

Nerve Balm Cream*

A potent topical cream for the natural treatment of nerve pain

* (Patent pending)



Sidney Kurn MD and Sandra Gustafson MHS RN

Introduction

Sidney Kurn MD: has practiced neurology for 40 years in Santa Rosa. In addition to mainstream neurology, he helped open an herbal pharmacy, Farmacopia, and co-authored a book, *Herbs and Nutrients for Neurologic Disorders*. After suffering from peripheral neuropathy, he formulated a cream to mitigate the pain and help the nerves regenerate. The cream has a silky, easy to apply texture and has a potent analgesic effect. The cream is also beneficial for arthritic joints and soft tissue injury and pain. The following is a somewhat technical manual on Nerve Balm Cream. Dr. Kurn is pleased to offer a potent cream for pain relief that is pleasant to use and has a regenerative effect on the injured nerves of peripheral neuropathy.

Sandra Gustafson MHS RN: Sandra has been a registered nurse, holistic healthcare and Bowenwork practitioner for over 30 years and mostly works with people with chronic pain conditions. She deeply admires Dr. Kurn's knowledge and dedication in creating a safe, effective, herbal and nutritional supplement to nourish and nurture clients' nervous systems and offer relief from the burden of chronic pain.

It is her pleasure to collaborate in writing with Dr. Kurn and present the rationale behind the formulation of Nerve Balm Cream – a truly innovative, scientific approach to addressing neuropathy and chronic pain. Both conditions are very difficult for people to live with, and for healthcare practitioners to offer relief. In a time where 10% of the population has neuropathy, and more than 1 in 5 adults experience chronic pain, the USA is facing one of the worst opioid-abuse crises of all time. Whilst non-opioid analgesic medications are available, many have deleterious side-effects, especially when taken long-term.

Oral medications, herbs and supplements are broken down in the gastrointestinal system before they can enter the circulation to be delivered to tissues and nerve-endings. Nerve Balm Cream is unique in that it delivers nutrients and plant-based compounds through the skin, directly to the tissues where nociceptive pain signals are generated, and positively changes the nerves' sensory reactivity.

The cream's ingredients are synergistically formulated to reduce inflammation and free radical damage, to calm and soothe affected nerve endings, and promote healing and nerve-regeneration.

The formulation of the cream reflects Dr. Kurn's years of research and clinical experience as a neurologist, his passion for integrating natural medicine to address patients' complex health conditions and seeking alternatives to pharmaceutical drugs for treating pain symptoms.

Neuropathy

Do you have numbness, burning, tingling, pressure, stabbing, shock-like sensations or an altered pain sensation in your hands or feet? These are the symptoms of a disorder in your peripheral nerves, the nerves that travel through your upper and lower extremities. The technical term for this is a sensory polyneuropathy. If, in addition, you have weakness in your limbs as well as sensory abnormalities, then you may have a sensorimotor polyneuropathy. The prevalence of neuropathy is about 8% of the general population. Neuropathy means an abnormality of the nerves and the word poly refers, in general to all the nerves that travel to your feet, and, perhaps, your hands. Most sensory neuropathies are "length-dependent", meaning the symptoms occur at the longest distance from the beginning of the nerves, that is, in the hands and feet. An abnormality of the motor nerves can also cause cramping, twitching of the muscle fibers and shrinkage of muscle mass. A recent clinical study found that almost 10% of the population have neuropathic pain (1). Neuropathic means an abnormality of the nerves resulting in pain.

There are other types of neuropathies. Another common type is a mononeuropathy, an abnormality of a single nerve. The most common mononeuropathy may be carpal tunnel syndrome, when the median nerve gets trapped in the "carpal" tunnel at the wrist. Carpal is Latin for wrist. A "pinched" nerve root in the cervical spine can cause pain to radiate out from the neck and potentially all the way to the hand. A pinched nerve root in the lumbar spine can cause pain that radiates from the low back through the buttock and potentially all the way to the foot (sciatica). One can also experience entrapment of the ulnar nerve at the elbow ("the funny bone") or at the wrist. Single nerves can be entrapped near the groin or at the inner aspect of the ankle.

Causes of Neuropathy

There are multiple potential causes of polyneuropathy and mononeuropathy. Diabetes and excess long-term consumption of alcohol are the most common

causes of polyneuropathy. 20 years after diagnosis, about 15% of diabetics suffer from polyneuropathy. Chemotherapy is another relatively common cause of neuropathy. Aging, vitamin deficiency, exposure to toxic substances, genetic abnormalities and auto-immune disorders are other potential causes of polyneuropathy. These disorders may cause a mononeuropathy as well, although entrapment is among the most common cause of a mononeuropathy.

Medical Diagnosis of Neuropathy

It is important to have a neurologic consultation along with blood tests and, at times, an electrical study, to adequately work up a patient with neuropathy. The electrical study can help determine whether the neuropathy stems from an abnormality of the insulation of the nerves, the myelin, or from the axon, the nerve fiber itself. This determination can narrow the number of potential causes of the nerve disorder. Unless the cause is obvious, such as diabetes, alcohol abuse or chemotherapy, blood tests may help diagnose a vitamin deficiency, such as vitamin B12 deficiency. In addition, a blood test can determine if you have been exposed to a heavy metal such as arsenic or whether you are presenting with an auto-immune disorder. These are treatable disorders including B12 injections, chelation of the toxic heavy metal, and specific treatment of the autoimmune disorder.

