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Potentials of Plant Oils in Pruritus Alleviation

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Authors' contributions

This work was carried out in collaboration between both authors. Authors HLS and NHKA designed the study. Author HLS managed the conceptualization, supervised search query hits and manuscript. Author NHKA performed the literature searches, interpreted the data and prepared the first draft of the manuscript. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Aims: To offer a summarized and systemized understanding of the incorporation of plant oils in pruritus alleviation.
Methodology: Literature was searched using online databases such as MEDLINE/PubMed, Google Scholar and Science Direct with the following inclusion criteria: 1) conducted/written no sooner than 1991 and published as full articles in journals; 2) each article meets the specific characteristics of its according type of therapies.
Results: A total number of 52 articles was found and 29 of which were directly enlisted into 4 categories: moisturizers, antihistamine, neuromodulators and topical cannabinoid; each was directly examined and reviewed.
Conclusion: Plant oils have high potentials in the alleviation of pruritus, with those in the moisturizers category show the most positive successful outcomes.

Keywords: Itch; pruritus; alleviation; moisturizers; antihistamines; local anesthetics; phytocannabinoid.

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1. INTRODUCTION

Pruritus, or itch, is commonly defined as an "unpleasant sensation that elicits the desire or reflex to scratch" [1]. It usually is a symptom of various diseases and generates a wide spectrum of intensity, from mildly irritating to incapacitating. Prior to the past two decades, pruritus was not of research interest because scientists regarded it as a sub-group of pain, thus need not having any special treatments, according to the intensity theory [2]. However, as perceptions changed with new theories arose, research interest shifts and a number of studies on the treatment of itch were conducted. Yet, their efficacy has not been adequately proved, and there laid grounds for novel therapies. Among other alternatives such as topical antihistamine, corticosteroids, etc., plant oils have recently been in the highlight because of their natural origin as well as seemingly side-effect free properties. Nevertheless, evidences for such plant-based therapy are either little or uncategorized. This review aims to summarize the existing works in plant oils' potentials to alleviate itch.

Plant oils are oils derived from plants by different methods such as distillation or solvent extraction. They can be extracted from various parts of the plants, such as root, stem, leaves, etc., thus yielding different constituents and properties. By that definition, the oils broadly fall into two categories – fixed and essential oils.

Fixed oils are customarily extracted from seeds or fruits of the plants and consist mostly of triglycerides, whose fatty acids such as linoleic or oleic acid are reported to have possible health effects. They usually appear dense and nonvolatile. Because of the high unsaturated to saturated fatty acids ratio, fixed oils remain liquid in room temperature or normal settings, thus making them a safe carrier for therapeutic drugs. Essential oils, on the other hand, are commonly extracted from flowers, leaves or the whole aerial part of the plant. They are responsible for the plants' aromas and flavors with high volatility. Their secondary metabolites such as terpenoids, shikimates, polyketides and alkaloids are unique and thus served as central highlights for researchers in phytochemistry.

This article is structured based on B. Elmariah's original review "Topical Therapies for Pruritus" [3] with several adjusted remarks. To be specific, the review shall not be covering all of the categories listed either because of their incompatibility to plant oils' properties or the lack of reliable evidences. Moreover, the exact mechanism of each category shall not be discussed as they have thoroughly been elaborated in the original article.

2. METHODOLOGY

To be included in this review, studies/overviews must meet the following inclusion criteria: 1) conducted/written no sooner than 1991 and published as full articles in journals; 2) each article meets the specific characteristics of its according type of therapies.

Articles were retrieved from 3 electronic databases: MEDLINE/PubMed, Google Scholar and Science Direct, the search terms differ according to their listed categories, as shown in Table 1. The authors do not claim to have included all of the existing pertinent literatures on the issue because of restrictions on database access. Also, the authors are well aware that studies of plant oils efficacy in medicinal practices are limited due to the overwhelming number of presence herbs in comparison to the inadequate amount of researches. The searches thus do not wholly reflect the potentials of plant oils at present but shall work as a guide to more directed approaches. In so doing, a total of 52 articles were examined, 29 of which served as direct sources of analysis. Table 2 enlists the aforementioned 29 articles.

