

# SPECIFICATION

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## [USE OF ERUCIC ACID IN ENHANCING BLOOD FLOW TO TISSUES]

### Background of Invention

- [0001] Erucic acid (Z)-13-Docosenoic acid is  $\Delta^{13}$  cis-decosenoic acid ( $C_{22}H_{42}O_2$ ) is a monoethenoid acid found in the seed fats of *Cruciferae* and *Tropaeolaceae* family of plants. It constitutes 40 to 50% of total fatty acids of rapeseed, mustard and wallflower seed, and it represents up to 80% fatty acids of nasturtium seeds (K. S. Markley, Fatty Acids Part I, Interscience, New York, 2<sup>nd</sup> ed., 1960).
- [0002] Erucic acid is prepared crudely by alkaline hydrolysis of rapeseed oil and refined by fractional precipitation or crystallization or by acid soap crystallization. Treatment with nitric acid yields brassidic acid. Erucic acid can also be isolated from rapeseed oil fatty acids by fractional distillation or multiple-solvent crystallization at low temperature (Stage, H., Fette Seifen Anstrichm. 1975. vol. 77, p. 165-204). In the case of fractional distillation, however, temperatures of up to 255 °C must be utilized which may result in by-product formation, which imparts an undesirable color to the erucic acid (Stage, H., World Conference on Oleochemicals into the 21st Century. T. H. Applewhite, ed. 1990. American Oil Chemists Society, pp. 142-160). Patent 5,633,151 describes an enzymatic process for the isolation of erucic acid from vegetable oils.
- [0003] Erucic acid is a naturally occurring fatty acid found in the storage triglycerides of plants of the family *Brassicaceae*. Rapeseed is a member of this family and is grown in several countries for its oilseed. Rapeseed oil contains a high content of erucic acid (more than 40%) and is important in industrial applications. Rapeseed

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(*Brassica napus*) is an interesting plant that has been bred as two varieties, yielding either a HEAR (High Erucic Acid Rape) or a Low Erucic Acid Rape oil (LEAR). HEAR oil contains as much as fifty percent of the unpalatable monounsaturated fatty acid, erucic acid (*cis*-13-docosenoic acid), and is used as an industrial lubricant. LEAR oil has less than two percent erucic acid, and enjoys commercial success under the name of canola oil: a vegetable oil with less saturated fat than corn oil or soybean oil. Erucic acid is present in rapeseed oil as glycerol trierucate, which is employed as a high temperature lubricant. Also, glycerol trierucate serves as an interim treatment, but not a cure, for adrenoleukodystrophy (ALD), a progressively debilitating disease involving the nervous system, adrenal cortex, and testis. ALD patients accumulate saturated very long chain fatty acids (VLCFA) whose levels may be reduced by ingesting Lorenzo's Oil: a mixture of glycerol trioleate and glycerol trierucate. The strategy is to shift the ALD patient from producing saturated VLCFA by liberally administering the monounsaturated fatty acids present in Lorenzo's Oil. Apparently, the unsaturated VLCFA consequently produced by the patient are less harmful than the saturated VLCFA normally generated in ALD. A further useful property of erucic acid is conferred by its amide, erucamide (*cis*-13-docosenoic acid amide), which has a high melting point of about 80 °C. The main uses of erucic acid are in producing erucamide, acid, alcohol, various erucic acid metallic salts and esters, are widely used as plastic auxiliary and surfactants. Polyethylene and polypropylene items such as bread wrappers, garbage bags, and plastic films all include a thin coating of erucamide that improves handling and prevents the plastic from sticking to itself. It is also used for textile fiber lubrication (e.g., fabric softeners) and in hair care products. Rapeseed oil is also used as cooking oil in Asia for many generations. However, its use in Europe and North America has been hampered by its toxicity: myocardial lipidosis, myocardial necrosis, and impaired oxidative phosphorylation. The toxicity was thought to be attributed to the erucic acid content, which comprises 40–50% of the total fatty acids in the oil. This has led to development of low erucic acid rapeseed (LEAR) oil (0.4–2%). Spanish toxic oil, which resulted in more than 800 deaths, consisted, however, mostly of LEAR oils. Prediction of the safety of LEAR oils in man is thus questionable. The LEAR cultivars

are high in glucosinolates. A second new type of rapeseed oil, low in both erucic acid and glucosinolates, called canola is now the major rape product. (D. V. Parke and N. L. Parke, J. Clin. Biochem. Nutr. 26(2), 51–61 (1999); J. Dupont et al., J. A. Coll. Nutr., 8(5), 360–75 (1989).

