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Plant-Derived Compounds with Potential Sedative and Anxiolytic Activities

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Abstract – *A wide variety of active phytochemicals such as flavonoids, alkaloids, saponins, etc., have been isolated and identified in different plants. Pharmacological and chemical investigations of medicinal plants have provided important advances in therapeutic approach to several pathologies as well as extremely useful tools for the theoretical study of physiology and pharmacology. With increased use of herbal medicine, medicinal plants are receiving more attention from the scientific and pharmaceutical communities. Several compounds have been isolated and evaluated for their sedative and anxiolytic properties. Although most of the reported works are more of academic interest and very few find entry at clinical trials; one is hopeful that as more discoveries of sedative and anxiolytic compounds from plants are made, it will lead to generation of more effective drugs.*

Key Words – *plants; sedative; anxiolytic; sleep; phytochemicals*

1 Introduction

One of the ailments that cut across all ages around the world is insomnia. Insomnia is the inability to fall asleep or an un-revivifying sleep. It is a prevalent and potentially serious condition that affects the well-being of individuals. There is enough evidence that insomnia is under-recognized, under-diagnosed and under-treated. Insomnia can be triggered by Psychological (such as stress, anxiety and depression), environmental (excess cold, heat, etc), dietary, medical (such as cough, chronic pain, apnea, circadian rhythm disorders, neural diseases, etc) and drug related causes [1].

Insomnia is treated pharmacologically and non-pharmacologically or a combination of both [2]. Relaxation, sleep restriction, stimulus control and sleep hygiene are known behavioural therapies for insomnia [3]. People who suffer from insomnia take prescription drugs such as benzodiazepines, zolpidem, zopiclone, zaleplon to sleep [4]. These drugs help to calm the nerves, reduce anxiety and decrease awareness of one's surroundings. Drugs containing H1 antagonist diphenylhydramine are also used for the treatment of occasional insomnia [5]. These drugs can easily lead to dependency and addiction. Apart from these negative factors, there could also be side effects such as drowsiness, dizziness, depression, nausea, etc. In order to eliminate these negative factors and the expected side effects researchers have resorted to nature for alternative ways of alleviating insomnia. The occurrence of natural products with medicinal properties has led to the widespread use of herbal remedies across the world. This is as a result of the development of several drugs and chemotherapeutics from medicinal plants [6].

In recent years, more and more studies have been conducted on the components and the pharmacological properties of these plants [7-9]. There are over 120 pharmaceutical products currently in use and some of these products were discovered through the use of these plants in traditional medicine. Medicinal plants constitute another option in the treatment of insomnia. There are many plants all over the world that the traditional health practitioners refer to as sleep inducers and tranquillizers that have been used to combat insomnia [10].

The aim of this review work is to bring to light the chemical components present in plants that have been shown to possess sedative and anxiolytic activity.

2 Method

The materials required were obtained online, university libraries and databases. The review work covers the period 1970-2013.

3 Result

Traditional health practitioners treat insomnia by making herbal preparations from leaves, stems, barks and roots of medicinal plants. Tea made from these plants and taken has been shown to be quite effective. Researchers have taken a step further to isolate and determine those bioactive principles in these plant parts; and there modes of action. A number of modern therapeutic agents have been derived from tropical forest species. Most pharmaceutical products currently in use are plant derived and some 75% of these were discovered by examining the use of these plants in traditional medicine. The isolated compounds are categorized into the following classes of phytochemicals (terpenoids, flavonoids, alkaloids, saponins, etc). Also considered are the sedative properties of different extracts and other compounds which are not referred to as phytochemcals. In this review work, a total of 28 plant families and 54 plant species were reported to exhibit sedative and/or anxiolytic properties. It was noted that Lamiaceae has the highest number of species with sedative and anxiolytic effects. Figs. 1-6 show the structures of some of the isolated pure compounds while Tables 1 shows the different plant species, plant parts and some countries where they can be found.

3.1 Terpenoids

Many essential oils and monoterpenes are used therapeutically as relaxing drugs and traquilizers. The monoterpenes are present in volatile oils of many plant species such as *Mentha piperita, Zanthoxyum schinifolium and Mentha X villosa* [11]. Recently, much attention has been focused on the sedative, relaxant activities and behavioural effect of medicinal plants in aromatherapy. It is believed that the inhalation of fragrance is a powerful means of relaxation. Some of the odours are used to treat depression, anxiety and tension. The inhalation of the crude extract of *Kaempferia galanga* L showed sedative effects at doses of 1.5 mg [12]. The essential oils Linalool [13]. 1, 8-cineole [14] and α-terpineol [15] were shown to possess sedative properties.

