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Mugwort (*Artemisia vulgaris*, *Artemisia douglasiana*, *Artemisia argyi*) in the Treatment of Menopause, Premenstrual Syndrome, Dysmenorrhea and Attention Deficit Hyperactivity Disorder

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ABSTRACT

Mugwort has many traditional uses around the world. The Chumash Indians of California use it to treat imbalances that women may suffer such as premenstrual syndrome, dysmenorrhea and menopausal symptoms. The plant contains a sesquiterpene that appears to work through a serotonergic mechanism and may be beneficial for women. Mugwort therapy is safer for menopausal women than hormone replacement therapy. Children affected by attention deficit hyperactivity disorder benefit from mugwort therapy. There is no doubt that mugwort therapy is safer for these children than methylphenidate or amphetamine.

Keywords: Mugwort; *Artemisia vulgaris*; *Artemisia argyi*; *Artemisia douglasiana*; Menopause; Attention Deficit Hyperactivity Disorder

1. Introduction

Mugwort is found in Europe (*Artemisia vulgaris*), Africa (*Artemisia vulgaris*), India (*Artemisia vulgaris*), Asia (*Artemisia argyi*) and America (*Artemisia douglasiana*). This plant may have been transported throughout the world by early humans who needed it for its medicinal and food value. It can be easily transported as seeds. The meaning of mugwort may be marsh root since it grows near permanent sources of water. In Chinese, mugwort is lou hao. In Chumash Indian, mugwort is molush. The scientific name *Artemisia* comes from Artemis, Greek Goddess of the hunt, wild animals, wilderness, childbirth and virginity. Artemis is capable of bringing or relieving disease in women.

The three species of mugwort differ somewhat in appearance, perhaps the result of growing in different habitats for thousands of years. Mugwort is easy to grow from seeds and likes shade. The perennial plants grow to 2.5 meters high and have variably lobed oblanceolate leaves with 1 to 7 lobes. The leaves can be up to 15 cm long, are green on top and white, tomentose on the underside. The stem and roots are woody. The flowers grow in panicles as small disciform heads, less than 5 mm in diameter, contain 5 - 9 pistillate flowers and 6 - 25 disk flowers.

2. European Traditional Uses

Mugwort, *Artemisia vulgaris*, is used in Europe as a bitter aromatic and is rarely used [1]. It is intended to stimulate gastric secretions in patients with poor appetite, is used against flatulence, distention, colic, diarrhea, constipation, cramps, worm infestations, hysteria, epilepsy, vomiting, menstrual problems, irregular periods, to promote circulation and as a sedative. This sedative effect may be responsible for internet reports of the use of *A. vulgaris* to induce dreams. The root has different uses, as a tonic, for psychoneuroses, neurasthenia, depression, autonomic neuroses, irritability, restlessness, insomnia and anxiety. *A. vulgaris* is described as an abortifacient without discussion of the preparation used [1].

The plant contains many active compounds including the monoterpenes, eucalyptol, camphor, linalool, thujone, 4-terpineol, borneol, α-cadinol, spathulenol and 21 others [1]. These monoterpenes are present in the essential oil that makes up 0.03% - 0.3% of the plant. The plant also contains sesquiterpenes and sesquiterpene lactones such as eudesmane, vulgarin, psilostachyin and psilostachyin C [1]. Flavonol glycosides are present including quercitin 3-O-glucoside, rutin and isorhamnetin 3-O-glucoside [1]. Coumarins are found such as aesculetin, aesculin, umbelliferone, scopoletin, coumarin and 6-methoxy-7,8-

methylene-dioxycoumarin [1]. Polyacetylenes, carotenoids and pentacyclic triterpenes are present such as sitosterol and stigmasterol [1].