[0004] Besides rapeseed, another significant source of erucic acid is mustard, which has been used in food for thousands of years in a number of cultures. Indian mustard is grown in many countries for the preparation of condiment mustard because of the hot-tasting and pungent-smelling compounds present in its seeds. It is also being used on a substantial scale on the Indian subcontinent, and in China and Russia for the production of cooking and salad oil. The original form of mustard contains erucic acid in the oil and hot-tasting glucosinolates, which are responsible for its "zing" in mustard. In some countries, such as India, mustard meal is used as a fertilizer or for cattle feed. The amino acid balance of the meal makes it suitable for feeding to mono-gastric animals such as pigs and poultry as a protein supplement, but the hot compounds are distasteful to pigs and may injure poultry. Thus, to make mustard a useful modern crop, it was necessary to reduce the levels of erucic acid and glucosinolates. Mustard oil (*Candida rugosa*) treated by commercially available lipase shows about ten fatty acids with erucic acid comprising about 16% of the fatty acid content.

[0005] Erucic acid can cause heart muscle degeneration if consumed in large amounts and edible oil used in developed countries must have less than two percent of erucic acid. Oral administration of rapeseed oil in rats has shown to result in extensive body accumulation of erucic acid, mainly in the adipose tissue (70–80%) and also in myocardium and liver (7–10%); females accumulate more erucic acid in myocardium and adipose tissue. Erucic acid also showed negative effect on the memory but no difference in the body weight gain was recorded. (D. Hrivnak and A. Wolf., Cesk. Hyg. 30(9), 456–64 (1985)). Erucic acid produces severe disorders and irreversible lesions in laboratory animals. (E. Turchetto and W. Ciusa., Quad. Merceol. 11(1)), 131–7 (1972)). Rats fed rapeseed oil show dermal lesions and alopecia (H. W. Hulan, W. G., et al., Can. J. Physiol. Pharmacol., 54(1): 1–6 (1976)). There are indications that other components, besides erucic acid, of rapeseed oil

may also affect myocardium (D. J. de Wildt, G.J. Speijers. Toxicol Appl Pharmacol 15:99–108, 1984)). Rats fed oils high in erucic acid show increased resistance to erythrocyte hemolysis (A. Varjewswari, et al., Biochem. Med., 29(1): 74–84 (1983)).

[0006] Oral intake of sources rich in erucic acid leads to accumulation of erucic acid in man also (G. L. Gatti, H. Michalek, Arzneimittelforschung, 25(10): 1639–42 (1975)). Since the use of rapeseed oil in daily diet is high in China, studies in Chinese children show accumulation of erucic acid in blood and other tissues. (M. D. Laryea, et al., Ann Butr. Metab., 36(5–6): 273–8 (1992). The effect of erucic acid on platelets in patients with adrenoleukodystrophy has been studied where treatment with Lorenzo"s oil (which is rich in erucic acid) lead decrease in mean platelet count and altered morphology of platelets. (T. S. Kickler et al., Biochem. Mol. Med., 57(2): 125–33 (1996)).

[0007] A variety of applications of plant oils derived from *Brassica* genus in the family of *Cruciferae* are described. For example, the U. S. Patent 5,476,492 to Urugand describes a body warmer for therapeutic purpose containing whole herb seeds of rubefacient mustard. A device containing these seeds is wrapped around the tissue wherein the body heat causes gradual release of vapors of rubefacient compounds from the herb seed. The vapors pass through the breathable shell of the body warmer and act on the body part to enhance body heat production. The herb seed used to obtain enhanced body heat production is white mustard (botanical name *Brassica alba*) and black mustard (botanical name *Brassica nigra*). A combination of the two in proportion 35–45 percent of white mustard and 55–65 percent black mustard has been found empirically to produce best results.

[0008] The U.S. Patent to Matsuda, et al., 5,773,073 describes how to manufacture an emulsion with high level of water using erucic acid as the main fatty component for food product formulations such as low–calorie margarine and butter cream.

[0009] This invention describes the effect of erucic acid on peripheral circulation, particularly, inducing localized enhancement of blood flow to the surface of tissue where it is applied in animals and humans. It is suggested that erucic acid may affect the peripheral vascular system. Vasoconstrictors and vasodilators are the

pharmacological agents that upon systemic or local application decrease or increase blood flow to the tissue. The mechanism involved in enhancing blood flow ranges from producing irritation (rubefacient) to reducing the tension of veins and arteries to muscle relaxation that leads to lower pressure on the vascular structure. Several significant effects can be achieved when blood flow to skeletal and other body tissues are altered. These include, but are not limited to, faster absorption of topically applied drugs, improved sensation to physical stimuli, engorgement of organs to produce erection of penis and clitoris, enhanced sensation of comfort in sensitive tissues, feeling of warmth, alleviation of pain and muscle stress, etc. Many topically applied products contain components labeled as rubefacient that enhance flow of blood to the surface by producing an irritation that causes the blood to rush to the site of application; the warmth produced as a result alleviates or soothes the pain.