Wesolowska et al., (2006) [16] showed that the bitter sesquiterpene lactones, Lactucin and Lactucopicrin which were isolated from *Lactuca virosa* and *Cichorium intybus* exhibited sedative properties in the spontaneous locomotor activity test on mice. Galphimine B, a nor-secotriterpenoid from *Galphimia glauca* (cav.) Kuntze (Malpighiaceae) was shown to exhibit a strong depressant activity on the nervous system [17, 18]. A-gurjuene, benzyacetone and (+)- Calarene which are the

main constituents of Agarwood oil (*Aquilaria sinensis*) and Spikenard (*Nardostachys jatamansi*) exhibited sedative activity when tested on mice; but it was noted that the most effective dose of the compounds was lower than their original content in the oil (α-Gurjuene (1.5%), Calarene (0.17%), Benzylacetone (0.1%)) [19]. The phytochemical screening of *Myricaria elegans* Royle (Tamaricaceae) led to the isolation of six terpenes from the chloroform fraction (Eleganene-A, eleganene –B, Corsolic acid, Betulin, Ursolic acid and Erythrodiol). These compounds were suggested by the researchers to be responsible for the mild sedative activity of the plant [20].

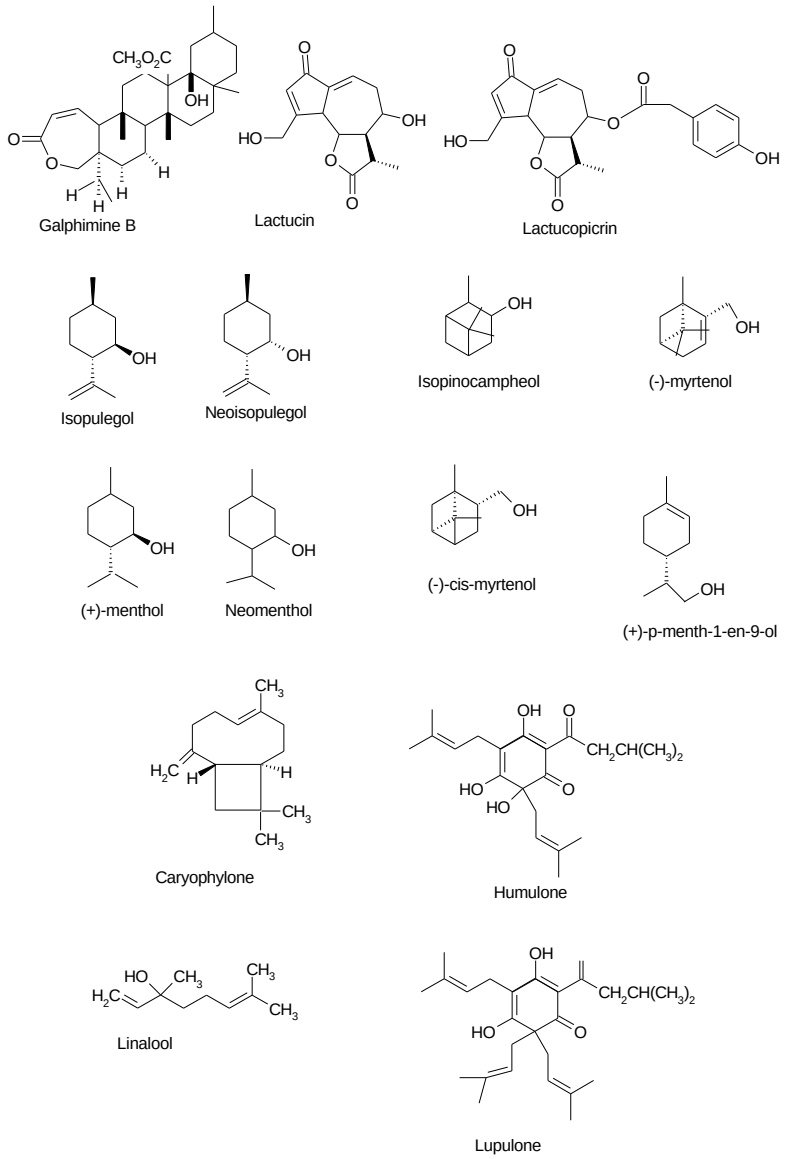


Fig. 1: Terpenoids with sedative and anxiolytic effects

A preliminary study of the sedative effect of monoterpene alcohols in mice led to the isolation of isopulegol, neoisopulegol, (±)-Isopinocampheol, (-)- myrtenol, (-)-cis-myrtenol, (+)-p-menth-1-en-9-ol and (±)-neomenthol. These compounds exhibited a depressant effect in pentobarbital-induced sleep

test, indicating a sedative property [11]. It was reported that Linalyl acetate isolated from *Lavandula angustifolia* Mill possess sedative activity. Caryphyllone and linalool volatile oils obtained from *Milissa officinalis* L. were shown to be responsible for the plants sedative properties. The resins humulone, 2-methyl-3-butane-2-ol and lupulone which are the main ingredients found in *Humulus lupulus* have been shown to possess sedative action [21].

