sedative and anxiolytic effects. Perry et al. (2003) reported that the mechanism of inhibition of acetylcholinesterase by constituents of *S. reuterana* was responsible for its sedative effects. In addition, it was reported that Miltirone inhibited the binding of [3H]flunitrazepam to central benzodiazepine receptor; and elucidated a major role for GABA receptor in its mechanism (Lee et al., 1991). Another study investigated volatile constituents of *S. reuterana* and showed that there are 21 components in the oil of plant (Mirza and Sefidkon, 1999). The authors found that (E)-β-Ocimene (32.3 %), α-gurjunene (14.1 %), germacrene-d (11.2 %) and hexyl acetate (7.6 %) were the major constituents in the oil of *S. reuterana* (Mirza and Sefidkon, 1999). In our previous study, we assessed sedative effect of hydroalcoholic extract of *S. reuterana* in mice by means of spontaneous locomotor activity test at a

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dose of 100 mg/kg (Rabbani et al., 2005). The total locomotor activity count measured in 15 minutes of the test was found to be significantly decreased in animals which received diazepam pretreatment and *S. reuterana* extract treatment. It is interesting to note that a decline in locomotor activity was also evident in 5 minutes. We also observed that an increase in the dose of the plant extract leaded to higher sedative properties.

Stachys lavandulifolia

Stachys lavandulifolia is widely distributed in Iran and known as Chaye Kuhi. As well as being administered for several medicinal purposes, the traditional use of *S. lavandulifolia* for its hypnotic and sedative effects has been of great importance. Rabbani et al. (2003) studied the impacts of *S. lavandulifolia* extracts upon ketamine-induced sleeping time and locomotor activity tests in mice and demonstrated that the extract produced hypnotic and sedative activities. It was shown that intraperitoneal doses of 100 and 300 mg/kg of *S. lavandulifolia* extract significantly prolonged the duration of sleep by 28 and 42 percent, respectively. It was also reported that a treatment with plant extract at doses of 100 or 300 mg/kg (30 minutes prior to ketamine treatment), significantly shortened the initiation of induced sleep (latency time) by 24 and 25 %, respectively. Moreover, they mentioned that the locomotor activity significantly diminished in *S. lavandulifolia*-treated mice at a dose of 100 mg/kg. The authors then demonstrated that at all three time intervals (5, 10 and 15 minutes), the decline in locomotor activity was evident; even so, greatest decline in locomotor activity was found to be during the initial 5 minutes.

Moreover, the mechanism of action of constituents of *S. lavandulifolia* has not yet been completely worked out, and only a few studies have been carried out on its active constituents. It was demonstrated that *S. lavandulifolia* contained volatile oil and a phenyl propanoid glycoside (Basaran et al., 1988; Sezik and Basaran, 1985).

CONCLUSION

Insomnia is a major health concern throughout the world and a highly prevalent sleep disorder in Iran. To elude deleterious side effects of artificial medicines abating insomnia, there has been a propensity for herbal remedies. Despite the fact that plants have been used in Iranian traditional medicine in order to preclude insomnia for centuries, special attention has recently been devoted to them as alternatives for synthetic medicines in Iran. In fact, plausible justification provided by previously mentioned Iranian studies has made it difficult to trivialize the role of these medicinal herbs in treatment of insomnia. Various herbs have been used for reliving insomnia in Iranian traditional medicine, *Valeriana officinalis*, Blue violte, *Salix aegyptiaca*, lotus flower, lettuce, and *Echium amoenum*, to name but a few. It is interesting to note that in our previous study, we investigated the sedative and hypnotic effects of *E. amoenum* by means of locomotor activity and ketamin-induced sleeping tests. The ethanolic extract of this plant increased the latency time and excreted no effect on total sleeping time. This extract also did not produce a significant effect in locomotor activity test. As a result, we suggested that this herb did not exhibit sedative and hypnotic effects (Rabbani et al., 2004).

Considering the fact that reviewed studies have been carried out on animals, further research on human provides a better insight concerning hypnotic and sedative effects of herbal medicines and approves their efficacy. Nonetheless, many pharmacological and toxicological studies are needed to be conducted prior to clinical trials. In fact, more work should be done to establish active constituents of these herbal medicines used for insomnia treatment. What has to be finally considered is that these medicinal herbs have not yet been approved. Therefore, they should undergo several approval processes. Indeed, there is

a long way from laboratory to market for these herbal medicines.

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