[0010]

The effectiveness of topical vasodilators or drugs that enhance blood flow to tissues can be measured by many techniques. In this study I used the technique of monitoring blood flow and skin temperature using laser Doppler imaging as it has been successfully used to measure skeletal muscle blood flow at rest and during exercise in human subjects (Radergran, G., Proc. Nutr. Soc., 58(4): 887–98, 1999) and to assess microcirculation (Eun, H.C., 13(4): 337–47, 1995). Obayashi et al describe the use of laser Doppler imaging in assessing the enhanced blood flow to penis and surrounding pelvic area. Administration of 25 mg dose of sildenafil citrate substantial increased skin surface temperature prior to and during an erectile response (J. Auton. Nerv. Syst., 80(1–2), 89–92, 2000). The laser Doppler technique measures blood flow in the very small blood vessels of the micro-vasculature, such as the low-speed flows associated with nutritional blood flow in capillaries close to the skin surface and flow in the underlying arterioles and venules involved in regulation of skin temperature. The tissue thickness sampled is typically 1mm, the capillary diameters 10 microns and the velocity spectrum measurement typically 0.01 to 10mm/s. The technique depends on the Doppler principle whereby low power light from a monochromatic stable laser (  $\lambda$  ) e.g. a Helium Neon gas laser or a single mode near infra-red laser diode, incident on

tissue is scattered by moving red blood cells and as a consequence its frequency broadened ( *b* ). The frequency-broadened light, together with laser light scattered from static tissue, is photo detected and the resulting photocurrent processed to provide a blood flow measurement. In a Laser Doppler blood flow Imager (LDI) the low intensity laser beam is scanned across a tissue surface in a raster fashion using a moving mirror. There is no direct contact with the tissue being assessed. Both large areas (such as a full torso) and small areas (such as part of a finger) can be scanned enabling the blood flow to be mapped and color coded images of the blood flow displayed. Regions of interest can be defined and statistical data calculated and recorded. Single point measurements give a high temporal resolution (40Hz data rates are typical) enabling rapid blood flow changes to be recorded, whereas the laser Doppler imager can provide spatial information and has the ability to average blood flow measurements over large areas ("Laser-Doppler Blood Flowmetry", ed. A.P. Shepherd and P. Å . Oberg, Kluwer Academic Publishers 1990 and "Laser Doppler", ed. G.V. Belcaro, U. Hoffmann, A. Bollinger and A.N. Nicolaides, Med-Orion Publishing Co. 1994.)There have been many discoveries of treatment modalities through enhancing blood flow to tissues. Some examples of relevant patents include:The US Patent 6,007,836 to Denzer is for a vasodilator delivery system for producing and maintaining the erection of a male penis during intercourse. The vasodilator is contained in a transdermal patch. The transdermal patch comprises a thin, smooth-edged layered structure for dispensing a suitable vasodilator to the penis skin surface. In each embodiment of the patch, a vasodilator is applied to the skin of the user and is sealed against unwanted contraindicated leakage and contact with the internal tissues of a sex partner.

[0011] The US Patent 6,103,765 to Neal is for the administration of a pharmaceutical composition comprising: (a) a vasodilator; and (b) a 15-hydroxyprostaglandin-dehydrogenase inhibitor is effective for the treatment of male erectile dysfunction.

[0012] US Patent 6,031,002 to Wysor is for a method for enhancing female sexual response in which topically administered to the clitoris of the female subject and the surrounding tissue is a pharmaceutically-acceptable composition whose

primary agent is a vasodilator, such as prostaglandin and whose secondary agent is a carrier therefor to deliver it to the clitoris and the surrounding tissue so that it is retained thereby.

[0013] The US Patent 5,900,249 to Smith is for topically applied compositions for transdermal administration of efficacious pain relief medication. The compositions contain several physiologically active components, which act synergistically to attack pain-causing aspects of an injury or disorder while simultaneously blocking the immediate transmission and sensation of the pain. As the source of the pain is progressively diminished, the patient is spared the sensation of current and transient pain. Thus the compositions provide the patient with relief of both systemic and perceived pain. The compositions include medically effective amounts of a vasodilator, a non-steroidal anti-inflammatory drug, a membrane stabilizer, and a seratogenic reuptake inhibitor, and a medically acceptable carrier into which the foregoing are incorporated. Medically effective amounts of a topical anesthetic and/or a steroid anti-inflammatory drug are also advantageously included. A method of relief of a patient's pain, which comprises topical administration to the patient of such compositions, is also described.