Investigation of the seed oil of jujube seed (*Zizyphus vulgaris*) showed that it possesses sedative properties [22]. *Aniba rosaedora* is an aromatic plant which is used in Brazil folk medicine for the treatment of insomnia. It was observed that the administration of the oil at doses of 200 and 300 mg/kg significantly decreased latency and increased sleeping time duration. The 100 mg/kg dose was shown to significantly potentiate the pentobarbital action thereby decreasing pentobarbital latency time and increased the sleeping time [23].

3.2 Flavonoids

Albizzia julibrissin Durazz flowers are used as sedatives in oriental traditional medicine. The phytochemical study of this plant led to the isolation of two flavonol glycosides, quercetrin and isoquercetrin. These compounds were observed to increase pentobarbital-induced sleeping time in a dose-dependent manner in mice [24].

Binding assays conducted on two CNS inhibitory targets: benzodiazepine and GABA (A) receptors showed that Luteolin-7-diglucoronide isolated from *Lippia alba* possess sedative properties with half maximal inhibitory concentration (IC_{50} = 101 and 40 micron respectively) [25]. The flavonoids Swertisin, Spinosin, 6'''-sinapoylspinosin, 6'''- feruloylspinosin and p-coumaroylspinosin isolated from the seeds of *Zizyphus vulgaris* Lamark var. spinosus Bunge (Rhamnaceae) were identified as some of the active principles responsible for its sedative properties. It was observed that the effective doses of these compounds were somewhat higher than expected for the pure effective components [26].

The seeds of *Ziziphus jujuba* Mill var. spinosa (Bunge) Huex. H. F. Chou are used as sedatives in China. Out of the eight flavonoids isolated from it only two of them (spinosin and Swertish) were shown to possess significant sedative activity. The oral administration of spinosin and swertish (4 x 10-5 mol/kg) was observed to prolong pentobarbital induced sleeping time by 29-31% when compared to the control. It was believed by some authors that the spinosin isolated from *Zizyphus. jujuba* is responsible for the sedative activity of the plant [26].

It was reported by Marder et al., (2003) [27] that the flavonoid 2S (-)-hesperidin isolated from *Valeriana officinalis* has sedative and sleep enhancing properties whereas 6-methylapigenin also isolated from *Veleriana officinalis* exhibited ability to increase the sleep enhancing properties of hesperidin. The sedative activity of the butanol fraction was attributed to the presence of flavonoids which constitute the major part of the butanol fraction [28]. Apigenin isolated from *Chamomilla recutita* (L) Rausch was shown to possess a mild sedative effect and a clear anxiolytic activity [29]. Nisar et al., (2011) [30] observed that the sedative property of *Eremostachys laciniata* (L) Bunge (Lamiaceae) was due to the presence of luteolin which is one of the 5 flavonoids isolated from in the plant.