3. Pharmacology of *Artemisia* Plants

Many monoterpenoids are pain and anxiety relievers due to inhibition of transient receptor potential cation channels [2]. These channels are found on sensory afferent neurons of the skin and are usually responsive to heat or cold. They are also found in the brain, spinal cord and lungs [2]. The involvement of the brain transient receptor potential channels in anxiety has not been investigated. Most of these channels have six transmembrane spanning units and large intracellular amino and carboxy terminal portions [2]. Most of them allow sodium and calcium to enter the cell. The vanilloid receptors (TRPV) have amino terminal ankyrin repeat domains and a carboxy terminal TRP box. The TRPA channels (ankyrin) have many ankyrin repeats in the amino terminal. The TRPM channels (melastatin) have a TRP box in the carboxy terminal. Several drugs are available that act on these channels, such as capsaicin (TRPV1) and menthol (TRPM8). More than a dozen drug candidates are in clinical trials that act on these channels to relieve pain. Typically an agonist at these channels causes transient channel opening that is followed by long term channel closing and pain relief [2].

Several monoterpenoids have reported pain relieving activity such as camphor [3-5], eucalyptol [4-6, also called 1,8-cineole], camphene [4,5], *β*-pinene [4-6], borneol [4,5,7] and thujone [8]. Most of the pain relieving monoterpenoids found in *A. vulgaris* are agonists for TRPV3 (heat sensing) including camphor [3,9,10], borneol, thujone and eucalyptol [10]. Camphor is also an antagonist for the TRPA1 (TRP ankyrin-repeat1, cold-sensitive) receptor and an agonist for the TRPV1 (heat-sensitive) receptor [3]. Eucalyptol has been shown to also be a TRPM8 (cold-sensitive) receptor agonist and to exhibit an antinociceptive activity comparable to or greater than that of morphine [11].

Some monoterpenoids have reported anti-inflammatory properties such as camphene and *β*-pinene [12,13]. The monoterpene, borneol has been shown to have high anti-inflammatory activity [14], which results from the inhibition of nitric oxide (NO) and prostaglandin E2 (PGE2) production due to inhibition of NF-κB activation (nuclear factor κB). The NF-κB mechanism involves increasing the expression of IKK (inhibitor of NF-κB kinase), iNOS (inducible nitric oxide synthase) and decreasing IκB*α* (inhibitor of NF-κB*α*) expression in dose-dependent manners [13,14].

Some sesquiterpenoids are anti-inflammatory agents [12]. In fact, a sesquiterpene from *Artemisia pallens* is reported to have strong anti-inflammatory activity and is topically active [15]. In other words, it penetrates the skin after topical administration and relieves inflammation. The mechanism of anti-inflammatory action of a sesquiterpene, 7-hydroxyfrullanolide, appears to be inhibition of an NF-κB pathway [16]. IKK*β* phosphorylation was shown to be inhibited by 7-hydroxyfrullanolide, which resulted in inhibition of NF-κB translocation into the nucleus. Several sesquiterpenes inhibit the production of inflammatory cytokines and adipokines. 7-Hydroxyfrullanolide inhibits the production of inflammatory adhesion proteins such as ICAM-1, VCAM-1 and E-selectin [16]. This inhibits monocyte induced inflammation. Patchouli alcohol, a tricyclic sequiterpene, inhibits tumor necrosis factor-*α*, IL-1*β* (interleukin-1*β*), cyclooxygenase-2, and iNOS production [17]. This results in less NO and PGE2 production, less inflammation and less edema. Parthenolide, a sesquiterpene lactone present in several plants, inhibits inflammation in the brain and other organs by decreasing IL-6, tumor necrosis factor-*α* and cyclooxygenase-2 production [18]. This results in lowered body temperature and occurs through an NF-κB inhibition mechanism. NF-κB activation is inhibited, especially in the hypothalamus. Alpha-bisabolol is another anti-inflammatory sesquiterpene that is found in several plants. Alpha-bisabolol has been shown to decrease iNOS and cyclooxygenase-2 production by inhibiting NF-κB activation [19]. A plant used by Native Americans, Eupatorium perfoliatum, has been found to be anti-inflammatory due to the presence of sesquiterpenes [20]. A structure-activity study of 26 sesquiterpene lactones was conducted to elucidate the structural requirements for inhibition of iNOS production and found potent inhibition down to micromolar levels [21]. This clearly indicates that sesquiterpenes are very useful anti-inflammatory and fever decreasing agents that have been used for centuries in plant medicines around the world.