[0014] The US Patent 5,683,710 to Akemi et al., is for a percutaneous absorption preparation for use in the administration of isosorbide dinitrate (ISDN) as a coronary vasodilator into the living body by percutaneous absorption, which has excellent adhesion to the skin and does not cause pain and damage to stratum corneum when peeled off, is disclosed. The pressure-sensitive adhesive layer comprises an acrylic copolymer prepared by copolymerization of a monomer mixture comprising a (meth)acrylic acid alkyl ester and a functional monomer as the essential components, a fatty acid ester having a specified number of carbon atoms, a monoglyceride having a specified number of carbon atoms, and ISDN, and the pressure-sensitive adhesive layer is cross-linked. Since its skin adhesive property is improved by the inclusion of the monoglyceride, release of ISDN is improved and the area of the preparation can be decreased.

[0015] The US Patent 5,576,329 to Hennessey is for a process useful in alleviating

inflammation of tendons and/or joints in a patient in need of such treatment. The process comprises administering a vasodilator to the inflamed tissue, either topically or by injection. Advantageously, the vasodilator is papaverine or a pharmaceutically acceptable salt thereof such as papaverine hydrochloride. Advantageously, the papaverine hydrochloride may be administered topically in a composition comprising a carrier. The carrier dissolves the papaverine hydrochloride and enables it to penetrate the skin and be absorbed into the inflamed tissue.

[0016] The US Patent 5,278,172 to Hennessey is for a process, which is useful in alleviating inflammation of tendons and/or joints in a patient in need of such treatment. The process comprises administering a vasodilator to the inflamed tissue, either topically or by injection. Advantageously, the vasodilator is papaverine or a pharmaceutically acceptable salt thereof such as papaverine hydrochloride. Advantageously, the papaverine hydrochloride may be administered topically in a composition comprising a carrier. The carrier dissolves the papaverine hydrochloride and enables it to penetrate the skin and be absorbed into the inflamed tissue.

[0017] The US patent 4,801,587 to Voss et al. is for an ointment for relieving impotence. The ointment generally consists of a primary agent, a carrier, and a base, and is applied directly to the penis. The primary agent is a vasodilator selected from the group consisting of papaverine, hydralazine, sodium nitroprusside, phenoxybenzamine and phentolamine. The carrier is used to assist absorption of the primary agent through the skin around the penis. When the primary agent enters the corpora cavernosa within the penis, it causes dilation of the corpora, resulting in an erection.

[0018] The US Patent 5,407,944 to Goldman et al is for the invention that provides compositions and methods for promoting hair growth. The methods generally comprise the administration to a patient of a therapeutically effective amount of the compositions, which employ a vasodilator in combination with estradiol and/or a 5-alpha reductase inhibitor in a pharmaceutically acceptable vehicle.



- [0019] The US Patent 4,311,707 to Birnbaum et al., is for a process for topically producing cutaneous vasodilation for the treatment of vasospastic or ischemic conditions This application discloses a process for producing cutaneous vasodilation which comprises the topical administration to an individual with a vasospastic or ischemic condition of an effective dosage of a prostaglandin vasodilator of the natural or synthetic prostaglandin analogs of the PGE, PGA, or PGF sub-beta types.
  
- [0020] The US Patent 4,112,115 to Coghlan is to relieve spasms in flexor and extensor muscles such as calf muscles by topically administering to the surface of the adjacent skin a nitrite vasodilator agent, such as glyceryl trinitrate, in a suitable carrier.
  
- [0021] The US Patent 5,854,291 to Laughlin et al is for a composition containing capsaicin together with another ingredient to neutralize the discomfort resulting from the application of capsaicin to the skin that can be used to treat many types of discomforts, including arthritis pain, hemorrhoid pain and itching, and poison ivy itching, without the discomfort normally associated with the topical application of capsaicin.
  
- [0022] The US Patent 6,071,507 to Zuluaga et al is for a composition and methods for its preparation and use, for the topical treatment of areas of a human body afflicted with arthritis and muscular pain, the composition comprising extracts obtained from branches and leaves collected from mimosa and capsicum plants. This invention is heated and used in the form of hot compresses and hot baths to treat small-afflicted areas and large afflicted areas, respectively. Applications may include, but are not limited to, use in eliminating the pain, swelling, and numbness experienced by people afflicted with arthritis and similar medical conditions.
  
- [0023] The US Patent 5,827,886 to Hersh is for a composition and method of using it for ameliorating inflammatory reactions and pain and other symptoms of the diseases of arthritis, lumbago, low back pain, myalgias and neuralgias. The composition includes reduced glutathione, a selenoamino acid and an anesthetic, such as capsaicin, in a suitable carrier for topical application.