Table 1. Keywords used for literature searching

Therapies	Keywords
Moisturizers, emollients and barrier protection	Pruritus, itch, plant oils, moisturizers, emollients, transepidermal water loss, barrier protection, itch, dry itch
Antihistamines	Itch, pruritus, antihistamine, H1/H4 antagonist, pruritus, allergy, bronchodilatory effect, plant oils, essential oils
Topical neuromodulators	Itch, pruritus, local anesthetic, sciatic nerve, plant oils, essential oils, antispasmodic effect, capsaicin, menthol
Topical cannabinoid	Itch, pruritus, plant oils, essential oils, phytocannabinoid, CB1/CB2 agonists, anti-inflammatory effects

Table 2. Retrieved articles serving as direct sources of analysis

No.	Category	Plant	Type of article	Reference
1,2	Moisturizers,	*Cocos nucifera*	Clinical trial	[9,10]
3	emollients and	*Helianthus annuus*	Research paper	[11]
4,5	barrier protection	Sunflower oleodistillate	Clinical trial	[12,13]
6		*Ricinus communis* *Brassica napus* *Linum usitatissimum* *Helianthus annuus* *Elaeis guineensis* *Cocos nucifera* *Simmondsia chinensis* *Prunus dulcis* *Sesamum indicum* *Persea americana* *Prumus armeniaca*	Review	[14]
7		*Sclerocarya birrea* *Adansonia digitata* *Citrullus lanatus* *Schinziophyton rautanenii* *Trichilia emetica* *Ximenia americana*	Review	[15]
8		*Aloe barbadensis* Mill.	Clinical trial	[16]
9		*Rosa damascena* Mill.	Research paper	[17]
10		*Hypericum perforatum* L.	Clinical trial	[18]
11	Antihistamines	*Lippia dulcis* Trev	Research paper	[19]
12		*Carum copticum*	Research paper	[20]
13		*Carum copticum*	Research paper	[21]
14		*Matricaria chamomile*	Research paper	[22]
15		*Lavandula augustifolia*	Research paper	[23]
16		*Bunium persicum*	Research paper	[24]
17		*Piper betle*	Research paper	[25]
18		*Croton nepetaefolius*	Research paper	[26]
19	Topical	*Alpinia zerumbet*	Research paper	[27]
20	neuromodulators	*Croton nepetaefolius*	Research paper	[31]
21		*Croton zehnteri*	Research paper	[32]
22		*Lippia alba*	Research paper	[33]
23		*Aniba rosaeodora*	Research paper	[35]
24		*Lavandula augustifolia*	Research paper	[34]
25	Topical cannabinoids	*Ocimum basilicum* L.	Research paper	[40]
26		*Farfugium japonicum*	Research paper	[42]
27		*Bupleurum fruticescens*	Research paper	[43]
28		*Cordia verbenacea*	Research paper	[44]
29		*Echinacea purpurea* L.	Research paper	[45]

3. RESULTS

3.1 Moisturizers, Emollients and Barrier Protection

There has been various studies on the efficacy of moisturizers as part of pruritus' treatment plans [4–6]. In brief, they do not treat itch by targeting the causes but alleviate the symptoms by hydrating the skin, enhancing barrier function and decreasing transepidermal water loss (TEWL). With high percentage of essential fatty acids, especially linoleic acid, plant oils are suggested to have such therapeutic abilities [7,8]. This is of essential need for patients suffering pruritus who seek for an inexpensive, temporary therapy, especially for a good night sleep.