Flavonols can be anti-inflammatory agents. For instance, women who have higher intake of flavonol rich foods, especially citrus fruits, have lower blood levels of inflammatory proteins, including VCAM, C-reactive protein, soluble tumor necrosis factor receptor-2 and IL-18 [22]. Kaempferol, kaempferol 3-O-alpha-L-rhamnopyranosyl-(1-6)-beta-D-glucopyranoside and quercetin 3-O-alpha-L-rhamnopyranosyl-(1-6)-beta-D-glucopyranoside have been found to be anti-inflammatory agents and can be topically active in paw edema tests [23]. These flavonols inhibit production of iNOS [23]. Some flavonols, such as papyriflavonol A, are phospholipase A2 inhibitors and potently inhibit the enzyme with IC50 values of 4 micromolar [24]. Inhibition of phospholipase A2 decreases leukotriene C4 production, decreases allergic reactions and results in less

inflammation [24]. A nasal spray made from *Artemisia abrotanum* is anti-inflammatory, contains monoterpenes and flavonols [25]. This spray was tested in a clinical trial and found to relieve bronchoconstriction in 50% of patients [25]. Allergic rhinitis was relieved by the nasal spray in 100% of patients [25].

Coumarins are pharmacologically important agents found in *Artemisia* plants. Umbelliferone, also called 7-hydroxycoumarin, is a pain relieving agent, relieves inflammation and relieves fever in animal tests [26]. It is also topically active. Umbelliferone also inhibits inflammatory cytokine production, such as IL-12 and interferon-gamma, produced by viral infections [27]. Umbelliferone is antihyperglycemic in rats and has activity comparable to glibenclamide [28]. It also decreases blood levels of total cholesterol, triglycerides, phospholipids, free fatty acids, LDL-C, VLDL-C and increases HDL-C in diabetic rats [29]. Aesculetin, also called 6,7-dihydroxycoumarin, is a lipoxygenase inhibitor that inhibits the proliferation of vascular smooth muscle cells in a model of atherosclerosis [30]. Aesculetin inhibits the activation of p42/44 mitogen activated protein kinase by inhibiting c-fos and c-jun transcription [30]. Aesculetin also inhibits activation of NF-κB, activator protein-1 and phosphoinositide 3-kinase [30]. Coumarin, umbelliferone and esculetin have antitumor activity [31,32] even in human clinical trials [32].

It may be important that *Artemisia* plants contain high amounts of both monoterpenoids and sesquiterpenes. Both classes of agents have anti-inflammatory activity due to inhibition of NF-κB activation. It is not known how monoterpenoids and sesquiterpenes may interact in this mechanism, perhaps to enhance anti-inflammatory activity and decrease fevers. This may involve decreasing cyclooxygenase-2 synthesis. The presence of flavonols may add to the anti-inflammatory effects of *Artemisia* plants due to inhibition of iNOS production and phospholipase A2 inhibition. Coumarins may increase the anti-inflammatory activity of the plants by inhibition of lipoxygenase. *Artemisia* plants may be potent pain relieving and anti-inflammatory medicines due to these compounds. Each class of compound may enhance the activity of the other classes through additive or synergistic mechanisms.

4. Traditional Recipes for the Use of Mugwort in Europe and India

In Europe a tea is made from 150 ml of boiling water poured over 1.2 g of dried *A. vulgaris* leaves, stems and flowers [1]. This is allowed to steep in a covered vessel for 5 min before it is strained and consumed. Two or three cups of this strong tea are drunk daily before meals. The German Commission E has not substantiated the efficacy of this preparation.