FOOTNOTES

[0024] The US Patent 5,061,724 to Gertner is for a method of treating inflammations of body joints in humans by topical application of anti-inflammatory agents that may be used to treat joints afflicted by arthritic conditions such as gouty arthritis. The steps of the method include dissolving a predetermined quantity of a known anti-inflammatory drug, applying the medium with dissolved anti-inflammatory drug directly onto the skin covering a body joint known to be inflamed and allowing the medium with dissolved anti-inflammatory drug to be absorbed into the skin. Possible non-steroidal, anti-inflammatory drugs, which may be used with the method, include indomethacin, phenylbutazone and colchicine. Steroidal non-inflammatory drugs may also be used.

[0025] The US Patent 4,753,942 to O'Sullivan for a method of treating arthritis and rheumatism in human patients comprises the topical application to an affected part of the patient's body of at least one zwitterionic aminosulfonic acid of the kind commonly known as Good buffers. The acid is preferably made up as a pharmaceutical composition such as a cream, and applied at a dosage of 50 microgram to 50 mg of the acid per day for at least 5 days, but usually several weeks.

[0026] The US Patent 6,103,771 to Galer et al is for methods of treating a host suffering from neuroma pain. In the subject methods, a topical local anesthetic composition is applied to a keratinized skin site of the host proximal to the neuroma responsible for the neuroma pain. Preferably, the topical local anesthetic composition comprises eucalyptol in addition to an effective amount of a local anesthetic. The subject methods find particular use in the treatment of pain associated with Morton's neuroma.

**Summary of Invention**

[0027] Topical applications of drugs that enhance blood flow to tissues are widely used for a variety of therapeutic purposes including, but not limited to, treatment of muscular and joint pain, induction and sustaining of erection of male and female sexual organs, enhancing and stimulating hair growth, improving circulation to peripheral veins, etc. In this invention, I have used erucic acid as a pharmaceutical

product for transdermal administration to humans and animals to enhance blood flow to the site of application. The preparations proposed here may contain other medicaments to increase the effectiveness of erucic acid or vice versa enhance the activity of other drugs intended for topical application. The medicaments that can be concomitantly administered with erucic acid include, but not limited to, anti-inflammatory agents (both steroidal and non-steroidal), analgesics, prostaglandins, antibiotics, steroids, anti-allergy medicaments, anti-psoriasis medicaments, antidandruff medicaments, medicaments enhancing blood flow to sexual organs such as sildenafil citrate acting centrally or apomorphine whether applied locally or taken systemically, local irritants (rubefaciants), etc. The components that increase the effectiveness of erucic acid may include, but not limited to, absorption enhancers or other vasodilators that might enhance penetration of erucic acid across the skin and through layers of epidermis and dermis when applied topically. Erucic acid acts by enhancing blood flow upon topical application.

[0028] Erucic acid was applied to various parts of body in human subjects and using laser Doppler imaging the changes in the skin temperature and blood flow to skin at the site of application were monitored. Substantial increase in skin temperature and blood flow was recorded upon application of erucic acid. The synergistic effect of erucic acid in modulating the activity of other drugs was studied. In another experiments where human subjects were administered a single 25 mg dose of sildenafil citrate orally and the rise in skin temperature to the pelvic area was monitored and compared with changes when erucic acid was also applied locally to pelvic area. Application of erucic acid produced significant increase in skin temperature. When the oral administration of sildenafil citrate and local application of erucic acid were combined as a therapy, the response time to male erection was reduced significantly. The invention described here thus can be used as a safe topical aid to induce enhanced blood flow to tissues and thus achieve many medical benefits from this mode of action. Erucic acid in its pure form or contained in oils rich in erucic acid can be used in a combination form with multitude of drugs to enhance their topical absorption.

## Detailed Description

[0029] While the invention will now be described in connection with a certain preferred embodiment in the following example so that aspects thereof may be more fully understood and appreciated, it is not intended to limit the invention to these particular embodiments. The invention relates to all alternatives, modifications and equivalents as may be included within the scope of the invention as defined by the appended claims. Thus the following examples, which include preferred embodiments will serve to illustrate the practice of this invention, it being understood that the particulars shown are by way of example and for purposes of illustrative discussion of preferred embodiments of the present invention only and are presented in the cause of providing what is believed to be the most useful and readily understood description of formulations or procedures as well as of the principles and conceptual aspects of the invention.

[0030] Erucic acid is a naturally occurring long chain (C22) fatty acid found in the storage as triglycerides of plants of the family *Brassicaceae*. Widely used in industrial applications mainly as a lubricant, it has been purported to have systemic toxicity to humans. While oils containing high levels of erucic acid are widely consumed in the underdeveloped world, the use of oils containing high erucic acid has been banned in the West. As a result, low erucic acid oils are used widely as a source of monounsaturated fats like canola oil.