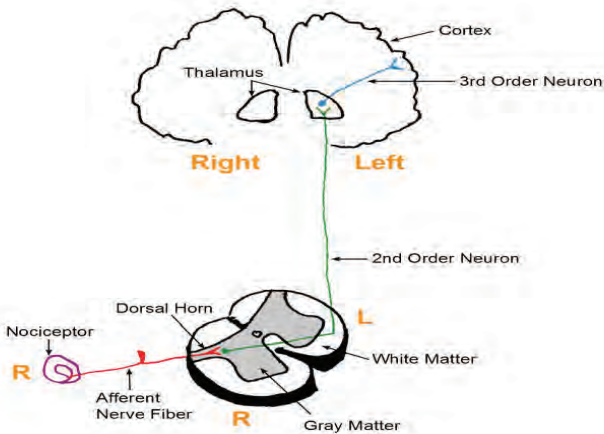
Distribution of Nociceptor (Pain) Nerve-endings

Whilst sensory nerve-endings known as nociceptors are present in any area of the body that can sense noxious stimuli, the skin and superficial fascia are the most highly innervated sensory organs in the body. When exposed to harmful or noxious stimuli, nociceptors trigger the sensation of pain and contribute to ongoing pain sensitivity (2). The thoracolumbar fascia is also richly innervated with nociceptors, a reason many people may be more prone to experiencing lower back pain than in other parts of the body (3).

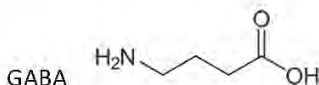
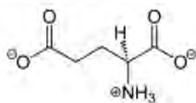
Neurotransmitters and Nerve Pain

The nerve cells (neurons) consist of the “body” of the cell and two types of projections out from the body of the cell, axons and dendrites. Dendrites transmit information into the cell body and axons transmit information out from the cell body. Nerve cells communicate with each other when the axon of one cell connects to the dendrite or body of another nerve cell. This connection is

called a synapse. At the end of the axon, a chemical, or neurotransmitter is released that acts on receptors on the dendrite or cell body. A painful stimulus to your hand or foot causes a signal to be transmitted into the cell bodies located next to your spine (dorsal root ganglia). Axons leaves this ganglion transmitting information into the back (posterior) area of the spinal cord. These axons synapse with another neurons whose axon then ascend the entire spinal cord to synapse with third neurons in an area of the brain called the thalamus. The axons of these neurons ascend to the cortex, the seat of consciousness. It requires three neurons then to transmit a pain signal from your body to the cortex where you become aware of pain. There are thousands of axons that travel to any one dorsal root ganglia. There is one ganglion for each spinal level. In the diagram, the nociceptor is a specialized sensory receptor that responds to a “noxious” stimulus, providing one of the bodies defense systems against harm (4).



Glutamate



The primary excitatory neurotransmitters in the synapses of the pain pathway are glutamate and substance P. Glutamate is the main neurotransmitter. It has an excitatory effect and 40% of synapses in the nervous system involve glutamate. Intense noxious stimuli or tissue damage causes glutamate to be released from peripheral sensory neurons (5, 6). Therefore, blocking the action of glutamate with a topical cream should help mitigate neuropathic pain. There is a pain inhibitory system as well. The main neurotransmitter of this inhibition is gamma amino butyric acid (GABA). Depending on the region of the nervous system, GABA is the neurotransmitter of 20 to 50% of synapses. Serotonin, dopamine and norepinephrine are other neurotransmitters involved in inhibiting pain. There is evidence of release of GABA from sensory nerve endings when the nerve is abnormal such as in peripheral neuropathy. This is a self-regulating effect at nerve endings, utilizing GABA (7). Hence, the application of topical GABA should reduce the pain of peripheral neuropathy.

In addition to neurotransmitters, there are other considerations to address in neuropathy. Another important abnormality is the excess of “free radicals”. A free radical is an atom that needs another electron to complete a “shell” of electrons around its nucleus. Free radicals can damage proteins, nucleic acids that make up our genes and fats (lipids). There are multiple examples of free radicals such as hydrogen peroxide, the hydroxyl radical, oxygen singlet, nitric oxide and so on. The specific free radicals depend upon the chemistry involved. Free radicals play a role in neuropathy including diabetic neuropathy and the neuropathy related to chemotherapy (8,9). Several studies have examined the effect of free radicals in peripheral nerves. One study found a decrease of the speed of nerve conduction with excess free radicals (10). Another study found a relationship of pain to the presence of free radicals (11). The body reduces free radicals with antioxidants. There are numerous antioxidants including vitamin C and E, alpha-lipoic acid as well as numerous molecules found in plants. Not only does alpha-lipoic acid reduce multiple types of free radicals, but it also recycles other antioxidants that have been oxidized by free radicals.

Inflammation and Neuropathy

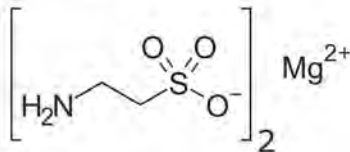
Another essential issue in neuropathy is inflammation. It appears to play a role in alcoholic neuropathy (12), diabetic neuropathy (13), and chemotherapy induced peripheral neuropathy (14). Even the neuropathy associated with aging, without other disorders, appears to have an inflammatory component (15). Inflammation is a complex process and is connected to the free radical – antioxidant system. Aging itself is associated with increased signs of inflammation. Natural compounds from plants have strong anti-inflammatory actions. Due to the complexity of the inflammatory process, natural compounds can mitigate inflammation in different ways.

Nerve Balm Cream Ingredients

Distilled Water, *Aloe barbadensis* leaf juice, Sesame seed oil (*Sesamum indicum*), Olive fruit oil (*Olea europaea*), Lanolin, Cetearyl alcohol (and) Cetearyl Glucoside, Magnesium Taurate, Gamma Aminobutyric Acid, Shankpushpi extract (*Convolvulus pluricaulis*), St. John's Wort extract (*Hypericum perforatum*), Brahmi extract (*Bacopa monnieri*), Lion's mane (*Hericium erinaceus*), Alpha-lipoic acid, Glycerin, Caprylyl Capryl Glucoside, Ethyl alcohol, Lecithin, Lavender oil (*Lavandula*), Rosemary oil (*Salvia rosmarinus*), Clove oil (*Syzygium aromaticum*), Peppermint oil (*Mentha piperita*), Vinpocetine, DMSO, Xanthum gum.

Discussion on Active Ingredients that Inhibit Pain

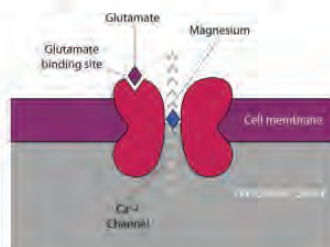
The potency of Nerve Balm Cream stems from basing the formulation on the known physiology of pain in the human body as well as the use of DMSO. The above introduction may be sufficient for most people. For those interested in learning more about the science of Nerve Balm Cream, we will now discuss the rationale for the use each active ingredient.