In India, mugwort (*Artemisia vulgaris*, nagadamni in Sanskrit) is used as an antispasmodic, expectorant, stomachic, tonic, laxative, antihysteric and anthelmintic [33]. It is used for menstrual problems, metorrhagia and to prevent abortion. In children it is used as a decoction against measles and as a leaf juice against whooping cough. Leaf powder is used against hemorrhage, dysentery, intestinal complaints, urinary tract problems and skin diseases. A strong tea is made from 14 - 28 ml of boiling water and 0.5 - 1 g of powdered leaves.

5. Chinese Traditional Uses

In China, mugwort (*Artemisia argyi*) is used mostly for moxibustion [34,35]. Moxibustion is direct or indirect. For direct moxibustion, a cone of dried *A. argyi* leaf powder is placed on the skin and burned. The cone can be taken off before the skin burns or can be allowed to burn and scar the skin. Indirect moxibustion involves using a cigar of *A. argyi* leaves to heat the skin. *A. argyi* is used to stimulate blood flow and qi at specific points on the skin, sometimes acupuncture points. This can be beneficial in pain, weakness, fatigue associated with aging and in turning fetuses for head down delivery. The dried leaves are also used as a tea for analgesia, excessive menstruation and bleeding during pregnancy.

A. argyi contains carveol, *α*-phellandrene, *α*-terpineol, 4-terpineol, eucalyptol, borneol, spathulenol, camphor, camazulene, *β*-caryophyllene, *β*-caryophyllene alcohol, chrysartemin A, chrystemin B, arteminolides, and moxartenolide. Triterpenes include glutinone, fernenone, lupenone, simiarenol, *α*-amyrin acetate and *β*-amyrin acetate. Flavones present are scopoletin, isoscopoletin, eupatilin, jaceosidin, apigenin, chrysoeriol and naringenin [35]. Several of these compounds have antiasthmatic effects including carveol, *α*-terpineol, 4-terpineol and *β*-caryophyllene alcohol [35]. Several compounds are analgesics including 4-terpineol, several of the monoterpenes, *α*-amyrin and *β*-amyrin as discussed in the pharmacology section [35]. Anxiolytic effects have been reported for *β*-amyrin and several monoterpenes [35].

6. Chumash Indian Traditional Uses

Mugwort, *Artemisia douglasiana*, is a traditional medicine of the Chumash Indians of California and is used in the treatment of menopausal symptoms, premenstrual syndrome and dysmenorrhea [36,37]. The traditional treatment for menopause is a mild, *A. douglasiana* tea. This tea is much milder than the European *A. vulgaris* tea above. *A. douglasiana* tea is made by placing a fresh or dried leaf in 300 ml of water. The mixture is warmed until it starts to boil at which time it is removed from the heat. The tea is allowed to steep for a few minutes prior

to drinking. Sugar, honey or other sweeteners are not added.

Anxiety is a learned disorder that must be unlearned [38]. It is treated, in part, with *A. douglasiana*. People with anxiety attacks are treated once with sagebrush tea in the evening. California sagebrush, *Artemisia californica*, leaves and stems are collected and put into a cloth sack. The patient sleeps with this sack for one week. During this time, meat must not be eaten. The sagebrush leaves are measured in the palm of the hand. About a half teaspoon of the dried leaves from the sack are mixed with 300 ml of water and allowed to sit in the sun for 2 hours. This is heated with a stick of cinnamon (*Cinnamomum* species) until it simmers. The patient drinks this tea and does not add sugar or honey. Overweight people should use a quarter of a teaspoon of sagebrush leaves, since sagebrush can produce a strong reaction in them. At the same time, four to six yerba santa leaves, *Eriodictyon crassifolium*, seven flowers and seven leaves of California jimson weed, *Datura wrightii*, and about ten leaves of white sage, *Salvia apiana*, are put in 1.5 l of water and allowed to boil moderately until the entire house smells of the preparation. The patient drinks the sagebrush tea while vaporizing over the *E. crassifolium*, *D. wrightii* and *S. apiana* steam.

