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Review Article

The *Spongia somnifera*: A Review Article

Suleiman Olimat*

Department of Medicinal Chemistry and Pharmacognosy, Jordan University of Science and Technology, Jordan

ABSTRACT

Spongia somnifera is considered the most important formula used in anaesthesia and has been developed over centuries by different physicians. Medicinal plants being the anchor ingredients in the various formulas (opium, mandrake, hemlock, henbane, ivy, mulberry, hops, wide lettuce). The aim of the present review is to evaluate the medicinal plants used in different formulas of *Spongia somnifera* as anesthetic agent with correlation with their modern applications, chemical compositions and pharmacology.

Keywords: Spongia; Somnifera; Opium; Mandrake; Hemlock; Henbane; Ivy; Wide Lettuce; Mulberry; Hops

INTRODUCTION

Anaesthesia is a very essential performance of surgical and other interventional procedures by rapidly, safely, and pleasantly producing analgesia, the primary goal of general anaesthesia is rendering a patient unconscious and unable to feel painful stimuli while controlling autonomic reflexes. Anaesthesia introduced to modern medicine in 1846 and a new era started in the development of surgery that would not be possible without anaesthesia [1]. *Spongia somnifera* is considered the oldest, most important formula used in anaesthesia and has been developed over centuries by different physicians. Medicinal plants being the only important ingredients in the various formulas (e,g. opium, mandrake, henbane, ivy, mulberry, hops, wide lettuce) [2]. Formula one consisted of three plants (mandrake, opium, and henbane); it was introduced in medicine by the famous Arabian scientist Ibn Sina (980 to 1037 CE), (Avicenna), in his authoritative Canon of Medicine, he described the Spongia somnifera, put all the ingredients together in a bowl with water and dip the marine sponge to absorb the dissolved water in which the recipe plants are placed, then place the sponge on the patient's nostril and quickly fall asleep. The second formula mentioned by Salernitan physicians. Michael Scot (1190 to 1250 CE), who recommends taking equal quantities of opium, mandragora, and hemp, grinding these plants and mixing them with water. When you want to saw or cut someone, just dip a rag in the water and place it on his nostril, he will sleep deeply and you can do with him whatever you wish [3].

Medieval medicine was highly innovative compared to ancient and early modern medicine. It also pertains to anaesthesia, which in the Middle Ages was developed from ancient methods of sedation. Medieval scholars perfected the method into achieving the first total anaesthesia, resorption/inhalation anaesthesia, and then local anaesthesia. Most of these sedative plants were members of a large botanical family, the Solanaceae family, *Solanum nigrum*, *Hyoscyamus niger*, *Cicuta minor*, *Datura stramonium*, and *Lactuca virosa*, are gathered, and a sponge is plunged into their juice freshly expressed. The sponge is then dried in the sun, the process of dipping and drying is repeated two or three times, and the sponge is then laid up in a dry place [4]. Formula three used by the middle ages doctors used a *Spongia somnifera* (soporific-sponge), consisting of a fresh seasponge soaked in opium, henbane, mulberry juice, lettuce seed, hemlock, mandrake and ivy, then dried in the sun. When it was needed for pain-killing, it was reconstituted with water inhaled or dripped into the mouth. Fennel root or vinegar was the antidote used to revive the patient. Formula four for *Spongia somnifera* was in the medieval medicine which is a combination with mandrake, poppy, hops, henbane, lactuca (wild lettice) and mulberry [5].

LITERATURE REVIEW

All the available information on *Spongia somnifera* was collected *via* a library and electronic search (using Web of Science, Pubmed, SciFindert, Scopus, Google Scholar...etc.).

Pharmacology and Chemical composition and mechanism of action of formulas one and two (mandrake, opium, and henbane).