[0031] In this invention, I have studied the effects of erucic acid when applied to human and animal skin and found that it causes an increase in the flow of blood to the site of application. Even though erucic acid has shown systemic toxicity, there is a little likelihood of it being toxic when applied locally because of the small quantities of erucic acid that can be absorbed through skin and into systemic circulation. This is particularly noteworthy that oils containing a small percentage (2–3%) are allowed for systemic human consumption in the West. Erucic acid is therefore considered nontoxic when applied to skin. The increase in the blood flow produced by erucic acid when it is rubbed on to body parts has many applications for treating or alleviating human and animal diseases and symptoms. The main applications of erucic acid include, but not limited to, are human sexual

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dysfunction function, joint and muscle pain, and defects in microcirculation or ischemia, enhancing absorption of pharmacological agents and as an adjuvant in physiotherapy. Solid at room temperature, erucic acid readily melts at body temperature allowing ease of application. Erucic acid is also stable chemically and physically for longer storage at room temperature. Erucic acid can also be formulated in pharmaceutical delivery systems suitable for ease of application. Erucic acid can also be made a component of drug formulations used for enhancing blood flow to tissues and to increase the activity of drugs that depend on faster absorption into blood or are intended to enhance blood flow themselves. Application of erucic acid to skin raises the temperature of skin as the blood flow is increased. This effect of erucic acid is easily measured by laser Doppler imaging. A significant advantage in the use of erucic acid is in its lack of irritation to skin, an undesirable characteristic of most rubefacients used to enhance blood flow to tissues. Erucic acid can therefore be a good medium for the base of pharmaceutical preparations containing pharmacological agents either for local or for deeper skin action where rubbing of preparation can be useful in augmenting the therapy.

[0032]

EXPERIMENT 1: A 35-yr old man was administered a single oral dose of 25 mg sildenafil citrate (Viagra<sup>®</sup>) and changes in blood flow to penis and surrounding pelvic areas was monitored using laser Doppler imaging. The blood flow increased by about 20% within 30 minutes of drug administration. This was followed by penile erection. The same subject took the same dosage of drug immediately after applying sufficient quantity of pure erucic acid to the genital areas. The laser Doppler imaging showed that 20% increased in blood flow was achieved in less than 5 minutes and an erection followed approximately 15 minutes earlier than observed when sildenafil citrate was taken without prior application of erucic acid. One week later, the same subject applied erucic acid to genital areas without taking sildenafil citrate; within 5 minutes of application, a warmth sensation appeared in the genital area and it was followed by an erection within 15 minutes of the application of erucic acid. This experiment demonstrates that erucic acid is effective in causing enhanced flow to genital areas that can result in penile erection. Also, when applied in conjunction with drugs taken systemically to

produce erection, application of erucic acid enhances the response time and also produces a better quality of sexual stimulation.

[0033] EXPERIMENT 2: A 40-yr old woman applied sufficient quantity of erucic acid to clitoris and its surrounding area and within 5-30 minutes of the application experienced a feeling of warmth, enhanced vaginal lubrication and sexual stimulation due to engorgement of clitoris. The laser Doppler imaging of the pelvic area showed enhanced blood flow and significant rise in surface temperature. This experiment shows that erucic acid can enhance blood flow to clitoral and vaginal areas resulting in sexual stimulation to women.

[0034] EXPERIMENT 3: A 55-yr old man with chronic arthritis, swelled joints and pain was applied erucic acid to knees and fingers. Within 5 minutes of application, the man felt warmth and a temporary relief of pain. This experiment shows that erucic acid can be used to reduce the pain of arthritic joints.

[0035] EXPERIMENT 4: A 23-yr old man had strained leg muscles due to overstraining in weight lifting exercises. Application of erucic acid massage to affected area produced warmth within 5 minutes of application and reduced the sensation of pain substantially. This study shows that erucic acid can be used to alleviate pain of skeletal muscles due to straining and injury.

[0036] EXPERIMENT 5: A 50-yr old arthritic man was using diclofenac gel for topical application to relieve pain of arthritis. Prior to application of diclofenac gel, the patient massaged the joints with erucic acid and then applied the diclofenac gel and reported a noticeable change in the onset of relief. This study shows that erucic acid can be used to enhance the absorption and effectiveness of drugs applied topically. In this study, there are two mechanisms involved, one that produces warmth of joints and thus relieves pain and the other is the absorption of another active pharmacological entity. To test both of these mechanisms, the subject was applied erucic acid alone, erucic acid prior to applying diclofenac gel or diclofenac gel alone. The patient reported the fastest and most complete alleviation of pain when erucic acid was applied prior to the application of diclofenac gel. This study further shows that the absorption of drugs used for local

action when applied to skin can be substantially increased if they are combined with erucic acid.

[0037] EXPERIMENT 6: A 70-yr old diabetic patient who had lost some sensation in his toes used erucic acid massage and noticed a substantial change in the sensitivity of toes along with a feeling of warmth. This study shows that erucic acid can be used to enhance the flow in the microvasculature of extremities.