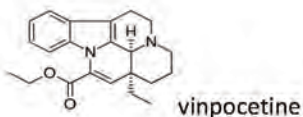
Magnesium – The magnesium in Nerve Balm Cream comes from the compound magnesium taurate, shown above. After absorption, this compound separates into magnesium and taurine. The importance of magnesium in Nerve Balm Cream

is its role in blocking the effect of the excitatory neurotransmitter glutamate on a particular neurotransmitter receptor, the NMDA receptor. Glutamate is an amino acid in the body. In addition to its incorporation into proteins, glutamate is the most abundant excitatory neurotransmitter in the nervous system. The balance between glutamate and GABA is very important. An excess of glutamate increases the risk of a seizure in epileptics, increased pain in pain disorders and even cell death in a process called excitotoxicity. It is also of interest that glutamate is metabolized to GABA in one enzymatic step. The image below depicts how magnesium blocks the function of the glutamate synapse by preventing calcium from entering the nerve cell body.

NMDA receptor



Taurine – the molecule attached to magnesium in the molecular image above, is related to the amino acids except it has a sulfur atom and not the carbon atom in the amino acids. It is one of the most abundant “amino” acids in the body and, surprisingly, measures at 0.1 percent of the total human body weight. It is found in multiple organs in the body including the nervous system. It has multiple functions in the central nervous system, including cytoprotection (protection of cells in the nervous system). It is thought that taurine prevents the action of glutamate by opening chloride channels in the cell membrane (16). A 2001 study at the University of Michigan revealed that taurine, in addition to reducing oxidative stress, also improved levels of nerve growth factor in diabetic peripheral nerves. It is known that nerve growth factor declines in diabetic peripheral nerves (17). As its name suggests, nerve growth factor (NGF) is a molecule involved in the growth, as well as the maintenance, proliferation, and survival of nerve cells (neurons). In fact, NGF is critical for the survival and maintenance of sensory neurons, the ones injured in sensory polyneuropathy.



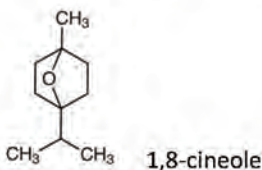
Vinpocetine is a compound derived from the lesser periwinkle plant that goes by the name myrtle or creeping myrtle (*Vinca minor*) in the US. The inclusion of vinpocetine in Nerve Balm Cream relates to its property of blocking sodium channels in the membrane of neurons. Nerves conduct an electrical signal by blocking or allowing various electrolytes such as sodium and potassium to go into and out of the nerve cells through their membrane as the signal travels down the long extensions of the cell. The electrolytes pass through the cell membrane through specific pores that open and close. If a molecule can bind to and block a pore, then the pore remains closed inhibiting the transmission of the electrical signal. This is one of the mechanisms of Dilantin, an anti-seizure medicine used for years to treat seizures. Vinpocetine also binds to the same pores as Dilantin with equal effect in the nerve cell membrane (18, 19). This property, as well as its anti-inflammatory and antioxidant effects, appears to explain its ability to reduce pain, particularly neuropathic pain.

Essential oils - are highly concentrated aromatic oils distilled from plants. They have been used throughout history with the first recorded documentation in the 1100's by Islamic writers in Spain. There has recently been a resurgence of interest in essential oils (aroma therapy) with oils taken orally, through the breath with a vaporizer as well as topically.

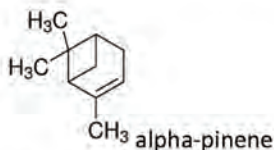
In an interesting article by David Stewart, Ph.D., R.A. he notes that the molecules in essential oils are small and lipid soluble, thereby being able to cross the blood-brain barrier (20). He goes on to describe the extreme concentration of molecules in essential oils, noting that one drop contains 40 million-trillion molecules. This is 40,000 times the number of cells in the human body. He notes that since a single molecule can affect a receptor site, inhalation of a small amount of an oil's aroma may have a significant effect on our body and how we feel.

One of the major chemical constituents of essential oils is called a terpene. The basic unit of a terpene is an isoprene unit consisting of 5 carbon atoms. It is a volatile hydrocarbon, and it is estimated that the world's vegetation emits 600 million metric tons of isoprene into the atmosphere, accounting for approximately 1/3 of all volatile hydrocarbons emitted into the atmosphere (21).

Two isoprene groups make up the monoterpenes and three the sesquiterpenes. Examples of monoterpenes include camphor, thymol, eucalyptol, linalool and menthol. Examples of sesquiterpenes include farnesene, germacrene, norpatchulenol and thujopsene. There are about 2000 monoterpenes, and over 10,000 kinds of sesquiterpenes. An interesting study from Brazil examined plant constituents with analgesic properties. Of the 43 “bioactive” compounds selected, 62.8 percent were monoterpenes, 18.6 percent were sesquiterpenes and 18.6 percent were other types of compounds (22). There is research interest in these compounds for their analgesic properties.

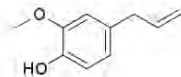


Peppermint essential oil contains the monoterpene 1-8 cineole (cineole). Cineole has the property of blocking a very specific pain receptor TRPA1, found in sensory nerves. TRPA1 appears to play a role in diabetic nerve pain as well as the nerve pain from chemotherapy (23). Another study demonstrated that cineole blocked conduction along nerve fibers like the effect of vinpocetine (24). Cineole is also noted to have antioxidant and anti-inflammatory properties (25).



Rosemary essential oil has many constituents including cineole and another monoterpene, alpha-pinene. Alpha-pinene also has pain relieving properties as well as protection against oxidative stress, inflammation, and neuronal damage (26). Although the mechanism is not well elucidated, alpha-pinene has been shown to relieve neuropathic pain (27).