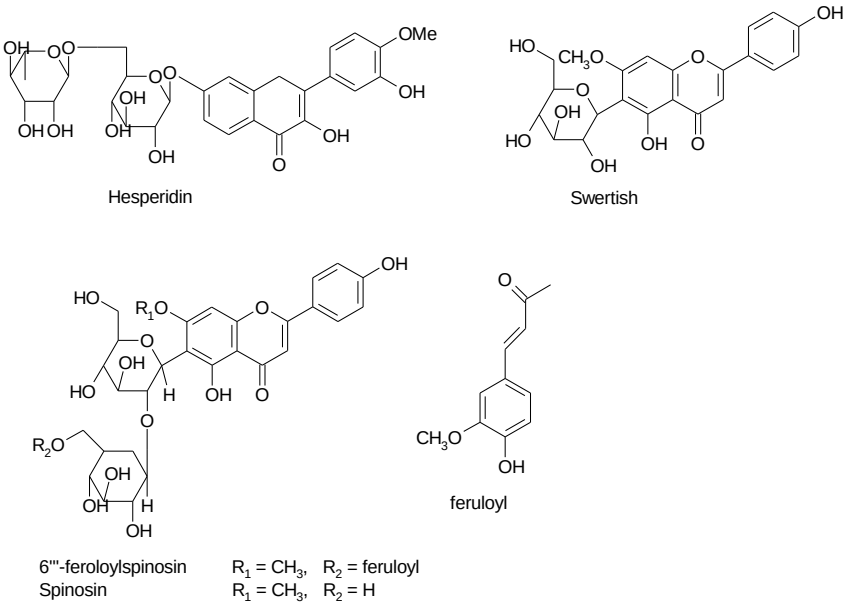


Fig. 2: Some flavonoids with sedative and anxiolytic properties

3.3 Alkaloids

Nugroho et al., 2012 [31] conducted animal experiments using the compounds isolated from the medicinal plant, *Salvia plebeia* (Labiatae). They showed that one of the isolated compounds, Rosmarinic acid was active at 10 mg/Kg (p.o) using pentobarbital-induced assay in mice. The researchers observed that Rosmarinic acid comprised the largest proportion in the plant (28.5% of the methanolic extract, 33.0% of the ethyl acetate extract, 4.46% of the dry weight of the *S. plebeia*). Sanjoinine-A and Nuciferine are alkaloids isolated from Sanjoin (*Zizyphus vulgaris*) showed strong sedative activity. Sanjoinine-A was observed to be very potent at a dose of 3 mg/Kg.

The alkaloids in sanjoin were found to exist in certain ratios and some drug interactions such as additivity, synergistic or counteracting interaction was postulated. In order to determine if there was any additivity, synergistic or counteracting interaction between the alkaloids isolated from the plant; the potent alkaloids were co- administered with the non-potent alkaloids. Coclaurine and sanjoinine-A were co-administered with nuciferine and sanjoinine-A with coclaurine. It was observed that there is additivity between sanjoinine-A and nuciferine, while coclaurine did not enhance the sedative activity of sanjoinine-A. The sedative activity of the alkaloid was monitored by measuring the hexibarbital induced sleeping time. It was also postulated that since the major constituent of the butanol fraction obtained was zizyphusine, a quartinary aporphine alkaloid which did not exhibit any sedative activity; the sedative activity of the butanol fraction was attributed to the presence of flavonoids or the minor components such as aporphine alkaloids (caeverine, N-methylasimilobine and Norisocorydine). It was also reported that sanjoinine-A and sanjoinine Ahl are interconvertible at a temperature of 220^{o}C but not at a low temperature treatment such as boiling in a water bath [32].

It was shown that the compounds atropine, hyoscyamine and scopolamine induce sleep and abolish the awaking effect. These compounds isolated from *Atropa bell-donna* L and *Datura stramonium* L. (Solanaceae) are thought to be responsible for the use of this plant in the treatment of insomnia [33]. The alkaloids lysergic acid amide, ergonovine, chanoclavine-1 and N-formylloline isolated from a

methanolic extract of endophyte-infected sleepygrass (*Stipa robust*) were shown to be responsible for the observed effects of sleepygrass on livestocks [34].