Mandrake, Mandragora

The mandrake, mandragora is the common English name of *Mandragora officinarum* L. and *M. automnalis* L. perennial herb belonging to the family Solanaceae, the roots and rhizomes are used in medicine, the plant is closely allied to the deadly nightshade, *Atropa belladonna* L. An old scholar book is known by

Correspondence to: Suleiman Olimat, Department of Medicinal Chemistry and Pharmacognosy, Jordan University of Science and Technology, Irbid, Jordan, Tel: +962 277 260 7116; Email: smalkhalil@just.edu.jo

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the name "Yabrouh", believed it is a Syriani word meaning "I need a soul" because of the root and rhizome resembling the human body, just needing a soul to be alive. The chemical composition of mandragora mainly tropane alkaloids and the sedative effect attributed to the presence of atropine and scopolamine alkaloids, based on the actions of the juice of the mandrake plant, it must contain an alkaloid that is one of the most active anesthetics, mainly the alkaloid scopolamine [6]. Nowadays the plant is known by different names like Tuffah el Majanin (Madmen's Apple) and Beid el Jinn (Eggs of the Jinn), this is due to the ability of the plant to invigorate and stimulate the senses even to the point of mental imbalance [7].

Mandragora extract was used as a juice, so the patient had to drink it rather than inhalation, when the juice taken orally has to be absorbed by mucus membranes, inhalation would be ineffective because atropine and scopolamine have a very low vapour pressure. Mandragora was a common drug that has been used as a sedative and to induce pain relief for surgical procedures; different dosage forms, tablets and friezes, had been developed since the 16th century. Mandragora anaesthesia acting to relieve pain by desensitizing the nerve endings [8].

Henbane

Hyoscyamus niger L. belongs to the family Solanaceae, its English common name is henbane or black henbane, which refers to the black colour of the seeds, which are used in medicine. Known in Arabic as "Banj", refers to its anaesthetic effect [9]. Henbane is rich in tropane alkaloids like other species belong to the family Solanaceae (*Atropa belladonna* and *Datura spp*.) Atropine is a racemic mixture (containing equal amounts of the isomers (-)-hyoscyamine and (+)-hyoscyamine, in addition to alkaloids (-)-hyoscyamine, there is no difference in their pharmacological activity, and (-)-scopolamine. Several tropane alkaloids are. Atropine, hyoscyamine, and scopolamine are muscarinic receptor antagonists and used as powerful anticholinergic drugs [9]. Tropane alkaloids work by inhibiting the parasympathetic nervous system. is a competitive antagonist of the actions of acetylcholine and other muscarinic agonists. The alkaloids atropine and scopolamine are qualitatively similar in their pharmacology, except atropine is CNS stimulant and scopolamine is a central depressant and can act as a sedative.

Pharmacology of opium

The constituents of opium alkaloids (morphine, codeine, thebaine) are exogenous opioid that produces analgesia, as a result of its affinity to bind to receptors normally acted upon by endogenous opioids. Morphine and close related alkaloids are biosynthesized from phenanthrene derivatives and include four or more fused rings, morphine is the major active constituent in opium in a concentration up to 20 percent. Morphinoid alkaloids and similar narcotic agonists have agonistic actions at the mu (μ), kappa (κ), and delta (δ) receptors [10]. This drug produces the majority of its analgesic effects by binding to the mu-opioid receptor within the Central Nervous System (CNS) and the Peripheral Nervous System (PNS). The net effect of morphine is the activation of descending inhibitory pathways of the CNS as well as inhibition of the nociceptive afferent neurons of the PNS, which leads to an overall reduction of the nociceptive transmission. Codeine, the 3-methyl ether of morphine, is found in opium in a concentration range of 0.7 percent- 2.5 percent. Codeine possesses the same pharmacological actions as morphine but is less potent. The analgesic properties of codeine stem from its conversion to morphine, about 10 percent of administered codeine undergoes O-demethylation to morphine, which is predominately mediated by the polymorphic CYP2D6 enzyme. Importantly, Codeine has an extremely low affinity for standard CNS mu (μ), delta (δ), and kappa (κ) opioid receptors. Thebaine has no medical applications, it occurs in opium extract to the extent of 0.1-2.5 percent [11], is important as a substrate in the semi-synthesis of other opium alkaloid. Thebaine alkaloid is an opioid analgesic, it is a partial mu (μ)-receptor agonist and kappa (κ)-receptor antagonist. It has a delayed onset of activity, and because of its property as a partial mu(μ)-opiate agonist.

