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Topical Medicine for Treatment of the Musculoskeletal

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Abstract: Twenty human volunteers (patients) with diverse conditions causing chronic pain obtained good treatment with use of a painex delivery system containing 1, 8-cineole (1%), phenolic compounds and combined camphor - ascorbic acid.

Keywords: Painex, Topical medicine, Chronic pain, Musculoskeletal

Introduction

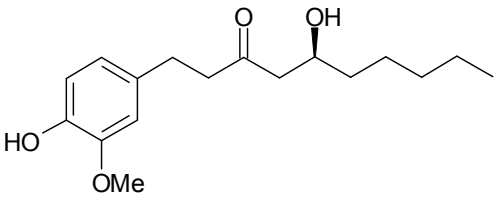
Botanists have identified and classified plants and become the preferred raw material for new pharmaceutical exploration. However, the low yield and difficulty in acquiring some biologically-active compounds have led chemists to investigate the virtues of synthesis and semisynthesis to ensure supply.

Ginger

Ginger is non-toxic and non irritant but in presence of light it slowly irritates, ginger is generally regarded as safe by the United States Food and Drug Administration (FDA)[1]. Over 400 different compounds have been identified in ginger[2]. The major component of ginger are [6]-gingerol, [8]-gingerol, zingerone, [6]-Shogaol and 1,8-cineole and play the major pharmacological activity due to presence of these compounds[3-6]. Ginger is shown to cause vogal stimulation and decrease both blood pressure and heart rate[7] . In addition to its effect on blood glucose and cholestrol, ginger also affects plate etc. aggregation. The exact mechanism by which ginger relieves pain remains unclear, studies indicate that ginger may inhibit key enzymes that lead to inflammation (inhibition of prostaglandin and leukotriene synthesis)[8-9].

[6]-Gingerol

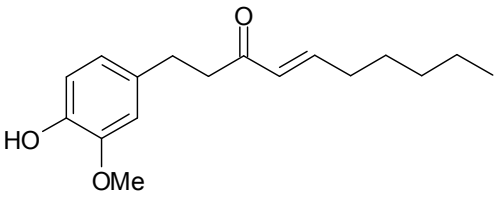
[6]-Gingerol a naturally occurring plant phenol, is one of the major components of fresh ginger, which can be converted to shogaols, zingerone, and paradol. 6-Gingerol has been found to possess many interesting physiological and pharmacological activities[9-10]. 6-Gingerol, possess useful anti-oxidant properties, anti-inflammatory and anti-tumor promoting activities[11-14].



(S)-5-hydroxy-1-(4-hydroxy-3-methoxy-phenyl)-3-decanone

[6]-Shogaol

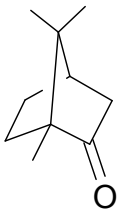
[6]-Shogaol is one of the major biologically active compounds found in ginger[15]. This compound was previously reported to have antipyretic and analgesic effects in addition to inhibitory effect on lipoxygenase activity[16-17]. Its presence in ginger may also contribute to the anti-inflammatory effects associated with the use of powdered ginger[18-19].



(E)-1-(4-Hydroxy-3-methoxy-phenyl)dec-4-en-3-one

Camphor

Camphor is highly volatile and readily absorbed through the skin. It produces a cool sensation and acts as a mild local anesthetic. Specifically, the (FDA) has approved camphor for topical use as a pain reliever and anesthetic in concentrations of 3% to 11%[20]. The essential oil is used externally in liniments for treating joint and muscle pains, balms for chilblains, chapped lips, cold sores, skin diseases, etc., and as an inhalant for bronchial congestion. The mechanism of action of the pain relief associated with the use of camphor is that it is a counter irritant. When applied externally, camphor numbs the nerve endings. The nerve endings then no longer transmit the sensation of pain[21].