Lavender essential oil contains both 1-8 cineole and alpha-pinene and therefore adds to the favorable properties discussed above.



eugenol

Clove essential oil - Cloves (*Syzygium aromaticum*) are the unopened flower buds of the clove tree native to old world tropics, particularly the Moluccas (Spice Islands) in Indonesia. It is an evergreen tree about 40 feet tall. The history of cloves is quite interesting. Clove was known in China at least 2000 years ago and in Europe by the fourth century A.D. Curiously, the Dutch, in an attempt to control the clove trade, cut down all the clove trees in the Moluccas except for one island. They held the monopoly for 150 years. Ultimately the French smuggled seedling clove trees to Mauritius, an island on the east side of Africa and by 1800 clove trees were cultivated in other islands in the Indian Ocean. Currently islands belonging to Tanzania produce 90% of the world's cloves.

Most of the research on clove essential oil focusses on eugenol although the oil contains 38 different compounds. Worldwide, eugenol is used as a dental analgesic. It definitely allays tooth pain. Multiple mechanisms are involved in its analgesic mechanism. It inhibits a type of sodium channel similar to the action of local anesthetics like lidocaine. The influx of sodium through sodium channels is essential to conduction of the nerve impulse (action potential) and nerve conduction cannot occur if the sodium channel is blocked. Another mechanism is the effect of eugenol on GABA receptors. A 2017 paper reported on a study showing that aqueous extracts of clove "significantly and specifically potentiated the GABA-induced current" (28). As discussed above, GABA is the main inhibitory molecule of pain. The fact that eugenol has these two mechanisms of action explains its potency in reducing nerve pain. Experimental studies in animals confirms that eugenol reduces neuropathic pain.

Aloe barbadensis (*Aloe vera*) is a succulent, perennial plant that naturally grows in extremely dry and poor soils. It will also grow in many different types of soil, from sandy to moderately fertile loam, if they have good drainage. It tends to grow in hot, dry climates and is found in Africa, Asia, Europe, and the Americas. Aloe vera belongs to the genus *Aloe* which contains over 500 species of flowering succulent plants. The plant contains 19 of the 20 known amino acids along with numerous other organic molecules. It has a long history of use in Chinese and Ayurvedic medicine and is considered by some authors one of the most commonly used medicinal plants in history (29). Some of its medicinal uses

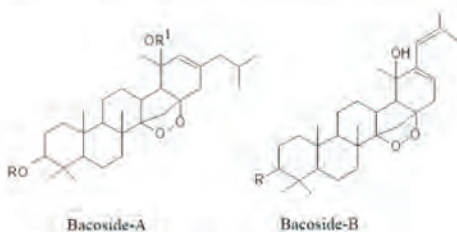
include use as a topical anaesthetic, a treatment for burns, prevention of skin complications from radiotherapy, a skin moisturizer, an anti-inflammatory for cold sores, for eczema and pruritis, diabetes and ulcerative colitis. Traditional uses include benefits in the treatment of tumors, arthritis, diabetes, enhancing immunity and lowering cholesterol levels. Topical Aloe vera blocks pain and is anti-inflammatory and antioxidant. These properties make it an important plant to consider for topical use for peripheral neuropathic pain. Multiple experimental studies on animals demonstrate its beneficial effect on neuropathic pain. Although there appears to be no controlled study of its use in humans for neuropathic pain, one author of an animal study concludes by stating that Aloe vera is “an important plant to consider for topical use for peripheral neuropathic pain” (30). The mechanism of blocking neuropathic pain by Aloe vera is not known, however, one author states, “Further studies to confirm the mechanism of action will help develop suitable A. vera formulations for neuropathic pain therapy” (31).



Sesame seed oil - is quite ancient with its use recommended in the Vedas. The Vedas are ancient texts from India dating to the second millennium BC. It was recommended in the Vedas to promote general health. Ayurveda, the indigenous medical system of India regards sesame oil as the queen of oils due to its benefit for so many health issues. In terms of its history, charred remains of sesame have been recovered from archeological excavations dating to 3500-3050 BC. Sesame was used by the Babylonians and the Persians. The plant, Sesame, tends to grow in tropical regions, particularly Africa and India. It will grow in drought like conditions when other plants fail to grow. Sesame seed has one of the highest oil content of any seed. Sesame seed oil is composed of linoleic acid (41% of total), oleic acid (39%), palmitic acid (8%), stearic acid (5%) and others in small amounts. In addition, the oil contains tocopherols with a predominance of gamma-tocopherol (90.5%).

There is a 2015 study on the use of topical sesame seed oil on patients in Iran with upper or lower extremity trauma. This was a controlled study in which the

experimental group received topical sesame oil on the painful traumatized areas and the control group received routine care. Pain levels and use of non-steroidal anti-inflammatory drugs (NSAIDs) was measured multiple times during the hospital stay. A significant benefit in pain control was noted in the experimental group with significantly less use of NSAIDs. The authors conclude, "Topical application of sesame oil could reduce pain severity and frequency of received NSAIDs in patients with upper and lower extremity trauma. Therefore, it is recommended to use this oil in complementary medicine for pain relief due to low cost, easy usage and lack of adverse effects" (32). Multiple experimental studies on animals are available on-line reporting the benefit of sesame seed oil for neuropathic pain. In one study, the authors conclude, "These results suggest that sesamin is one of the active compounds found in sesame oil and justify the antinociceptive and anti-inflammatory properties of this product" (33). Sesamin has been shown to have neuroprotective properties. In particular, sesamin appears to enhance nerve growth factor's effect on nerve regeneration (34).

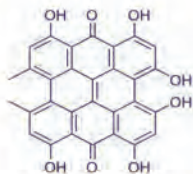


Bacopa – is also called water hyssop, Brahmi, herb of grace or Indian pennywort, is an annual creeping plant found in the wetlands of southern and eastern India as well as Australia, Europe, Africa, Asia and the Americas. The name Brahmi derives from Brahma, the first of the Hindu trinity of Gods. The aerial parts of the plant

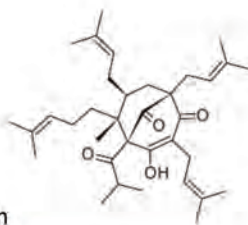
are used medicinally. When it is infused in sesame oil it is called Brahmi oil. Bacopa is part of the ancient Ayurvedic medical system of India used for mental disorders and loss of intellect and memory. Multiple experimental studies are available online and it is suggested that the neuropharmacological effects appear to be due mainly to molecules called bacoside A and B. One interesting study suggested that an extract of Bacopa acted on the opioid receptors since its effect was blocked by naloxone, a drug that blocks the opioid receptor. The specific molecules responsible for this effect was not discussed in the article (35).