Poison hemlock, Conium maculatum L. belonging to the family Apiaceae (formerly Umbelliferae), known in English by the name hemlock or poisonous hemlock and in Arabic known as Shoukaran or Shykaran [12] It is a tall biennial, which typically forms a basal rosette in the first year of growth. The hemlock species is native to the Mediterranean region. It has leaves and white flower heads resembling those of parsnips, carrots; The long, fleshy, white taproot has a main stem with characteristic light red spots and a disagreeable smell, a dead rat smell. The flowers are small with 5 white petals, numerous in compound flat-topped umbels at the ends of stems, produced from April to early July. All parts of hemlock are poisonous. The generic name of the plant-derived from the Greek word "Konas", meaning to whirl about, upon consumption of the plant, causes vertigo and leading to death. The species macualtum meaning (spotted) and referred to the dark spots on the stem. However, the common name hemlock is derived from the Anglo-Saxonwords hem (border, shore) and leác (leek or plant); other authors mentioned that the name (hemlock) was derived from the word helm (straw), from which the word (haulm) was derived. Historical background, Socrates death.

The juice of hemlock, hemlock cup, was administered in ancient Greek to criminals. The Greek philosopher Socrates is one of the most famous people who chose to be executed by drinking hemlock tea. The closing pages of Plato's Phaedo provide a stunning picture of the effects of poison upon the body of Socrates. Plato describes a slowly ascending paralysis, beginning in Socrates' feet and creeping steadily up his legs toward his chest, with Socrates' mind remaining clear until the end. Death arrives calmly and peacefully [13]. After Socrates drank the poison, he walked a few steps but felt that his feet could not hold him, and one of his attendants advised him to lie on his back, and the poison began to spread in his body from bottom to top until he felt the difficulty of breathing and his last words were 'Crito, we owe a cock to Asclepius. Pay it and do not neglect it.

Pharmacology and chemical composition

Twelve piperidine alkaloids have been identified in C. *maculatum*, two of them, γ-coniceine and coniine are generally the most abundant and they account for most of the plant acute and chronic toxicity. Coniine is the major alkaloid present in the plant, in a concentration of 2% in fruits and 0.5% in leaves, however, It is the first alkaloid the chemical structure of which was established (in 1881). Coniine provokes a skeletal muscle relaxation effect on the neuromuscular junction, whereas cicutoxin causes seizures. The general symptoms of hemlock poisoning are effects on the nervous system (stimulation followed by paralysis of motor nerve endings and CNS stimulation and later depression), vomiting, trembling, problems in movement, slow and weak later rapid pulse, rapid respiration, salivation, urination, nausea, convulsions, coma and death. It is a nicotinic acetylcholine receptor antagonist, which

leads to inhibition of the nervous system, eventually causing death by suffocation in a mammal.

E-Mulberry

Mulberry belongs to the genus Morus of the family Moraceae and it is found in East, West and South-East Asia, South Europe, South of North America, and some areas of Africa. There are 24 species of Morus, the most commonly known species in the Morus genus are white mulberry, known in Arabic as Toot Abiad, (*Morus alba* L.), black mulberry, known in Arabic as Toot Aswad, (*Morus nigra* L.) and red mulberry, known in Arabic as Toot Ahmar, (*Morus rubra* L.)

Pharmacology and chemical composition of mulberry

Mulberry species are rich in phenolic compounds mainly flavonoids, flavonoid glycosides, phenolic acids and anthocyanidins. M. *nigra* main components are anthocyanins recognized as cyaniding 3-pelargonidin 3-O-glucoside, cyaniding 3-O-rutinoside, pelargonidin 3-O-glucoside and pelargonidin 3-O-rutinoside. M. nigra showed higher amounts of phenolic compounds than M. *alba.* Phytochemical analysis of *M. alba* showed that the abundant anthocyanins compounds which are cyanidin 3-O-rutinoside (60%) and cyanidin 3-O-glucoside (38%). The minor anthocyanins (totally 2%) are pelargonidin 3-O-glucoside and pelargonidin 3-O-rutinoside. *M. alba* quercetin 3-O-glucoside, quercetin 3-O-rutinoside, kaemferol 3-O-rutinoside, and 5-O-caffeoylquinic acid. Caffeic acid is considered the most abundant acid in *Morus spp.*

Caffeic acid, which selectively inhibits leukotriene biosynthesis

Leukotrienes are significantly involved in immunoregulation and a variety of diseases, including asthma, inflammation and various allergic conditions. They are initially biosynthesized by 5-lipoxygenase from arachidonic acid, which can also be metabolized to prostaglandin endoperoxide by cyclooxygenase. The specific inhibitors for 5-lipoxygenase, caffeic acid, would be a useful tool for the regulation mechanism of leukotriene biosynthesis. I think the role of mulberry is to regulate ale asthma in the patients due to the presence of caffeic acid [14].