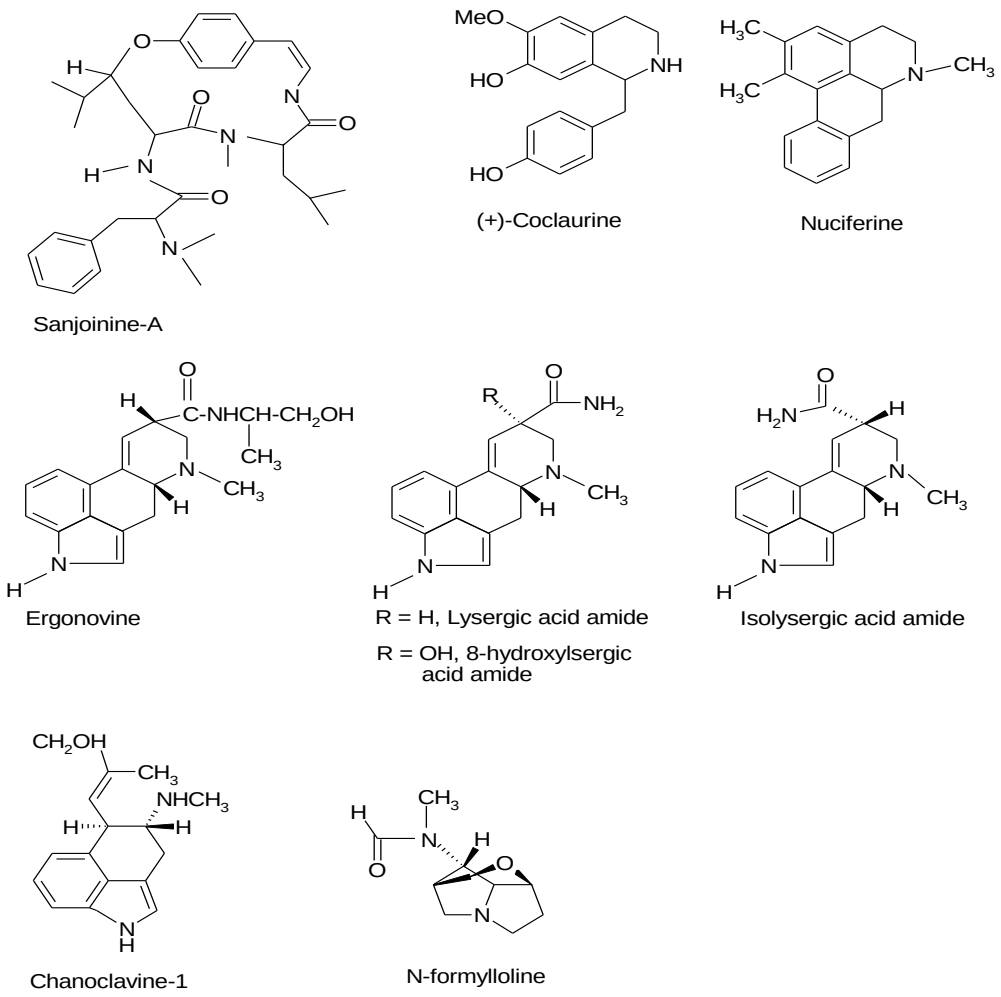


Fig. 3: Alkaloids with sedative and anxiolytic effects

3.4 Steroids

Two bufadienolides known as diagremontianin and bersaldegenin-1, 3, 5-orthoacetate isolated from *Kalanchoe diagremontiana* were shown to have a pronounced sedative effect [35, 36]. Aquirre-Hernandez et al., (2007) [37] observed that β-sitisterol isolated from *Tillia americana* var, Mexicana exhibit sedative activity at a dose of 30 mg/Kg in mice. A dose response curve of β-sitisterol in the range of 1-30 mg/kg doses indicated that this compound produces an anxiolytic-like action from 1-10 mg/kg and a sedative response when the dose was increased to 30 mg/kg. These effects were observed to resemble those produced by diazepam (0.1 mg/kg).

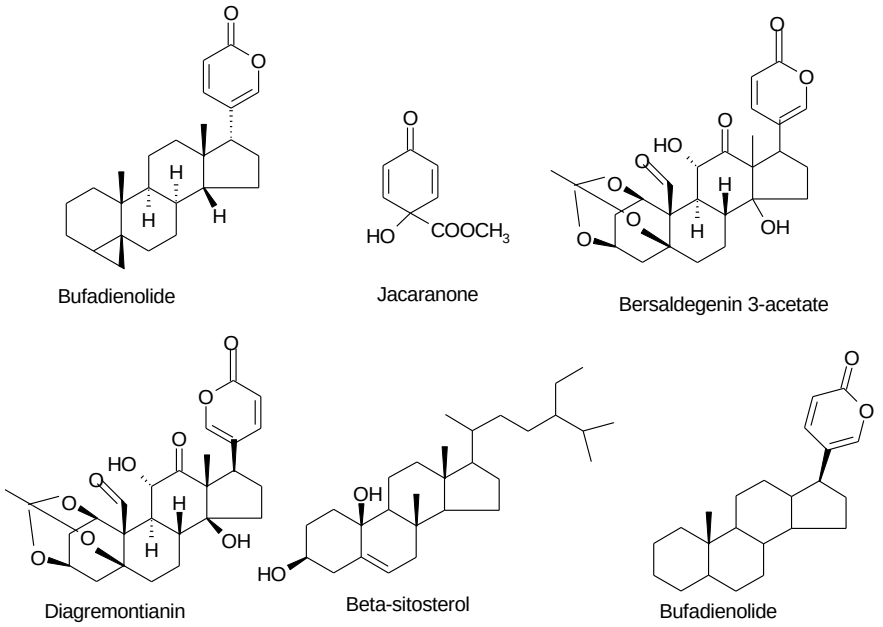


Fig. 4: Steroids with sedative and anxiolytic effects

3.5 Saponins

The saponins jujuboside A and B isolated from the seeds of *Zizyphus vulgaris* Lamark var. spinosus Bunge (Rhamnaceae) was thought to be partly responsible for the sedative property of the plant Wu et al., (2010) [38] observed that jujuboside A had no inhibitory activity but exerts a synergism with phenylalanine on the central nervous system function, therefore concluded that jujuboside A is not a sedative agent. But Jiang et al., (2007) [39, 40] showed that saponins extracted from the species *Ziziphus jujuba* Semen that grows in China exhibited significant effect on walking time and coordinated movement, and prolonged the suprathreshold barbiturate induced sleeping time.

3.6 Quinoids

Ternstroemia pringlei is used in Mexico for the treatment of insomnia. Bioactivity guided fractionation of the methanolic extract led to the isolation of the sedative compound jacaranone which is a quinoid. It gave a dose-dependent response of ED_{50} = 25 mg/Kg mouse weight [41].