Although plant oils are both diverse and abundant, only a selective few possess moisturizing ability while merely over a handful of

them has been scientifically proven. A prominent candidate would be virgin coconut oil (VCO), which originates from fresh coconut milk and is left unrefined. Evangelista et al. [9] studied the effect of VCO comparing with mineral oil on pediatric atopic dermatitis (AD) patients. The 5 mL topical application on full body of each assigned oil lasted for 8 weeks and results were analyzed based on the SCORAD index, TEWL, and skin capitance values. Overall, VCO showed superior efficacy in all three categories, which was suggested to result from its skin penetratory as well as anti-inflammatory activities. Another research by Al. Agero and V.M. Verallo-Rowell [10] studied the effect of VCO as a moisturizer in xerosis patients and concluded that "coconut oil is as effective and as safe as mineral oil".

Sunflower seed oil has been tested as an effective moisturizing agent, either in direct topical application [11] or being incorporated as an active ingredient [12,13]. In the former study, sunflower seed oil massage on a mouse model significantly induced a rapid recovery of TEWL, as well as exhibiting a long lasting effect in comparison with other vegetable oils. On the other hand, the latter studies examined the efficacy of 2% sunflower oleodistillate (SOD) emollient in skin barrier disorders, notably atopic dermatitis. SOD is a byproduct of the original oil extracted by molecular distillation, which in turn bears a 10-fold increase in its unsaponifiable content. Results showed that both studies proved the effectiveness of 2% SOD emollient and suggested its use in the management of related skin disorders.

In a review by A. Lubbe and R. Verpoorte [14], several plant oils were enlisted for their use in cosmetic products, notably as corporated in moisturizers and emollients, such as castor oil (*Ricinus communis*), jojoba oil (*Simmondsia chinensis*), almond oil (*Prunus dulcis*), sesame oil (*Sesamum indicum*), avocado oil (*Persea Americana*), apricot kernel oil (*Prumus armeniaca*), rapeseed oil (*Brassica napus*), linseed oil (*Linum usitatissimum*), sunflower seed oil (*Helianthus annuus*), palm oil (*Elaeis guineensis*), and coconut oil (*Cocos nucifera*). Also, seven African seed oils having moisturizing effects were reviewed in a paper by I. Vermakk et al. [15] with varying amounts of scientific evidences. *Sclerocarya birrea* seed oil, or marula oil, being the most scrutinized, underwent clinical tests of "skin hydration, transepidermal water loss and increase in skin smoothness". It was also shown to reduce itching and skin redness. Other seed oils listed were *Adansonia digitata* (baobab), *Citrullus lanatus* (Kalahari melon), *Schinziophyton rautanenii* (manketti/mungongo), *Trichilia emetica* (mafura butter) and *Ximenia americana* (sour plum). Their efficacies in improving defected skins were mainly due to the high essential fatty acid content in each oil's components.

Despite not being well-researched as the aforementioned, aloe vera extract, rose absolute oil (RAO) and St. John's wort extract (*Hypericum perforatum*) still hold sufficient evidences for their therapeutic effects. A randomized vehicle-controlled study on 20 volunteers assessed the effect of different *A.vera* extract's concentrations resulting in a notable improvement in skin hydration [16]. RAO was proved to be capable of enhancing keratinocytes differentiation and accelerating skin barrier recovery on mouse models by the use of immunohistochemistry [17]. St. John's wort, on the other hand, is valued for its main active ingredient – hyperforin, which was shown to stimulate differentiation markers as well as exhibiting superiority over the vehicle when incorporated into hypericum-cream (1.5% hyperforin) in topical treatment of mild to moderate AD [18].

3.2 Antihistamine

The group of J. Görnemann [19] assessed the influence of the essential oil of *Lippia dulcis* Trev. on histamine/carbachol – induced contractions in guinea pigs' bronchial segments. Concentration-response curves were constructed accordingly, with atropine, mepyramine as positive controls, DMSO as a negative control and the essential oil (50-100 μ g/mL) as our protagonist. Acquired data showed that the histamine curve was shifted to the right significantly under the influence of 100 μg/mL of the essential oil ($P < 0.05$), along with a depression in the maximal histamine response (from 106±6 to 64±7%). The authors thus suggested a noncompetitive antagonistic activity to histamine exerted by the essential oil of *Lippia dulcis* Trev. with camphor, its main constituent, suspected to be the main acting ingredient.