The next step, that evening, is a massage. The massage oil is prepared by making a sun tea of four to six tobacco leaves, *Nicotiana quadrivalvis* or *Nicotiana glauca*, and four to seven leaves of *S. apiana* in 1.5 l of sea water. This is brewed in the sun for a few hours, then put on the stove to boil moderately until the entire house smells of the preparation. Some of the tea is cooled, strained and mixed with olive oil or baby oil to make a massage oil. The massage should especially treat the areas under the arms and below the butt.

For the next several weeks, the patient drinks 300 ml of hot chocolate containing a *S. apiana* leaf and an *A. douglasiana* leaf, every night before bed. It is best to use a traditional chocolate such as Chocolate Ibarra that is high in flavonols. Heat 300 ml of water to boiling. Remove it from the heat. Melt two or three tablespoons, 55 g, of the chocolate in the water with a whisk. Add the *S. apiana* leaf and *A. douglasiana* leaf to this and steep for a few minutes. Remove the leaves and drink the tea.

When the anxiety attacks decrease, the patient puts a stick of cinnamon in 300 ml of water and heats it to a simmer. The patient removes this from the heat and adds a leaf of *S. apiana*. The tea is allowed to steep for five min before drinking. This continues until the anxiety is no longer a problem. One month or more of treatment is needed to relieve anxiety attacks. Overweight people may need to be treated longer than a month.

Attention deficit hyperactivity disorder is treated by stuffing dried *A. douglasiana* leaves into a cloth 5 pointed star. The star should be the size of the palm and fingers of the adult making the star. The child should play with the star daily, especially during times of excessive activity. The child should also sleep with the star. After a few weeks, the child will respond and become less active.

A. douglasiana is also called dream sage (sagebrush) by Chumash Healers [36]. To induce dreams, place the stems and leaves, under a pillow and sleep on the pillow. The fragrance helps with dreaming. When the plant dries, strip the leaves and stuff them into a small pillow. Place this under the regular pillow and continue sleeping on both pillows. This is a traditional use of *A. douglasiana* especially in very ill or aged people who cannot dream. Dreaming is considered an essential part of life and healing.

American *A. douglasiana* contains a variety of pharmacologically active compounds including many sesquiterpene lactones such as vulgarin and psilostachyin [39-50], and probably monoterpenoids such as thujone and alpha-pinene [51]. Of course, the very lipophilic monoterpenoids, such as thujone, will not extract into an aqueous tea. However, the sesquiterpene lactones can be extracted into hot water [52]. A sesquiterpene lactone isolated from *A. douglasiana*, dehydroleucodine, inhibits the release of serotonin from gastroduodenal and other cells [39-41]. It is possible that *A. douglasiana* may have a serotonergic mechanism of action in decreasing menopausal symptoms and attention deficit hyperactivity disorder. On the other hand, if dehydroleucodine inhibits NF-κB activation, like other sesquiterpenes, it may decrease body temperature and inflammation. This is discussed in the pharmacology section.

Many of the monoterpenes found in *A. douglasiana* are pain relievers and anxiolytic [53-60]. Pain relief comes from inhibition of transient receptor potential cation channels [53,57,58]. The mechanism of relief of anxiety is not known but may involve brain transient receptor potential cation channel inhibition. The monoterpene thujone, found in *A. douglasiana*, has been found to be safe in European medicines and foods [61].

The biochemical imbalance that results in attention deficit hyperactivity disorder is not known. The fact that amphetamine like compounds are used to treat the disorder, suggests that inadequate neurotransmitter release may be involved in the disorder. Amphetamine is known to enhance the release of dopamine, norepinephrine and serotonin in the brain and neuronal synapses. Recent evidence suggests that aberrant kinase activity is involved in attention deficit hyperactivity disorder. An aberrant deactivation of striatal dopamine (D1) receptor cAMP protein kinase A DARP32 may be important [62]. DARP32 is dopamine and cAMP regulated neuronal phosphoprotein 32. G-Protein coupled receptor kinase interacting protein-1 (GIT1) has also been implicated in

the disorder [63]. In addition, guanylyl cyclase-C may be involved in attention deficit hyperactivity disorder [64]. Of course, guanylyl cyclase-C makes cGMP that activates several kinases. It is interesting that a recent meta analysis suggests that several drugs that do not act through an amphetamine like mechanism are effective in the disorder [65]. These drugs include clonidine, desipramine, guanfacine and atomoxetine. Clearly, the disorder is more complex and less well understood than some reviews suggest.