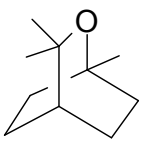


1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one

Cineol

Cineol has been demonstrated to be capable of reducing inflammation and pain. It has also been found to be able to kill leukaemic cells in vitro[22]. Cineol inhibited the growth in vitro of Staphylococcus aureus, Pseudomonas aeruginosa, Bacillus subtilis, Enterococcus faecalis and Escherichia coli[23-24]. Cineol was shown to be an effective treatment for nonpurulent rhinosinusitis in a placebo controlled trial. Treated subjects experienced fewer headaches on bending, frontal headache, and sensitivity of pressure points of trigeminal nerve, impairment of general condition, nasal obstruction, and rhinological secretion

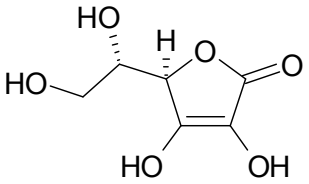
Side effects from treatment were minimal[25]. 1, 8-cineole diffuses faster by inhalation than by oral administration or through the skin[26-27]. Its presence can be detected in blood 5 min after inhalation, with maximal concentration being reached within 18 min.[28]. 1, 8-Cineole inhibited prostaglandin biosynthesis in vitro at a concentration of 37mmol/l[29]. 1, 8 -Cineole have status as "Generally recognized as safe" in the USA and is approved for use in food and topically[30].



1,3,3-Trimethyl-2-oxabicyclo[2.2.2]octane

Ascorbic Acid

Ascorbic Acid (Vitamin C) is a water soluble alpha hydroxy acid that functions as an antioxidant and a required chemical for several metabolic reactions. It occurs naturally in plants particularly in fruits and some animals are able to synthesize this vitamin. Ascorbic acid can also be produced in large scale using a two-step fermentation process of glucose. It was found that ascorbic acid is necessary for the thin oxidation- reduction mechanism of body tissue including the nerve cells[22]. The action of ascorbic acid is important in maintaining the cellular normal functions and needed to make collagen, the "glue" that strengthens connective tissue[31]. Preliminary human studies have suggested that ascorbic acid supplementation in non-deficient people can speed healing of various types of trauma, including musculoskeletal injuries[32-33].



(R)-3,4-dihydroxy-5-((S)-1,2-dihydroxyethyl)furan-2(5H)-one

We improved new topical medicine to be treated the musculoskeletal system, which include bones, muscles, joints, ligaments, tendons, and bursae (fluid-filled sacs). Any of these components can be injured by trauma or affected by a number of diseases causing joint, tendon, and muscle problems.

The name of this new medicine is painex (pain-expulsion). Painex can treats chronic pain and increase the patient ability to function.

A painex containing 1,8-cineole (1%) and other components, has been developed for treatment of muscular and joint aches and pains associated with overexertion, strains, sprains and muscle tension, as well as relief from simple backache and arthritis pain. The topical formulation may be applied 1 – 2 times daily and provides for deep penetration of the active ingredient. Appling painex on more than 20 patients with various chronic pain syndromes. Painex describe successful use of the formulation in treatment most of patients.

Materials and Methods

Chemicals: Phosphoric acid, ethanol, isoprepanol, camphor and L-ascorbic acid were obtained from Sigma- Aldrich Ltd and used without further purification.

All the other chemicals used in the base cream were Chinese chemicals

Natural oils and ginger were purchased from the local Gaza-Palestine market. All the other chemicals used were of analytical grade.

1,8-Cineole Isolation: 1,8-Cineole can be isolated from any natural oil contains more than 60%. By adding phosphoric acid to the natural oil, 1,8-cineole readily forms addition product ($C_{10}H_{18}O.H_3PO_4$) with m.p 84 ^oC. The solid product can be decomposed by hot water and the solution cooled at 1 ^oC, the 1,8-cineole then can be collected on cold system[34].

Ginger Extraction: 1:1 Ethanol – isoprepanol mixture was added to the dried granulate ginger. The mixture was stirred for 6 hours, then the mixture was filtered and the solvent was evaporated. The crude product was used as it is in the medicine.

Camphor-Ascorbic Acid Combination: Camphor in ethanol was added with stirring to a solution of ascorbic acid.The mixture was then kept at room temperature overnight. The mixture was then used as it is in the medicine.