The essential oil of *Carum copticum* was screened for antihistaminic activity in a study by M.H. Boskabady and J. Shaikhi in 2000 [20]. Guinea pigs' tracheal chains were incubated in indomethacin, propranolol hydrochloride,

atropine sulfate in 3 sets of experiments for histamine acid phosphate-induced contractions, followed by the construction of a cumulative log concentration-response curve. The results showed competitive antagonism effects of the oil at histamine H1 receptors, which was projected to be resulted from muscarinic blocking effects. Thus, the authors speculated that such activity may largely be attributed to α-pinene, a constituent of the oil, whose anti-cholinergic activity was examined in a study by L.N. Bogats and M.M. Ephstein, 1959. Differences in H1 receptor blocking effects of extracts and oil from *Carum copticum* may be due to incoherency in extraction methods, as indicated in the study.

The group of M.H. Boskabady [21] extended their research on the essential oil of *Carum copticum* by evaluating the relaxant effects on contracted guinea pig tracheal chains of its 4 different fractions collected after each 25 mL of the elution (with solvent being mixtures of petroleum ether and chloroform). Of the 4 fractions, fraction 2 was presumed to be carvacrol as indicated by their similar R results. The data suggested volume-dependent bronchodilatory effects of fractions 1, 2, 3 of the oil, with the latter two being more potent. Besides, β_2 – adrenergic stimulatory effect was not observed in the fractions' relaxant actions, indicating carvacrol's seemingly major role in the oil of *Carum copticum*'s bronchodilatory activity.

The essential oil of German chamomile flower [22] was obtained from the flower's ethyl acetate extract and briefly tested for its ability in alleviating compound 48/80-induced itch. The results showed a concentration-dependence effect, with 100-300 mg/kg, *p.o*, as a safety range for motor activities.

H. M. Kim and S. H. Cho [23] evaluated lavender oil's therapeutic effect in type I hypersensitivity in mice and rats. The oil was applied topically and intradermally in experiments of ear swelling response and PCA induction in order to test mast-cell mediated skin allergic reaction. Its effects on both tested subjects were proved significant as compound 48/8-induced ear swelling response in mice and anti-DNP IgE-induced PCA in rats were inhibited. Besides, the potency of topical lavender oil was deemed more significant than that of the intradermally applied oil in the 2 types of tests. Moreover, histamine release from peritoneal mast cells was effectively blocked by the said oils in application. The authors also suggested an action on membrane permeability of the oil to be the protagonist of its examined effects.

M. H. Boskabady and A. Moghadas [24] conducted a study of *Bunium persicum* antagonist effect at histamine H1 receptors in incubated guinea pig tracheal chains under 3 different conditions: (1) 1.4 μM indomethacin, (2) indomethacin, 1 μ M propranolol, and 10 nM atropine, and (3) indomethacin and propranolol (n = 8). The results were interpreted from recorded responses by a kymograph. Overall, the authors suggested that *B. persicum* showed antihistaminic effects on H1 receptors, which could be resulted from the stimulatory effect on β – adrenergic receptors.

R. Hajare et al. [25] performed a similar but much simplified study on the antihistaminic activity of *Piper betel* leaf by examining its ethanolic extract and essential oil. The experiments were set up using isolated guinea pig tracheal chain and ileum models, both of which could indicate the tested activity. At 100 μg/mL each, *P. betel*'s extract and essential oil were able to inhibit histamine-induced contractions of the 2 pig's body parts. Such ability occurred in a concentration-dependent manner.