Shankpushpi - refers to 4 different herbs in Ayurvedic medicine, the indigenous ancient medical system of India. For our purposes we are referring to *Convolvulus pluricaulis*. Shankpushpi belongs to a class of herbs that can improve memory and intellect. Acetylcholine is well known as an important neurotransmitter for memory. Studies have shown that extracts of *Convolvulus pluricaulis* reduces levels of acetylcholinesterase, the enzyme that breaks down acetylcholine (36). Inhibiting acetylcholinesterase thereby raises levels of acetylcholine. Of interest is that acetylcholine can modulate pain signals in peripheral sensory neurons (37, 38). Specifically, acetylcholine blocks a specific receptor, the muscarinic receptor, to reduce the transmission of pain. In addition, multiple studies suggest that the molecular components of convolvulus act on the GABA receptor, the major inhibitor of pain (39). The specific components that act on the GABA receptor have not been identified. The combination of the ability of Shankpushpi to increase acetylcholine and its GABA activity helps to explain its beneficial effect on neuropathic pain.



hypericin



hyperforin



St John's wort oil – dates back to classical antiquity (Greco-Roman empire) and apparently was a component in a Theriac, or panacea (from Panacea, the Goddess of universal remedy). The history of Theriacs, dating over 200 years is of interest, and initially conceived as a universal antidote to an external toxic agent. The power of Theriacs apparently led to the conception of a panacea.

[For the reader interested in the clinical history of St. John's Wort, I would recommend the on-line article by Christopher Hobbs PhD, "*St. John's Wort: Ancient Herbal Protector*".]

In addition to its ancient use for wounds, and the bites of any venomous creature, it was also used for kidney disorders, and as a febrifuge, vermifuge, as well as for gout and rheumatism. It was also known for repelling undesirable influences and promoting good luck. It is best known for its use in "nervous disorders", particularly depression (40). The reader should note that although there are some recent studies in peer reviewed journals, the bulk of information on the clinical use of St. John's Wort comes from its traditional usage in herbal medicine. For example, in an online article by Angela Justis (41), the author quotes the herbalist Mary Bove, who states, "St. John's Wort is known for helping to diminish pain". Justis goes on to state that St. John's Wort can diminish pain "both externally and internally". She further notes, "Specifically indicated for trauma and damage to the nervous system whether through injury or viral infection. St.

John's Wort is the herbalist go-to for painful issues such as neuralgias, sciatica, Bell's palsy, head and spine trauma, pinched nerves, after surgical and dental work, as well as injuries to any area that is rich in nerve endings".

There are multiple articles studying the effect of St. John's Wort (SJW) on pain transmission. One study in experimental animals, demonstrated that a St. John's Wort extract, in particular, hypericin, blocked pain on its own and potentiated the effect of morphine (42). Of interest is that another molecule in SJW (hyperforin) also reduces neuropathic pain but, unlike hypericin, acts through the opioid system. So, two different molecules in St. John's Wort help block pain signals coming from the periphery of the body. The antioxidant and anti-inflammatory properties of St John's Wort will be discussed below.

GABA – is the main inhibitory neurotransmitter in the nervous system. It is well established to exist in the central nervous system. An interesting study in 1999 demonstrated the presence of GABA receptors on 14% of the small unmyelinated peripheral nerve fibers. These are called C-fibers that carry the slow response to a noxious, painful stimulus. GABA at a physiological level inhibited the pain from the injection of the noxious agent, formalin, into the paw of experimental animals (43). Another study using formalin injected into the paws of experimental animals demonstrated reduced pain when Gabapentin (a pharmaceutical medication) was injected along with the formalin (44). The mechanism of Gabapentin involves an indirect effect on the role of the GABA receptors. It is widely used for a variety of pain disorders, including peripheral neuropathy. An interesting 2019 study demonstrated that Gabapentin causes an increase in GABA receptors thereby increasing the effect of existing GABA at the synapse. Nerve Balm Cream contains GABA itself which will reduce pain by acting on the peripheral GABA receptors.

The Role of Free Radicals in Peripheral Neuropathy

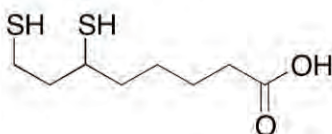
Free radicals play an important role in peripheral neuropathy. As a recent paper notes, "mammalian nerves are especially susceptible to free radicals, including oxygen (ROS) and nitrogen reactive species (RNS), due to their high content in phospholipids and axonal mitochondrion; in addition, neuronal antioxidant defenses are weak" (45). The mechanism of an imbalance between free radicals and antioxidants is different depending on the cause of the neuropathy. For example, in diabetic neuropathy, the metabolism of an excess amount of glucose causes an increase of free radicals generated by the breakdown of the glucose molecule. The neuropathy caused by chemotherapy appears due to both the high

levels of free radicals caused by multiple chemotherapy agents as well as a loss of antioxidants. As noted above, this is a particularly serious problem for neurons. A similar mechanism seems to occur in the neuropathy caused by chronic alcoholism. Once there is an excess production of free radical, the oxidative stress is a deleterious process that can seriously alter the cell membranes and other structures such as proteins, lipids, lipoproteins, and deoxyribonucleic acid (DNA).

The antioxidant system of the body is complex. There are specific antioxidants such as vitamin C, and E that interact with specific free radicals. Antioxidants can inhibit the activity or expression of free radical generating enzymes or enhancing the activity or expression of intracellular antioxidant enzymes.