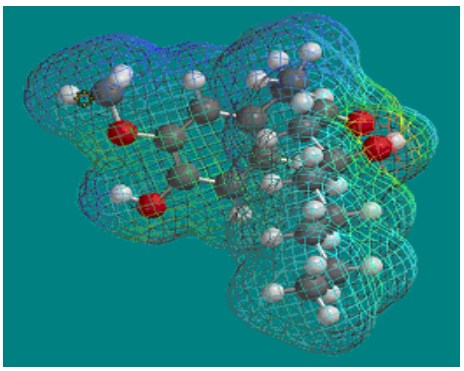
Painex Cream: Each 100 gram of painex cream contains **active:** 1,8-cineole 1%, 6-shogaol 1-1.5%, 6-gingerol 1-1.5% and combined camphor-ascorbic acid 5%. **inactive:** purified water, ethanol, stearyl alcohol, cetyl esters wax, glyceryl monostearate, polyoxyethylene stearyl ether, isopropyl palmitate, methylparaben and propylparaben.

Test of Painex Bioactive Components: Analytical TLC was carried out
on Merck precoated silica gel plates using ethyl acetate solvent system. Spots on TLC were detected under UV light**.**

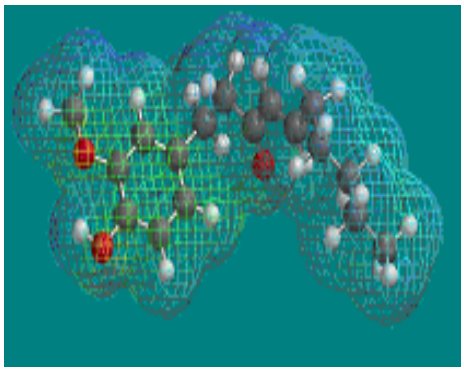
Painex Application: Twenty human volunteers (patients) with chronic pain have been applied painex twice daily, which contains well known safe ingredients. Patients suffering from musculoskeletal problems were discharged in less than four weeks.

Results

In this study we have formulated new topical medicine painex from active natural components, 1, 8-cineole, 6-shogaol, 6-gingerol and combined camphor-ascorbic acid. TLC has been showed that painex is stable product at room temperature.The activity of painex have been compared with other popular topical medicines for treatment of chronic pain, painex was found not to be an anesthetic medicine but treats the causes of pain.Through, studying the electron density of the active materials of painex and other popular topical medicines Table1, show that there is significant difference among them



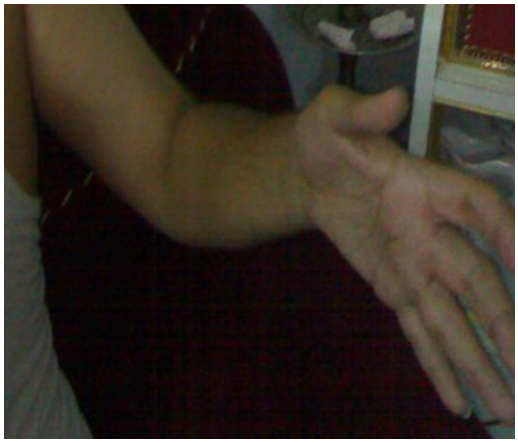
6-Gingerol



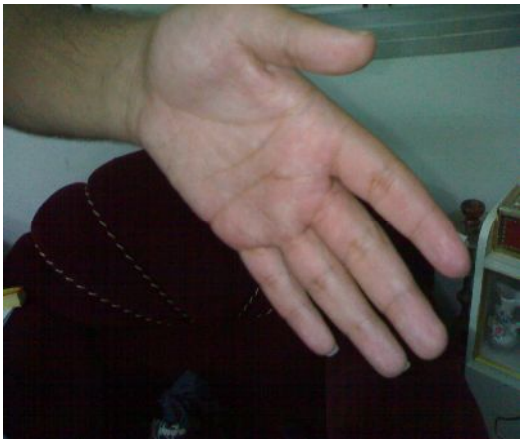
6-Shogaol

Table1: Comparison of electron density for active materials of painex and other popular topical medicines. Electron densities were calculated using Spartan'02 software.