J. H. Leal-Cardoso et al. [26] performed a study on the ability of *Croton nepetaefolius*'s essential oil (EOCN) to interfere with histamine-induced activities by examining its electrophysiological effects in celiac neurons. Although this does not resemble the mechanism of antihistamine, it was suggested from the study that EOCN block histamine's effect by affecting midway events in the signal transduction pathway following H1 receptor activation. This is of noteworthy consideration since there is little evidence for plant oil's antihistaminic activity, and regarding EOCN as an alternative which produces a comparable effect should yield more options for pharmacists. However, more studies should be conducted before the thought can be realized.

3.3 Topical Neuromodulators

3.3.1 Local anesthetics

Lidocaine and prilocaine, two well-known local anesthetics, exert their antipruritic effects by blocking voltage-gated sodium channel, thus stabilizing nerve sensory fibers. Following the logic, essential oils of the like should act on those channels or blocking the compound action potential (CAP) generated by sodium influx.

The action of the essential oil of *Alpinia zerumpet* (EOAZ) was addressed by Leal-Cardoso's group [27] by measuring changes in the compound action potential (CAP) parameters – CAP peak-to-peak amplitude and CAP conduction velocities - on sciatic nerves dissected from rats. The oil also exhibited a dose-dependent effect on CAP, as well as a complete blockade by the 2000 μ g/mL concentration. The CAP peak-to-peak amplitudes and conduction velocity were reduced. EOAZ-washed out nerves recovered to normal values during the latter 180-min period. Such records suggested that EOAZ may possess local anesthetic property, which is compatible to previous studies on the property of its constituent – 1,8-cineole [28] and other essential oils' constituents having similar structures such as eugenol [29] or α-terpineol [30]. The authors also proposed that EOAZ had a slow-course action on nerve cells, leading to probably higher effects on CAP parameters if the exposure time was more than 3 hours. Furthermore, other than tackling neurons' membranes, EOAZ could affect cells intracellularly because of the observed slow changes. In conclusion, EOAZ were found to be active on nerves in a concentration-dependent manner, blocking CAP generation and conduction.

In 2006, P. M. Lima-Accioly et al*.* [31] examined the same influences on nerve cells but by a different essential oil – that of *Croton nepetaefolius* (EOCN)) – and its constituent 1,8-cineole. The experimental design remained unchanged with two additional measurements – chronaxie and rheobase. Regarding peak-to-peak amplitude and conduction velocity, substantial reductions were observed in the applications of 500, 1000 μg/mL EOCN (n = 6) and 4, 6, 8 mmol/L 1,8-cineole (n = 6). At the end of the 180-min bathing time, rheobase and chronaxy values were recorded to have increased. Such data tellingly suggested the dose-dependent manner of EOCN and 1,8-cineole's ability to block nerve excitability. However, such inhibitory effect was more potent in 1,8-cineole in a lower dose (0.81 mmol/L) than that of EOCN (4 mmol/L), as well as a total recovery after the washout was only exhibited by the substance. Thus, the authors proposed that 1,8-cineole alone could be insufficient to wholly take responsibility in EOCN's actions on nerve excitability, and the roles of other constituents such as E-caryophyllene and bicyclogermacrene should be considered. Another remark made was the EOCN and its main constituents' mechanism of action, which was postulated to interfere with sodium channel activation, as well as exhibiting intracellular alterations such as axonal metabolism due to the slow time-course reaching for steady-state conditions. Nevertheless, more lights have to be shed on the subject before any convincing conclusions are to be made.

Another essential oil extracted from *Croton zehnteri* (EOCz) and its main constituent - anethole was found to possess local anesthetic activity using the same experimental procedure [32]. With concentrations ranging from 0.1 to 10 mg/mL, the tested substances reduced peak-to-peak amplitude and CAP conduction velocity in a dose-dependent manner, as well as increasing chronaxie and rheobase values. At 0.60 mg/mL concentration, EOCz and anethole completely inhibited all CAP waves. Comparion test regarding lidocaine, EOCz and anethole was conducted, showing similar modes of action among the three. Overall, the author group proposed that EOCz may act as a local anesthetic agent, and its effects could be traced back to anethole – the main constituent.