F-Ivy

Ivy is *Hedera helix* L. belonging to Araliaceae family, known by English common name English ivy, common ivy, and in Arabic known by the name Muddad. *H. helix* is an evergreen Climber growing to 15 m by 5 m at a medium rate. It is in leaf all year, in flower from October to November, and the seeds ripen from May to June. Leaves and berries have been applied in medicine in ancient times for the treatment of various diseases (e.g. jaundice and dysentery). Nowadays, only the leaves are applied and only in the treatment of respiratory diseases. According to European Pharmacopoeia, Hederae folium is the whole or cut, dried leaves of *Hedera helix* L. collected in spring, with a minimum hederacoside content of 3.0%.

Pharmacology and chemical compositions

H.helix leaves contain 2.5%-6% triterpene saponins, based on the aglycones hederagenin, oleanolic acid and bayogenin. The majority of the saponins are bisdesmosides, with the main compound hederacoside C (hederasaponin C). Monodesmosides (such as alpha-hederin) are present in smaller amounts. Further secondary metabolites are caffeic acid derivatives, flavonoids, coumarins and polyacetylenes. Phenolic constituents isolated from a commercial dry extract of Hedera helix were included rutin, kaempferol 3-O-rutinoside, quercetin 3-O-glucoside, kaempferol 3-O-glucoside, quercetin, kaempferol, chlorogenic acid, neochlorogenic acid, 4,5-O-dicaffeoyl-quinic acid, 3,5- O-dicaffeoyl-quinic acid as well as rosmarinic, caffeic, and protocatechuic acids. Juice of ivy was an ingredient in *Spongia somnifera* in medival times. The expectorant effect of ivy is more complex (or more precisely described) than those of other saponin-containing plants, due to the stimulation of beta2-adrenoreceptors leads to increasing surfactant production. Flavonoids and caffeic acid derivatives with less pronounced activity may also contribute to the effect54. Structure-related saponins like hederacoside C and hederagenin did not influence either the binding behavior of beta 2 AR or the intracellular cAMB level [15]. I think the juice of wood-ivy in *Spongia somnifera* is due to its effect on the respiratory system.

G-lettuce seeds

The seeds of Lactuca scariola Linn belonging to the family Asteraceae, is commonly known as "Prickly Lettuce" seeds or "Wild Lettuce" seeds, in Arabic known as Buzrul khas. The species *Lactuca sativa* L. is the common or garden variety, known in Arabic as Bustani Khas. The generic name Lactuca and the common name Lettuce derived from the Latin world lactus (milk), a milky fluid that flows from the stems when they break or are cut. The seeds medicinal properties were described by Hippocrates (430 BC). The common reported pharmacological actions are anxolytic, sedative, antipyretic, diuretic and analgesic. From the general properties of the medieval general anesthesia in general and the so-called *Spongia somnifera* in particular using lettuce seeds, I am with opinion that Lactuca scariola is used in the formula [16].