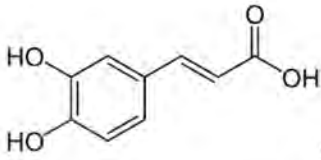
lipoic acid



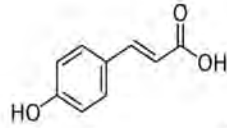
dihydrolipoic acid

Alpha-lipoic acid (ALA) and its reduced form, dihydrolipoic acid, is an important and powerful antioxidant. The oxidized form, lipoic acid, has lost an electron to a free radical, hence the two sulfur atoms are sharing an electron, and hence the bonding between them. ALA scavenges hydroxyl radicals, hypochlorous acid, peroxynitrite, and singlet oxygen (examples of free radicals). ALA also scavenges superoxide and peroxy radicals (more examples of free radicals) and can regenerate thioredoxin, vitamin C, and glutathione, which in turn can recycle vitamin E. ALA acts as an antioxidant in the extracellular water phase and the lipid intracellular phase. ALA plays an important role in Nerve Balm Cream, in the immediate reduction of free radicals and setting the stage for recovery of injured peripheral nerves.

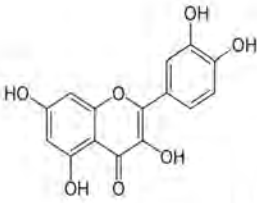
Multiple other ingredients in Nerve Balm Cream have antioxidant properties:



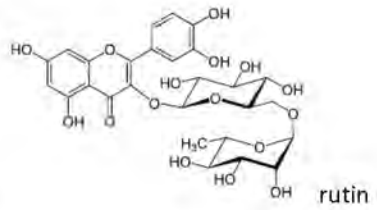
caffeic acid



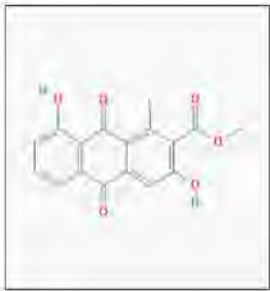
coumaric acid



quercetin



rutin



aloesaponarin I

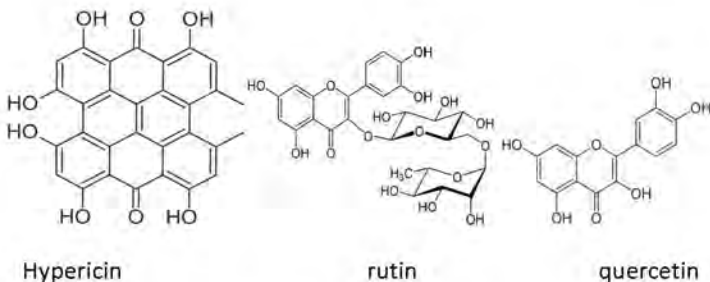


palmitic acid

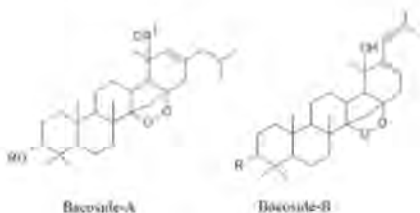


Aloe vera has numerous medicinally beneficial constituents. There are multiple studies on the antioxidant properties of Aloe vera. There is some evidence that the phenolic compounds provide the strongest antioxidant potential. Phenolic compounds contain the hexagonal carbon ring with three double bond and have hydroxyl groups attached to the ring. Flavonoids (types of organic molecules) are more complex as shown by quercetin and rutin pictured above. Anthroquinones, such as aloesaponarin I and II are also antioxidant as are tannins such as palmitic acid.

Essential oils – all four essential oils in Nerve Balm Cream have antioxidant properties. Although the large number of different flavonoids (a type of organic molecule) in essential oils act as antioxidants, alpha-pinene, 1,8-cineole and eugenol provide a significant percentage of the antioxidant properties of lavender, peppermint, rosemary and clove essential oils. Eugenol has an interesting antioxidant mechanism. A recent experimental study found that eugenol causes an increased expression of a gene, whose protein, nuclear factor-erythroid 2 related factor 2 (Nrf2), is a central regulator of cellular responses to oxidative stress, in a dose dependent manner (46). 1-,8 cineole also appears to increase Nrf2 creating more antioxidant capacity of the affected cells. The antioxidant mechanism of alpha-pinene is unknown although up regulation of Nrf2 has been proposed.



St. John Wort – Based on a review of the literature, St. John’s Wort has a significant antioxidant capacity. On the other hand, it is not clear which molecules provide the strongest antioxidant effect. This would depend on the specific free radical, its concentration, and when the plant was harvested. On the other hand, there seems to be a consensus that flavonoids, containing benzene rings, may provide the best antioxidant capacity. In general, there are multiple mechanisms of the chemistry of antioxidant behavior. An antioxidant can either donate or receive a single electron from a free radical. A complex molecule like the flavonoids noted above can “de-localize” an electron. That is to say, the probability of finding the extra single electron can be spread out over the entire molecule. St John’s Wort is rich in flavonoids. Three examples are illustrated above.

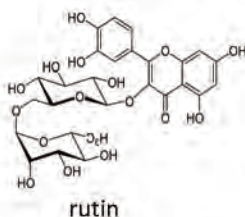


Bacopa is also known to have antioxidant properties, as do most herbs. One extensive article on the antioxidant properties of Bacopa suggests that the Bacoside molecules are mostly responsible for the antioxidant behavior (47). The reader will note that these molecules do not have benzene rings, although they do have an extended hexa-cyclic ring structure. On the other hand, another review article noted that studies on Bacopa found that Bacoside A administration increased the activities of antioxidant enzymes [superoxide dismutase (SOD) and catalase] (48). Catalase reduces hydrogen peroxide and superoxide dismutase reduces the superoxide radical.