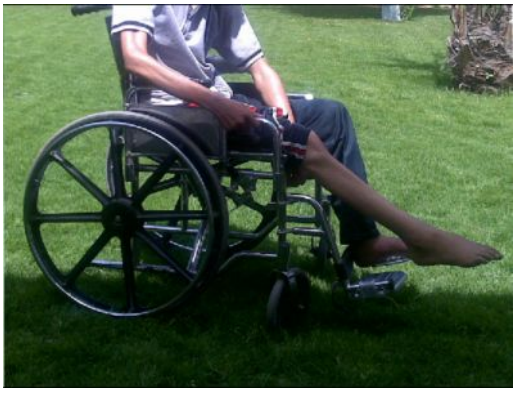
Medicine	Active Material	Electron Density Range	
Painex	6-Gingerol	-66.4559	24.8266
Painex	6-Shogaol	-64.4791	22.9605
Dromoran	levorphanol	-66.2345	38.0205
Zostrix	Capsaicin	-72.6767	34.2787
Maxilene	Lidocaine	-75.7773	25.7822
Emla	Prilocaine	-74.5881	25.4956
Ametop	Amethocaine	-70.5253	32.9488



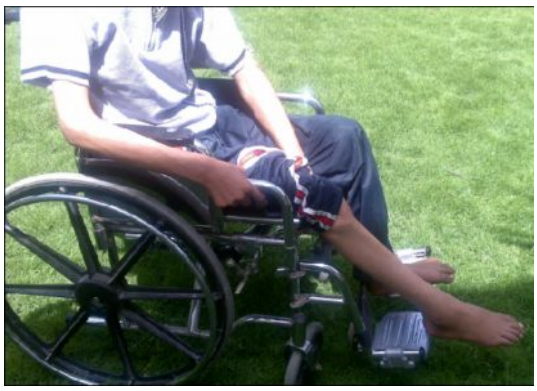
1- Muscle atrophy before treatment, (Dislocation of the shoulder during birth) Age: 21 years old (man)



2- After 30 minutes of treatment



3- Muscle atrophy before treatment, (Palsy 5 years ago) Age: 17 years old (boy)



4- After 60 minutes of treatment

In some cases, painex treats and stimulates nerve function in minutes, but some cases may require few days. Such as arthritis, tensile nerve and muscle atrophy, the pain might increase during the treatment course which required strong anesthetic medicine with painex until the disappearance of all pain. In some cases, muscle growth may appear in the pictures 1, 2, 3 and 4.

Discussion

Painex contains greet active materials, which have been found to possess many interesting physiological and pharmacological activities and have been chosen to give excellent action on the damage area. 6-Gengerol and 6-shogaol were added to inhibit the enzymes that facilitate production of several pro-inflammatory factors, and there therapeutic effects could be related to inhibition of prostaglandin and leukotriene biosynthesis, thereby working as a dual inhibitor of eicosanoid biosynthesis[35].

The study shows the 6-Gingerol and 6-Shogaol -like levorphanol in electron density which might reflect a new relation between the pharmacological activity and electron density, because levorphanol have been used for treatments and relieving chronic pain due to nervous system damage[36].

The electron density of the active materials of painex and other popular topical medicines, show that there is significant difference among them.

and that means 6-gingerol and 6-shogaol have a moderate electron density which might facilitate the entrance of these active materials through the living wall cells[37].

Camphor is readily absorbed through the skin and produces a feeling of cooling and acts as slight local aesthetic. It is a pretty good anesthetic and very effective for local anesthesia. It causes numbness of the sensory nerves and the related area of application. It also calms down nervous disorders and

stimulates circulatory and the nerve cells.

1, 8- cineole causes the blood vessels to dilate (open, relax). When this occurs more blood can flow through these vessels bringing more oxygen and nutrition to the surrounding muscles, tissues and tendons causing these to relax

Ascorbic acid is essential to all the body's chemical reactions, is essential to synthesis of collagen (connective tissue) promoting repair of damaged muscle and cartilage[38].

All painex combined ingredients makes it fast, effective and safe according to the safety of its ingredients as mentioned above. Therapeutic activity of painex can be attributed to the fact that the basic components have a low electron density, which may facilitate the entry of living cells

Thin layer chromatography has been studied to show no chemical reactions between the combined materials which make the painex a stable medicine

Conclusion

We come to the conclusion that the application of painex on patients indicates that topical therapy with combined 1, 8-cineole (1%) and other components cream (painex - pain expulsion) provides a substantial benefit to patients suffering with various chronic pain syndromes. The topical treatment has been succeeded and offers an alternative or add-on to systemic therapy. As safety Issues: painex contains ginger components and ginger is on the FDA's GRAS (generally recognized as safe) list as a food, and the treatment dosages of ginger are comparable to dietary usages. No significant side effects have been observed for this reason painex is absolutely safe and useful.

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