A similar experimental strategy was applied to address the essential oil of *Lippia alba* (EOLa) and citral (its constituent – 75% of the oil in this specific study)'s actions on rat's nerve excitability [33]. Results showed that there was a preference of both EOLa and citral for the second CAP component, which comprises of small myelinated motor fibers. A lower threshold concentration for citral (n = 6) – 10 μg/mL - than that of EOLa (n = 7) – 30 μ g/mL, together with a shorter time course to achieve full blockade (90 min in comparison to 180 min of EOLa) indicated more powerful depressor effects of the constituent. Regarding the CAP components' conduction velocities, EOLa and citral both reduced this parameter in a dose – dependent manner. However, it is noteworthy that only at 300 and 100 μ g/mL for each respectively, the CAP amplitudes were completely blocked to the point that the conduction velocities could not be measured. Chronaxy and rheobase values also increased at 60 μg/mL EOLa and 30 μg/mL citral, indicating a hindrance to the generation of action potential. The data showed a correlation between EOLa's effects and its constituents for there was only a mere gap between the 2 threshold concentrations, along with a high (75%) amount of citral in the tested sample. It is clear that among the essential oils of *Alpinia zerumbet, Croton nepetaefolius* and *Lippia alba,* the third one exhibited changes on conduction velocities at the lowest concentration. The authors

proposed EOLa to possess local anesthetic activity due to its blockade of nerve excitability, and that EOLa and citral may behave similar to linalool and carvacrol by acting directly on Na^+ channels.

Lavandula augustifolia, a flowering plant native to the Mediterranean, is known for its therapeutic use as a relaxant, especially in the oil form. In this regard, N. Ghelardini and C. Galeotti et al. [34] sought to elucidate the proposed local anesthetic activity of such essential oil. Using the *Citrus reticulate* Blanco and *Citrus limon* (L.) Burm.f.'s essential oils as negative controls, procaine and lidocain as reference drugs, as well as linalool and linalyl acetate as targeted subjects, the authors conducted rat – phrenic hemidiagram test and rabbit conjunctival reflex for proof of anestheticity. In the former experiment, the 3 tested subjects, within the range of 0.1 – 1000 μg/mL were capable of eliciting reductions dose-dependently in the electrically evoked contractions *in vitro*, to the point of complete elimination of the contractions. The former experiment carried out *in vivo* saw a rise in the number of stimuli needed for provoking the reflex when treated with the oil (30 – 2500 μg/mL) and its constituents. Since linalool and linalyl acetate exhibited similar behaviours to that of *L. augustifolio*'s essential oil, it was proposed that they may take responsibility for the oil's activity. On the other hand, although the mechanism of action of *L. augustifolio* was not a direct study's interest, the authors speculated a relation to antimuscarinic activity regarding to observations in the rat phrenic hemidiagram test. Also, a blockage of Na^+ and/or Ca^{2+} channels resulting from the local anesthetic activity was proposed.

Linalool-rich rosewood oil (87.7%) was tested for its influence on neuronal excitability by the sciatic nerve model as described above [35]. Data showed irreversible blockades by various concentrations of the oils with their respective increasing inhibiting powers, from 75% at 2 μg/mL to 95% at 100 μg/mL. The question whether the effect occurs exclusively due to the oil's main constituent is still open. Besides, it was suggested from the study that rosewood oil exert its activity probably by acting on voltage-dependent Na^+ channels.