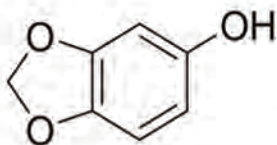
superoxide radical



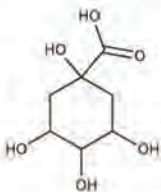
superoxide



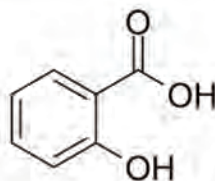
Shankpushpi (*Convolvulus pluricaulis*) – Shankpushpi has antioxidant properties apparently due in large part to scopoletin, pictured above (49). The molecular image reveals one benzene ring. It is not as strong as rutin, a flavonoid found in other species of convolvulus. Note that it has two benzene rings increasing its antioxidant potential. The antioxidant property of Shankpushpi plays a beneficial role in age-related cognition decline. In Nerve Balm Cream, Shankpushpi plays an important role in quenching free radicals found in different types of neuropathies.



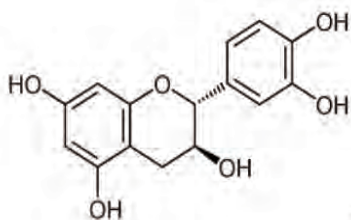
Sesamol



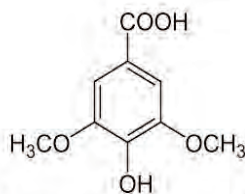
sesamin



quinic acid



catechin



syringic acid



Sesame seed oil - is highly antioxidant, higher than apple, pomegranate, banana, or citrus peels. It contains 16 polyphenolic compounds; a few examples are illustrated above. In addition, sesame seed oil exhibited higher oxidative stability than soybean, corn and other vegetable oils.

Lion's mane (*Hericium erinaceus*) – Lion's mane is an edible mushroom native to north America, Europe, and Asia. It has a long history of use in Chinese medicine, used for disorders of the brain and other organs. Buddhist monks were said to have used Lion's mane mushroom powder as a tea to enhance brain power and heighten their focus during meditation. A recent study demonstrated a significant reduction in reactive oxygen species using water and alcoholic extracts in an experimental study using neurons from a mouse hippocampus. There was an increase in the antioxidant enzyme, catalase, and the important antioxidant glutathione. There was also a significant reduction in the pro-inflammatory molecule nitric oxide (50).

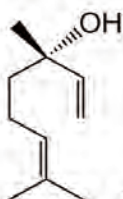
The Role of Inflammation in Neuropathy

It is known that damage to peripheral nerves leads to a local inflammatory response which contributes to the generation of hypersensitivity or neuropathic pain. Looking more closely at specific causes of peripheral neuropathy such as

diabetes; “DPN (diabetic peripheral neuropathy) is related to the increase of inflammatory cells in peripheral nerves, abnormal cytokine expression, oxidative stress, ischemia, and pro-inflammatory changes in bone marrow” (51). Cytokines are small proteins involved in signalling from one cell or organ to another cell or organ. In this case, the cytokine signalling is probably of a nature to increase an inflammatory process.

Regarding chemotherapy-induced peripheral neuropathy, a review article states, “evidence has demonstrated a chemotherapy-induced increase in peripheral pro-inflammatory cytokines and a strong correlation with peripheral neuropathy” (52).

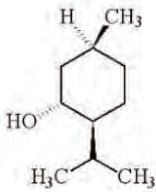
Alcoholic neuropathy is multifactorial in origin including the toxic effect of alcohol on peripheral nerves and dietary nutrient deficiencies. Other studies have shown a direct, negative effect from alcohol and its many metabolites on the nervous system. Axonal degeneration and demyelination of neurons were seen in both humans and lab mice receiving alcohol. The cause is a diverse multifactorial process caused from damage by free radicals, the release of inflammatory markers, and oxidative stress (53). There appears to be an increase in protein kinase C, which is directly involved in activating an inflammatory reaction. Inflammation and oxidative stress are closely connected. Inflammation may cause an increase in free radical production and oxidative stress may increase an inflammatory response. This suggests that the discussion on the antioxidant potential of ingredients in Nerve Balm Cream applies to inflammation as well. Some ingredients have a particularly strong anti-inflammatory effect. In general, essential oils inhibit inflammation through the regulation of the release of inflammatory cytokines involved in multiple inflammatory signaling pathways.



linalool



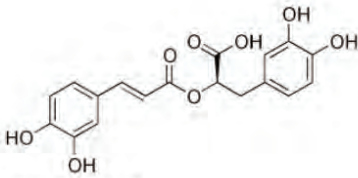
Lavender essential oil – A recent experimental study demonstrated that lavender essential oil extracted at the beginning of the flowering period reduced multiple pro-inflammatory cytokines. In particular, the messenger RNA (precursor to protein production) and the inflammatory proteins, IL-6, IL-1beta and IL-8, were all reduced by lavender essential oil (54). It is thought that linalool, pictured above, is one of the main anti-inflammatory molecules in lavender essential oil.



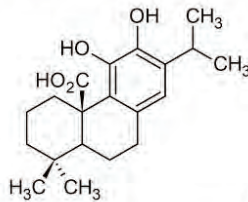
menthol



Peppermint essential oil – in an experimental procedure, Peppermint essential oil inhibited inflammatory mediators, namely tumor necrosis factor – alpha and IL-1-beta (55). Although peppermint essential oil has as many as 80 constituents, menthol, pictured above, appears to be the main anti-inflammatory constituent.



carnosic acid



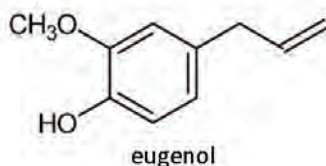
rosmarinic acid



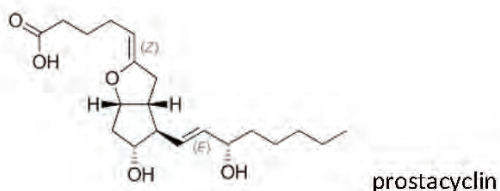
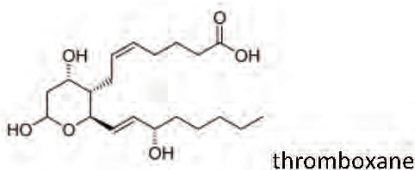
Rosemary essential oil - A literature review found that rosemary essential oil contains 150 chemical compounds. The anti-inflammatory mechanisms appear to involve suppression of a molecule NF-kappaB involved in the gene transcription of pro-inflammatory molecules. Rosemary essential oil also inhibits the arachidonic acid cascade. This cascade starts with an essential fatty acid and ends with pro-inflammatory molecules (56). The literature also suggests that the two molecules, carnosic acid and rosmarinic acid, pictured above, are important to its anti-inflammatory properties.