[0038] EXPERIMENT 7: A 34-yr old woman with history of back pain was undergoing physical therapy for compressed disc. Application of erucic acid to lower back followed by the normal therapy produced much quicker relief of pain. The patient was receiving infrared exposure as part of her therapy. In one instance, the infrared lamp exposure was substituted with application of erucic acid. The patient reported a similar level of relief obtained from the application of erucic acid as she was used to getting after exposing to infrared heating lamp. This study shows that erucic acid can be used in routine physical therapy to provide the warming of skin required to augment relief of pain.

## Claims

- [c1] I claim that erucic acid increases blood flow to tissues when applied topically or transdermally to humans and animals.
- [c2] I claim that erucic acid can be used to enhance the activity of drugs applied topically to cure or alleviate a disease or symptom(s) of disease or condition (s) in humans and animals.
- [c3] I claim a method as set forth in claim 1 that erucic acid can be used to treat male erectile dysfunction and female impotence by applying it locally to sexual organs and peripheral areas in quantities sufficient to enhance blood flow within 1 to 60 minutes of application.
- [c4] I claim a method as set forth in claim 2 that erucic acid can be used, when applied locally to sexual organs and surrounding areas in both males and females, to enhance the effectiveness of any drug taken systemically or applied locally and known to cause stimulation of human sexual organs; examples include but not limited to sildenafil citrate, apomorphine, prostaglandins, capsaicin, phentolamine, phenoxybenzamine, yohimbine, nitroglycerin, thymoxamine, nicotiny alcohol, imipramine, verapamil, isoxsuprine, naftidrofuryl, tolazoline, and papaverine, etc.
- [c5] I claim a method as set forth in claim 1 that erucic acid can be used to reduce the pain resulting from arthritic joints or straining or injuring of skeletal muscles or nerves (neuralgia) by applying it directly to the affected areas.
- [c6] I claim a method as set forth in claim 2 that erucic can be used, when applied directly to arthritic joints and aching muscles, to enhance the effectiveness of antiarthritic and analgesic drugs taken either systemically or applied locally; these include, but are not limited to NSAIDs (non-steroidal anti-inflammatory drugs), steroidal drugs, salicylates, capsaicin, or other topical other analgesics or muscle relaxants.
- [c7] I claim a method as set forth in claim 1 that erucic acid can be used to treat



the problems of ischemia, poor blood circulation to extremities, in diabetic patients when applied directly to body areas such as feet or any other part of body where the efficiency of the microvasculature system is compromised.

[c8] I claim a method as set forth in claim 2 that erucic acid can be used to enhance the activity of drugs taken systemically or locally with intent to improve circulation to a specific part of the body if erucic acid also applied to that specific part of the body in debilitated patients with vasospastic or ischemic conditions.

[c9] I claim a method as set forth in claims 1 and 2 wherein erucic is combined with another drug, synthetic or natural, or part or parts of plants or animals known to enhance blood flow to organs to obtain a synergistic effect.

[c10] I claim a method as set forth in claim 1 that erucic acid can be used to enhance the effectiveness of any physical therapy where the intent is to bring warmth to specific parts of body by massaging or by exposing the body to heat or infrared sources.

[c11] I claim a method as set forth in claim 2 that erucic acid can be used to enhance the absorption of drugs applied topically to achieve enhanced local or systemic effect of these drugs including but not limited to drugs purported to produce muscular relaxation, enhance hair growth, treat symptoms of psoriasis or dandruff.

[c12] I claim a method as set forth in claims 1 and 2 wherein the invention claimed here is a formulation that contains other components to impart it pharmaceutical elegance and ease of administration wherein the concentration of erucic acid ranges from less than 1% to greater than 99%.

[c13] I claim a method as set forth in claims 1 and 2 wherein the formulation takes the form of an ointment, cream, solution, gel, gauze, foam, spray, liposomal carrier or another dosage form or device suitable for administration of the preparation to humans and animals.

[c14] I claim a method as set forth in claims 1 and 2 wherein the primary agent is the vegetable oil of a variety that naturally contains substantial quantity of erucic acid or its derivatives. This includes, but not limited to, rapeseed oil, Lorenzo's oil, mustard oil, nasturtium oil, wallflower oil, etc.

[c15] I claim a method as set forth in claim 1-11 wherein the primary agent is the animal fat that naturally stores substantial quantity of erucic acid or its derivatives.

[c16] I claim a method as set forth in claims 1 and 2 wherein erucic acid is a component of a formulation intended for application to humans with intent to enhance blood flow when applied locally to a human or animal organ.