3.3.2 Menthol

Menthol, a terpene derived from mint species, has been found to possess many therapeutic effects, especially when serving as a neuromodulator. It exerts anti-pruritic [36], anesthetic [37], anti-noiciceptive [38] activities by primarily acting on thermo receptors, desensitizing TRPV1 receptors as well as showing weak kappa-opioid receptor agonisticity. Yet, menthol-containing oils such as peppermint or eucalyptus oil [39] have yet been studied much upon, particularly the anti-itch property. Still, there laid hopes for the said oils in the treatment of itch as they contain menthol, a multipotent compound, and their anti-inflammatory, antinociceptive potency have been proved, which share several related neurotransmitting pathways to the anti-itch activity.

3.3.3 Capsaicin

Unlike menthol, which activates cold receptors in the peripheral nerves, capsaicin exerts its effect on the heat receptors, or the TRP family of proteins to be specific. Thus, the application of topical capsaicin on human skin initially causes a prickly sensation often associated with pain or itch, and subsequently "numbs" the nerves if prolonged action is maintained. In other words, desensitization of noiciceptors is the main mechanism of the extract that leads to its use in treating painful syndromes. That being said, patients with itching conditions are thus frequently prescribed capsaicin for symptom alleviations, because pain and itch share related transmitting pathways.

3.4 Topical Cannabinoids

α-Amyrin, a pentacyclic triterpene, was proved to exert agonistic effects on CB1 and CB2 receptors with varying degrees of potency. It is also a main constituent of *Ocimum basilicum* L. essential oil (OBV), whose topical anti-inflammatory activity was tested in the study of Okoye et al. 2014 [40]. By the application of doses of 50, 100, 200, and 400 μg/ear on a modified acute topical edema model, OBV and 3 other tested subjects, *Ocimum basilicum* L. hexane extract (OBHE), *Ocimum gratissimum* L. essential oil (OGV), *Ocimum gratissimum* L. hexane extract (OGHE), were screened for anti-inflammatory activity. Statistical analysis showed that all of them possessed inhibitory effect on edema at the concentration of 50 μg/ear, and they were dose-independent. Notably, OBV seemed to be the most potent of all, even more effective than hydrocortisone, a control. The authors later elaborated that varying degrees of activity may be due to different extraction

methods, which resulted in diverse anti-inflammatory constituents. Furthermore, OBV bears additional substances, especially α -amyrin, that were shown to exhibit said activity [41] which may explain its highest potency. Thus, *Ocimum basilicum* L. essential oil might act as a CB1/CB2 agonist as well as an antipruritic agent because it possesses topical anti-inflammatory activity and α-amyrin as a main constituent.

Another phytocannabinoid that fully agonizes CB2 receptors is β-caryophyllene, found in both cannabis and non-cannabis plant. In particular, *Farfugium japonicum* essential oil bearing 12.26% of β -caryophyllene was screened for topical anti-inflammatory activity in a study of J.Y. Kim et al. [42] by determining nitric oxide (NO) and prostaglandin (PGE_2) productions in lipopolysaccharide (LPS) – activated RAW 264.7 macrophages. Inhibition of production was present in both tests, and the authors suggested such potency be restricted not only to the oil's toxicity but also its active constituents. Also, test of safety for human skin application of the oil was conducted on human dermal fibroblast, which further shed light on the possibility of incorporating this oil in topical treatment of anti-inflammatory – related diseases. That being said, *Farfugium japonicum* essential oil may be utilized as an antipruritic agent for its speculated CB2 agonistic effect.

The essential oil of *Bupleurum fruticescens* exerted anti-inflammatory effects in the test of carrageenan – induced hind paw edema, administered orally [43]. Its main constituents are hydrocarbon, notably β-caryophyllene (30.55%), a prospective CB_2 agonist.

G. F. Passos et al. [44] evaluated *Cordia verbenacea* essential oil and its main constituent – (−)*trans*-caryophyllene for anti–inflammatory effects. Both were administered orally in the carrageenan – induced rat paw edema, and showed significant improvements at 300-600 mg/kg for the oil and 50 mg/kg for the active compound. Tellingly, (−) *trans*-caryophyllene is also called β-caryophyllene.