A. douglasiana has been reported to induce abortion [36]. It is not clear what preparation of *A. douglasiana* was used or the mechanism of induction of abortion. Estragole has been found in some species of *Artemisia* (*Artemisia dracunculus*, tarragon). Estragole induces cancer, especially in female mice. However, *A. dracunculus* is on the FDA list of GRAS agents and is not known to induce cancer in humans. Mugwort (*A. douglasiana*) has not been reported to contain estragole.

Desvenlafaxine has been found to effectively decrease the incidence of hot flashes in menopausal women [66]. Desvenlafaxine is a serotonin and norepinephrine reuptake inhibitor [67]. It is not known how this mechanism relates to the relief of menopausal hot flashes. Desvenlafaxine has adverse drug effects including increased suicidality, serotonin syndrome, increased blood pressure, and increased blood cholesterol [68]. Gabapentin also appears to decrease the incidence of hot flashes [69] and has an off label indication for hot flashes. Gabapentin activates presynaptic $GABA_B$ heteroreceptors on glutamatergic neurons resulting in less release of glutamate [70]. How this mechanism decreases hot flashes is not known. Gabapentin has adverse drug effects including seizures and sudden unexplained death [66]. *A. douglasiana* is much safer therapy for menopausal symptoms than these drugs.

Hormone replacement therapy was used until the about 10 years ago for menopausal symptoms when it was found that hormone replacement therapy is hazardous to women. The hazards may include increased heart attack, stroke, breast cancer and Alzheimer's disease [71-75]. *A. douglasiana* is much safer than hormone replacement therapy.

There are several medicines, such as antimalarials and drugs used against AIDS, which induce vivid dreams and nightmares. Dreaming is not considered essential to the clinical uses of these drugs. *A. douglasiana* is a safe and effective way to produce dreams, even in cancer chemotherapy patients. Patients find these dreams comforting.

Attention deficit hyperactivity disorder is normally treated with amphetamine and methylphenidate. Both of these drugs are addictive and can cause seizures. *A. douglasiana* is much safer and should be the therapy of choice in this condition.

The essential oil of mugwort (*A. vulgaris*) is available from several sources. Some people have tried to use the essential oil in place of mugwort leaves (*A. douglasiana*) to make a tea. The essential oil of mugwort is made by steam distillation of the leaves, flowers and stems of mugwort. It contains only those compounds in mugwort that vaporize below 100˚, especially the monoterpenoids α-thujone, β-thujone, cineole, camphene and camphone. Vendors of mugwort essential oil (armoise, *A. vulgaris*) recommend using it for aromatherapy, massage therapy and other external uses, not internally. The authors know of people who have suffered seizures and kidney damage from drinking *A. douglasiana* essential oil tea. Several internet sites claim the essential oil causes abortions.

7. Conclusion

Mugwort is used similarly wherever it is found, especially for menstrual concerns, such as premenstrual syndrome and dysmenorrhea. Mugwort should be tested in clinical trials for menopausal symptoms. Abortions or protection against miscarriage are both uses of mugwort. It is likely that high dose mugwort is used for abortions and lower doses are used to prevent miscarriage. It is also likely that other plants are added to mugwort in the induction of abortions. Mugwort should be tested in clinical trials for use in attention deficit, hyperactivity disorder. The sedative, antianxiety and dreaming effects of mugwort should be tested in clinical trials. Medicine frequently neglects dreaming as an essential part of healing.

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