[c17] I claim a method as set forth in claims 1 and 2 wherein the carrier for the primary agent may include a substantially water-insoluble transdermal penetration enhancing compound selected from the group consisting of C7 to C16 aliphatic group substituted acetals, hemi-acetals and morpholines and further comprising a physiologically acceptable water soluble polar compound selected from the group consisting of alcohols, glycols, lactams, urea, cycloethylene urea, 1,3-dioxolone, 2-methyl-1,3-dioxolone, 1,3-dioxane, 2-methyl-1,3-dioxane, morpholine, N-methylmorpholine, N-dimethylformamide, dimethylsulfoxide, methylacetate, ethyl lactate, monosaccharides, polysaccharides, amino acids, amino alcohols, diethylamine and cycloethylene carbonate. The polar compound may be selected from a group consisting of alcohol, glycol, dioxolane, formamide, carbonate, glucose, urea and mixtures thereof. Alternatively, the polar compound may be an alcohol glycol mixture or lactim.

# [USE OF ERUCIC ACID IN ENHANCING BLOOD FLOW TO TISSUES]

## Abstract of Disclosure

Erucic acid is a naturally occurring fatty acid found in the storage triglycerides of plants of the family *Brassicaceae*. Rapeseed is a member of this family and is grown in several countries for its oilseed. Rapeseed oil contains a high content of erucic acid (more than 40%), primarily as glycerol trierucate, and is important in industrial applications, mainly as lubricant. Rapeseed oil is also used as cooking oil in Asia for many generations. However, its use in Europe and North America has been hampered by its toxicity: myocardial lipidosis, myocardial necrosis, and impaired oxidative phosphorylation. The toxicity was thought to be attributed to the erucic acid content, which comprises 40–50% of the total fatty acids in the oil. This has led to development of low erucic acid rapeseed (LEAR) oil (0.4–2%). A second new type of rapeseed oil, low in both erucic acid and glucosinolates, called canola is now the major rape product. Besides rapeseed, another significant source of erucic acid is mustard, which has been used in food for thousands of years in a number of cultures. Indian mustard is grown in many countries for the preparation of condiment mustard because of the hot-tasting and pungent-smelling compounds present in its seeds. It is also being used on a substantial scale on the Indian subcontinent, and in China and Russia for the production of cooking and salad oil. The original form of mustard contains erucic acid in the oil and hot-tasting glucosinolates, which are responsible for its "zing" in mustard. In some countries, such as India, mustard meal is used as a fertilizer or for cattle feed. The amino acid balance of the meal makes it suitable for feeding to mono-gastric animals such as pigs and poultry as a protein supplement, but the hot compounds are distasteful to pigs and may injure poultry. Thus, to make mustard a useful modern crop, it was necessary to reduce the levels of erucic acid and glucosinolates. Mustard oil (*Candida rugosa*) treated by commercially available

lipase shows about ten fatty acids with erucic acid comprising about 16% of the fatty acid content. This invention describes the effect of erucic acid on peripheral circulation, particularly, inducing localized enhancement of blood flow to the surface of tissue where it is applied in animals and humans. It is suggested that erucic acid may affect the peripheral vascular system. Vasoconstrictors and vasodilators are the pharmacological agents that upon systemic or local application decrease or increase blood flow to the tissue. The mechanism involved in enhancing blood flow ranges from producing irritation (rubefacient) to reducing the tension of veins and arteries to muscle relaxation that leads to lower pressure on the vascular structure. Several significant effects can be achieved when blood flow to skeletal and other body tissues are altered. These include, but are not limited to, faster absorption of topically applied drugs, improved sensation to physical stimuli, engorgement of organs to produce erection of penis and clitoris, enhanced sensation of comfort in sensitive tissues, feeling of warmth, alleviation of pain and muscle stress, etc. Many topically applied products contain components labeled as rubefacient that enhance flow of blood to the surface by producing an irritation that causes the blood to rush to the site of application; the warmth produced as a result alleviates or soothes the pain. The effectiveness of topical vasodilators or drugs that enhance blood flow to tissues can be measured by many techniques. In this study I used the technique of monitoring blood flow and skin temperature using laser Doppler imaging. Topical applications of drugs that enhance blood flow to tissues are widely used for a variety of therapeutic purposes including, but not limited to, treatment of muscular and joint pain, induction and sustaining of erection of male and female sexual organs, enhancing and stimulating hair growth, improving circulation to peripheral veins, etc. In this invention, I have used erucic acid as a pharmaceutical product for transdermal administration to humans and animals to enhance blood flow to the site of application. The preparations proposed here may contain other medicaments to increase the effectiveness of erucic acid or vice versa enhance the activity of other drugs intended for topical application. The medicaments that can be concomitantly administered with erucic acid include, but not limited to, anti-inflammatory agents (both steroidal and non-steroidal), analgesics, prostaglandins, antibiotics, steroids,



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