Pharmacology and chemical composition of *Lactuca scariola*

Triterpenoid saponin, 3β-O-[α-l-rhamnopyranosyl]-30-norolean-12,19-diene-28-oic acid 28-O-[β-d-glucopyranosyl-(1→4)-O-β-d-galactopyranosyl]-ester has been isolated from the stems of *L.a scariola*. Another triterpenoid saponin, 3-O-[β-Dgalactopyranosyl-(1 →3)-O-β-D-xylopyranosyl-(1→4)-O-α-Lrhamnopyranosyl]- oleanolic acid; has been isolated from the seeds of *L. scariola*. Oilseed lettuce Because of the bitter taste of its leaves, this type is not eaten as a vegetable. Oilseed lettuce is characterized by a high percentage (35%) of oil in the seeds, which is used for cooking. The oil contains Vitamin E, an essential nutrient. Seed oils of *Lactuca scariola Linn., L. sativa Linn.*, were found to contain epoxy acids in 10.0% (6.0% coronaric + 4.0% vernolic), 27.4% (16.9% coronaric + 10.5% vernolic) and 20.0% (16% coronaric + 4.0% vernolic) amount, respectively, along with normal fatty acids. *L sativa* seed oil has demonstrated a pronounced sedative effect and potentiated the hypnotic effect of barbiturates in animal models. The alkaloid, lactucin, isolated from the seeds exhibited antipyretic activity Methanolic extract of *L. scariola* can produce significant analgesic activity [17]. The alkaloids lactucine and its derivatives lactucopicrine and 11-β, 13-dihydrolactucin, were evaluated for sedative and analgesic and sedative properties in animal model. Lactucopicrine alkaloid showed to be the most potent analgesic of the tested compounds. Extract of *L. scariola* showed significant analgesic activity at low dose of 300 mg/kg. even better analgesic effect than the reference drug and the dose level of l000 mg/kg. The relaxation of airway muscles after the administration of the methanol extract of *L. scariola* was found to be due to the dual mechanism (i.e., muscarinic antagonist and Ca++ channel blockade). The bronchodilator effect may possibly be mediated through Ca++ channel blockade. Interestingly, muscarinic antagonists are today used in the treatment for the relief from asthma and similar diseases.

H-Hops

Hops is a dioecious perennial species the dried female inflorescence (strobili) of *Humulus lupulus* L. belonging to the family Canabinaceae, it is known in English by the common name Hops and in Arabic known by the name Hashishat ed dinar. The female cones (stobili) are widely used for beer brewing due to their bitter taste.

History

Around 77-79 A.D, Humulus lupus became known as a plant grown in the wild. It wasn't until around 736 A.D that they began being cultivated by humans for use. They used the Hops to treat anxiety and restlessness, as well as insomnia. For insomnia, they would fill a pillow with the Hops and the person would sleep on it and have no trouble going and staying asleep. George III, King of the United Kingdom (1738–1820), was a huge proponent of hops as a sleep aid. He used a pillow of hops in his bed to calm him and assist with sleep. who was supposedly bedded on pillows filled with hops to calm him [18]. The physician Kahnt (1905), in his book on phytotherapy, recommended the use of hop pillows, teas, or extracts for sleeping problems associated with nervous disturbances. According to the EMA, hops can be used as a traditional herbal medicinal product in the form of tea, dry herbal substance, liquid or dry extracts to the relieve of mild symptoms of mental stress and to aid sleep.

Pharmacology and chemical composition of hops

The bitter taste of the hop stems from its prenylated phloroglucinols (also known as alpha-acids or humulones and beta-acids or lupulones. The essential oil content of the inflorescence makes the taste more complex. Flavonoids, including special prenylated ones and chalcones xanthohumol, iso-xanthohumol and 6-prenylnaringenin are characteristic of the genus. The most important component from the aspect of bioactivity is 2-methyl-3-buten-2-ol. Although only traces of this compound are to be found in freshly harvested hops, its amount increases during storage because of the decomposition of phloroglucinols. The hop contains isovaleric acid in low concentration. The mode of action of this plant is not fully understood. Isovaleric acid may contribute to the action the degredation product α-acid content, 2-methyl-3-buten-2-ol is of greater importance, the flavonoid xanthohumol and the terpene myrcenol. The sedative effect of hop extracts has been confirmed in multiple animal experiments. With pure phloroglucinols, this effect cannot be achieved. However, following the administration of 2-methyl-3-buten-2-ol, the bioactivity of the plant extract can be reproduced, the main mechanism of action of hops is to modulate the activity of the neurotransmitter γ-aminobutyric acid (GABA) receptors.

CONCLUSION

The results give further insights into the pharmacological activity of *Spongia somnifera*, ethnopharmacological research revealed that many of these plants are still used in medicine, e.g. opium, henbane, ivy, mulberry, lettuce and hops; other plants are toxic not used anymore in medicine e.g. mandrake and hemlock.

CONFLICT OF INTEREST

The author has stated that there is no conflict of interest associated with the publication and no financial support, which could have influenced the outcome.

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