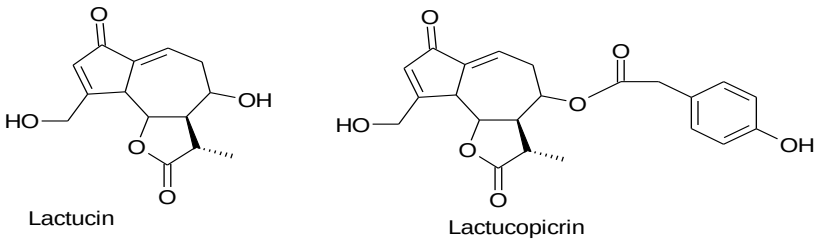
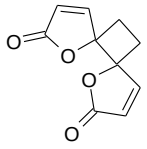


Fig.5: Quinoids with sedative effects

3.7 Compounds not referred to as phytochemicals

3.7.1 Lactones

Two lactone compounds protoanemonin and anemonin isolated from the flowering aerial parts of *Pusatilla alpine* Subsp. Apiifolia were shown to exhibit sedative activity [42].



Anemonin

Fig. 6: A lactone with sedative effect

3.7.2 Cannabinoid

Pickens (1981) [43] showed the sedative activity of cannabidiol which was isolated from *Cannabis sativa.* It was observed to be the major constituent of the plant, representing about 40% in its extract.

3.7.3 Cinnamates

Ethyl trans-p-methoxycinnamate and ethyl cinnamate obtained from the n-hexane extract of *Kaempferia galanga* was shown to possess sedative effects at 0.0014 g and 0.0012 mg respectively. They showed significant reduction of locomotor activity [12].

3.7.4 Nitrite

Ixora pavetta Vahl. (Rubiaceae) is a small tree whose flowers are used for the treatment of insomnia. The amyl nitrite isolated from the flowers exhibited sedative effects [44].

3.7.5 Valepotriates and iridoids

In Bulgaria *Valeriana officinalis* L. (Valerianaceae) roots are used to treat insomnia. Its powerful sedative action was observed to be due to the presence of valepotriates and epoxy-iridoid esters [45].

3.8 Extracts

Mentha arvensis Linn (Labiatae), a plant used in traditional medicine in India was explored for its pharmacological activities. It was observed that the methanolic extract of the leaves showed potentiation of pentobarbitone induced sleeping time. The sedative activity was based on the fact that the CNS depressant drugs potentiate a sub-hypnotic dose of pentobarbitone [46]. The aqueous extract

of the stems of *Cissus quadrangularis* Linn strongly increases the total sleep time induced by diazeparm (50 mg/kg i.p). This plant is found in the savannah areas in Africa [47, 48].

Bhadoriya et al., (2009) [49] reported that the methanolic extract and essential oil of *Zanthoxylum budrunga* W exhibited sedative activity in albino mice. *Byrsocarpus coccineus* Schum and Thonn (Connaraceae) is a shrub found in west and central African countries and used to aid sleep. The Y-maze, elevated plus-maze and hexabarbitone sleeping time and hole-board models were used to investigate the sedative activity of this plant. It was observed that doses of 50 and 100 mg/kg significantly increased the cumulative time spent in the open arms in the Y-maze and elevated plus-maze models. At these doses with hexabarbitone sleeping time test, an increase was observed at the onset and then a decrease in the duration of sleep. But at dose 200 and 400 mg/kg the duration of sleep was observed to have increased significantly; while the effects in the hole-board method were observed not to be significant. This shows that the plant possess dose dependent anxiolytic and sedative properties with no exploratory activity and locomotion as reported by the researchers. The researchers suggested that the sedative and anxiolytic properties are as a result of the presence of flavonoids, alkaloids and terpenoids in the plant [50].

The crude hexane extract of *Tillia americana* var mexicana at 10 and 30 mg/kg i.p and some pooled fractions at the same doses were observed to potentiate sodium pentobarbital-induced sleeping time and caused a significant increase in the time spent at the open-arm sides in the plus-maze test. A reduction in the exploratory behavioural pattern was reported to manifest as ambulatory activity [51]. *Dolichandrone falcata* seem (Bignoniaceae) is a deciduous tree that thrives well in India. 400 mg/kg of the ethyl acetate extract of the stem bark was shown to produce a significantly high anxiolytic effect in a dose dependent manner by increasing the time spent on and the number of entries into the open arms of the elevated plus-maze and by decreasing the number of marbles buried by mice in marble burying test [52].