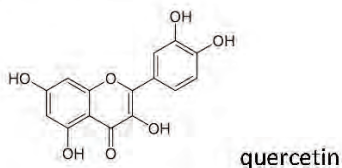
Clove tree flowers



Clove essential oil - A recent experimental study found that clove essential oil (CEO) significantly reduced inflammation in an experimental model. To quote from the paper, "It significantly inhibited the increased production of several pro-inflammatory biomarkers such as vascular cell adhesion molecule-1 (VCAM-1), interferon γ -induced protein 10 (IP-10), interferon-inducible T-cell α chemoattractant (I-TAC), and monokine induced by γ interferon (MIG). CEO also significantly inhibited tissue remodelling protein molecules, namely, collagen-I, collagen-III, macrophage colony-stimulating factor (M-CSF), and tissue inhibitor of metalloproteinase 2 (TIMP-2). Furthermore, it significantly modulated global gene expression and altered signalling pathways critical for inflammation," (57). There is extensive literature on the specific anti-inflammatory effects of eugenol in clove oil (image above).



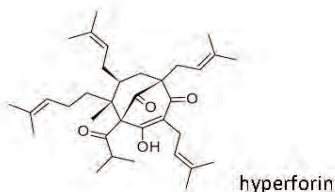
Sesame seed oil – has well known anti-inflammatory properties. A recent literature review notes that Sesame seed oil inhibits COX (cyclooxygenase), and the pro-inflammatory cytokine NF-kB, inhibits MAPK signaling and the prostaglandin synthesis pathway (61). COX is an enzyme that produces a group of pro-inflammatory molecules called prostanoids such as thromboxane and prostacyclin, illustrated above. NF-kappaB is a transcription factor, a molecule that promotes certain genes to manufacture proteins. NF-kappaB signals pro-inflammatory genes to manufacture inflammatory proteins. MAPK is a chain of proteins in the cell that communicates a signal from a receptor on the surface of the cell to the DNA in the nucleus of the cell for protein production. In this review, the MAPK signalling is apparently responsible for the production of inflammatory molecules.



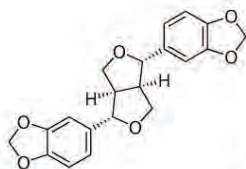
Bacopa – in a 2022 study, it was discovered that a particular compound in Bacopa, quercetin, reduces the production of nitric oxide (an important pro-inflammatory molecule) and downregulates the gene expression of COX-2 and nitric oxide synthase (the enzyme that produces nitric oxide) (62).

Lion's mane (*Hericium erinaceus*) – perhaps more than any other ingredient in Nerve Balm Cream, Lion's mane is the most neurotrophic factor, promoting nerve regeneration. The above diagrams show only one family of hericenones and erinacines in Lion's mane. These compounds induce the synthesis of nerve growth factor in nerve cells. Unfortunately, the mechanism of induction of NGF production is unknown.

An experiment reported in 2019 was performed on mice who developed peripheral neuropathy from the anti-cancer drug cisplatin. After receiving an aqueous extract of Lion's mane, they observed a significant regeneration of axons and myelin as well as an improvement in the physiology of the peripheral nerves. They conclude, "HE (*Hericium erinaceus* – Lion's mane) exhibited therapeutic effects on a mouse model of peripheral neuropathy. HE may be an efficient and safe therapeutic agent to be used in peripheral neuropathy. Therefore, our study warrants further detailed investigation of HE as a potential therapeutic agent" (64).



St. John's Wort - a 2007 report on an experiment using hyperforin, a constituent of St. John's Wort, states, "hyperforin induces neuronal axonal sprouting like a nerve growth factor in a TRPC6-dependent manner. These findings support the role of TRPC channels in neurite extension..." (65). TRPC6 stands for transient receptor potential cation channel, subfamily C, member 6, a specific human gene encoding a protein by the same name. TRP is a group of ion channels located mostly on the plasma membrane of numerous animal cell types. The channels are relatively non-selective for cations, including sodium, calcium and magnesium. These cations can pass through these channels between the intra and extracellular spaces. TRPC6 is apparently the molecular target for hyperforin, and this experiment suggested a role for these channels in neuronal axonal sprouting. These channels are now being studied for their role involving growth factors such as NGF.



sesamin

Sesame seed oil - An interesting paper in 2019 reported on experiments using sesamin, from sesame seed oil, on PC12 cells. PC12 cells are precursor cells for neurons derived from a pheochromocytoma cell line (a tumor of the rat adrenal medulla). Nerve growth factor was used at two different strengths and sesamin was added with the lower NGF level. Neuron-like differentiation and neurite lengths were studied. They report, "Sesamin effectively enhanced the PC12 neuron-like cell differentiation and neurite length under insufficient conditions of NGF... synaptic connections were significantly increased in combination treatment between sesamin and NGF". They also note that two important proteins involved in neurogenesis (formation of neurons) were increased by sesamin, phospho-ERK1/2 and SIRT1 (66).

Conclusion

We appreciate the forbearance of the reader with all the technical details supporting the efficacy of the constituents of Nerve Balm Cream. The cream is a unique and complex product that provides rapid relief from neuropathic pain as well as joint and soft tissue pain. It also has a variety of neuroprotective as well as neurotrophic properties. The neurotrophic properties promote healing of nerves injured by a variety of disorders such as diabetes, chemotherapy, trauma or alcohol abuse. The product has a patent pending, and is available at Supplementcreams.net, at various herbal pharmacies and from Integrated healthcare practitioners.

Sidney Kurn MD (Founder of the herbal pharmacy, *Farmacopia*, and co-author of *Herbs and Nutrients for Neurologic Disorders*).

For more information visit:

www.supplementcreams.net

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