Okomolo et al., (2011) [53] showed that the plants *Millettia thonningii, Ocinum sanctum* and *Securitaca longepedunculaca* which are used in Cameroon traditional medicine to induce sleep possess significant sedative activity. They were shown to increase significantly and in a dose dependent manner the total sleep time induced by diazepam. *Ducrosia anethifolia* (DC) Boiss. (Apiaceae) grows in the wild in Iran. It is also found in Afghanistan, Pakistan, Syria, Lebanon, Iraq and countries along the Persian Gulf. Using the elevated plus-maze assay, this plant was shown to increase the percentage of open arm time and entries at a dose range of 25-200 mg/kg. the plants essential oil was also reported not to suppress spontaneous motor activity and did not alter the katamine-induced sleep parameters indicating that the essential oil do not possess any sedative effect [54].

The methylene chloride, ethanol and ethyl acetate extracts of *Lavendula angustifolia* Mill, *Melissa officinalis* L, *Origanum vulgare* L, *Crataegus monogyna* Jaeq, and *Crataegus oxyacantha* L exhibited sedative activity. This activity was attributed to the presence of flavonoids, polyphenolics and triterpenoid compounds [55].

Cecropia pachystachya Mart. is a herbal medicine used extensively in south America. It is found in neotropical rainforest in Argentina and in temperate regions. Both types were found to decrease the spontaneous locomotion and exploratory behaviour in mice at doses between 180-600 mg/kg. It was shown that the neotropical species could potentiate the effect of 3.0 mg/kg diazepam but was not antagonized by 0.5 mg/kg flumazenil. Amphetamine at 5 mg/kg was able to prevent its sedative effect. The researchers recommended that its sedative effect could be helpful in the treatment of cough [56].

Casimiroa pringlei is native from Mexico and Central America. The sedative activity of this plant was evaluated using wistar rats as experimental models. It was noted that in the Irwin test carried out that the extract oil exhibited similar behavioral, sensory and motor effects to those induced by bromozepam and significantly different from the effects of caffeine administration. In the elevated plus-maze test, it was noted that the extract increased exploration of the open arms without decreasing spontaneous activity in the open field. It was also observed that a higher dose (1000 mg/kg) significantly reduced open filed activity. The researchers concluded from these results that the plant extract possesses anxiolytic effect [47].

The plants *Citrus sinensis, Citrus limon, Ternstroemia pringlei, Ternstroemia sylvatica, Casimiroea edulis, Galphimia glauca*, and *Cymbopogon citratus* are used in Mexico traditional medicine to aid sleep. The researchers noted that the most active extracts were those of *Galphina glauca* methanolic extract (ED_{50} = 20.06 ± 5.6 mg/kg) and *Cymbopogon citratus* hexane extract (ED_{50} = 27.01 ± 2.9 mg/kg), *Citrus senensis* leaves methanolic extract (ED_{50} = 38.48 ± 8.0 mg/kg) and the flowers (ED_{50} = 47.04 ± 12.0 mg/kg), whereas *Ternstroemia sylvatica* ethanolic extract (ED_{50} = 61.88 6.42 mg/kg), *Galphimia glauca* hexane extract (ED_{50} = 76.85 ± 20.9 mg/kg) and *Cymbopogon citratus* dichloromethane extract (ED_{50} = 77.11 ± 15.0 mg/kg) exhibited a lower sedative activity [57]. Akindele et al. (2012) [58] investigated the anxiolytic activity of the hydroethanolic extract of the aerial parts of *Allium ascalonicum* (Lilliaceae) using hole-board, elevated plus-maze, light/dark exploration, open field and social interaction tests. The researchers noted that peak anti-anxiety effects occurred at the dose of 100mg/kg showing that the plant extract contains anxiolytic properties.

Table 1: Some medicinal plants used in the treatment of insomnia

Botanical name	Family	Plant part used	Some locations where found	Reference
Mentha piperita	Lamiaceae	Volatile oil	Bulgaria, Egypt, Greece	Sousa et al., 2007
Zanthoxyum schinifolium	Rutaceae	Volatile oil	Japan, Korea, China	Sousa et al., 2007
Mentha viollosa	Lamiaceae	Volatile oil	NS	Sousa et al., 2007
Kaempferia galanga L	Zingiberaceae	Volatile oil	India	Huang et al., 2008
Lactura virosa	Asteraceae	NS	England, Australia, Pakistan, India	Wesolowska et al., 2006
Cichorium intybus	Asteraceae	NS	USA, Canada, France	Wesolowska et al., 2006
Galphimia glauca (cav.) Kuntze	Malpighiaceae	NS	Mexico	Teketa et al., 2004
Aquilaria sinensis (Agarwood)	Thymelaeaceae	Volatile oil	India	Tekemoo et al., 2008
Nardostachys jatamansi (Spikenard)	Valerianaceae	Volatile oil	India , Egypt, Rome	Tekemoo et al., 2008
Myricaria elegans Royle	Tamaricaceae	NS	East Asia, India	Khan et al., 2010
Lavandula angustifolia Mill	Lamiaceae	NS	Spain, Mediterranean region	Ravitzky, 1996

Botanical name	Family	Plant part used	Some locations where found	Reference
Millissa officinalis L	Lamiaceae	Volatile oil	Southern Europe, Mediterranean area	Ravitzky, 1996
Humulus lupulus	Cannabaceae	Leaves	Europe, Asia, North America	Ravitzky, 1996
Albizzia julibrissin Durazz	Fabaceae	Flowers	Asia	Keng et al., 2000
Lippia alba	Verbenaceae	NS	South America, Caribbean, Texas	Hennbelle et al., 2008
Zizypus vulgaris Lamark var. spinosus Bunge	Rhamnaceae	Seeds	China	Chin et al., 1981
Ziziphus jujuba Mill var spinsa (Bunge) Huex. H. F. Chou	Rhamnaceae	Seeds	China	Cheng et al., 2000
Valeriana officinalis	Valerianaceae	Roots	Bulgaria	Mader et al., 2003
Chamomilla recutita (L) Rausch	Asteraceae	NS	North America, Asia, Europe, Australia	Mader et al., 2003
Eremostachys laciniata (L) Bunge	Lamiaceae	NS	Mediterranean area	Nisar et al., 2011
Citrus senensis	Rutaceae	Leaves	Mexico	Gutierrez et al., 2009
Citrus limonum	Rutaceae	Leaves	Mexico	Gutierrez et al., 2009
Ternstroemia pringlei	Theaceae	Dried fruits	Mexico	Gutierrez et al., 2009
Ternstroemia sylvatica	Theaceae	fruits	Mexico	Gutierrez et al., 2009
Casimiroea edulis	Rutaceae	NS	Mexico	Gutierrez et al., 2009
Cymbopogon citratus	Poaceae	NS	Mexico	Gutierrez et al., 2009
Salvia plebeia	Labiatae	NS	Asia, Africa	Nugroho et al., 2010
Atropa belledonna	Solanaceae	NS	Europe, Asia	Ivandera et al., 2006
Datura stramonium L	Solanaceae	NS	Africa, Europe	Ivandera et al., 2006
Stipa robust	Poaceae	Leaves	Southern USA	Petroski et al., 1992
Kalanchoe diagremontiana	Crassulaceae	NS	SW Madagascar, Florida, Puerto Rico, Hawaii, Canary Island	Supratman et al., 2005
Allium ascalonicum Linn.	Lilliaceae	Aerial parts	Africa	Akindele et al., 2012

NS – Not stated

4 Discussion

In the last decade there has been a worldwide renewed interest in indigenous medicine. In poor countries, the healthcare is based on the cultural or traditional methods, although modern medicine may be available in some communities. But the interest in herbal remedies has led to the search of new phytochemicals that could be potentially useful as new drugs for the treatment of insomnia. Some of these compounds have complex structures that present no possibility of synthesis. These compounds can be considered as potential candidates for the development of phytomedicines and chemical biomarkers. On the other hand, compounds that possess simple structures can be synthesized. These compounds can serve as templates to synthetic drugs. Some of the isolated compounds from plant extracts have not been tested for cytotoxicity and in-vivo this might be due to the fact that small quantities of these compounds are isolated. This seriously limits their potential as future drugs. A limitation that cannot be overlooked is the fact that compounds which are shown to be active in-vitro can be inactive in-vivo. Also, since natural products are metabolized, the pharmacokinetics has to be taken into consideration. Moreover, some of the active compounds were shown to exhibit activity at very high doses which may not have any meaningful therapeutic value. The determination of the cytotoxicity is important so as to evaluate the selectivity indices (cytotoxicity/activity) of these bioactive compounds which will then serve as a basis for their being considered as potential drugs [59].

Another factor to take into consideration is the validation of the medicinal plants. This will help in the standardization of the plant extract to be evaluated, and aid in the identification and quantification of chemicals and/or biomarkers. This will lead to the development of efficient and safe phytomedicines in a short period of time and at a relatively low cost. Factors such as ontogeny and phenology, abiotic (age, light, moisture, nutrient availability) and biotic (different physiological and growth stages) have been shown to affect the quality and quantity of secondary metabolites present in plants. This makes it mandatory for standardization of medicinal plants.

Unlike synthetic drugs that contain single entities of known composition and specific therapeutic actions, herbal drugs are derived from plant extracts of mixed composition. It is believed that the components of the extract might have an additivity, synergism and/or counteracting interactions among them. These effects are probably due to the structural diversity of the components.

5 Conclusion

There are optimistic perspectives on the continuing search for bioactive compounds from medicinal plants used in traditional medical practice for the treatment of insomnia and these will certainly lead the scientific community to the discovery of new and efficient molecular templates and phytomedicine for this disease.

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