Alkylamides found in the *Echinacea* genus can act as full agonist on CB_2 receptors, as reported by C. Sharma et al. [41]. Also, the essential oil of *Echinacea purpurea* L. was examined for its anti-inflammatory activities by tests of xylene-induced ear edema and egg albumen – induced paw edema in mice, with results showing significant improvements in the middle and high dose groups [45].

4. DISCUSSION

This compilation of 52 articles, 29 of which were used as direct sources of analysis, shows that plant oils are indeed of practical use in itch alleviation. To be more specific, plant oils as moisturizers or skin-hydrating agents are the most studied and applied, with oils from 21 species assessed both in clinical trials and cosmetic uses. The second category, local neuromodulators, though only has its tested subjects performed in *in vitro* condition, the results were tellingly unanimous in that the six oils examined may well act as local anesthetizing agents. In contrast, the remaining two categories, topical antihistamines and topical cannabinoids, have very few findings with mere speculated therapeutic prospects. However, on a positive outlook, the fact that they could act similar to their synthetic counterpart reserves room for future conducts.

In a more detailed note, the studies' design (i.e tests of TEWL, skin capitance values, etc.) of the moisturizer category rests upon the role of essential fatty acids in hydrating and improving skin barrier functions. As vegetable oils, in this particular case, are high in said substances, especially in linoleic acid (Table 3), the results ensued that they acted accordingly to their main components. Moreover, linoleic acid is also a precursor of arachidonic acid, which in turn undergoes oxidation to produce eicosanoids, whose subfamilies such as prostanoids partake in mediating symptoms of inflammation. In that regard, vegetable oils may be superior to synthetic moisturizers in alleviating itch, which shares related pathway to topical inflammatory conditions, by in part soothing the inflamed skin. However, the aforementioned studies either had few sample sizes (18-25 patients) or were carried out *in vitro*. Furthermore, there have not been exact formulations of the topical creams nor systemic reviews on whether their therapeutic effects well excel over other on-the-counter products.

The use of antihistamine in alleviating itch is debatable despite being frequently prescribed. According to P.A. Klein's systematic review in 1999 on the efficacy of antihistamine in alleviating pruritus, few studies had been conducted to assess the said effect, and none of them obtained a well-designed model for

Table 3. Fatty acid compositions of selected vegetable oils

Fatty acid	Coconut oil	Sunflower seed oil	Sesame oil	Rapeseed oil	Palm oil
C8:0	4.6 - 10.0	ND	ND	ND	ND
C10:0	5.0 - 8.0	ND	ND	ND	ND
C12:0	45.1 - 53.2	ND-0.1	ND	ND	ND-0.5
C14:0	16.8 - 21.0	ND-0.2	ND-0.1	ND-0.2	0.5-2.0
C16:0	7.5 - 10.2	5.0-7.6	7.9-12.0	1.5-6.0	39.3-47.5
C16:1	ND	ND-0.3	0.1-0.2	ND-3.0	ND-0.6
C18:0	2.0 - 4.0	2.7-6.5	4.8-6.1	0.5-3.1	3.4-6.0
C18:1	5.0 -10.0	14.0-39.4	35.9-42.3	8.0-60.0	36.0-44.0
C18:2	1.0-2.5	48.3-79.0	41.5-47.9	11.0-23.0	9.0-12.0
C18:3	ND-0.2	ND-0.3	0.3-0.4	5.0-13.0	ND-0.5
C20:0	ND-0.2	0.1-0.5	0.3-0.6	ND-3.0	ND-1.0
C20:1	ND-0.2	ND-0.3	ND-0.3	3.0-15.0	ND-0.4
C22:0	ND	0.3-1.5	ND-0.3	ND-2.0	ND-0.2
C22:1	ND	ND-0.3	ND	>2.0-60.0	ND
C24:0	ND	ND-0.5	ND-0.3	ND-2.0	ND

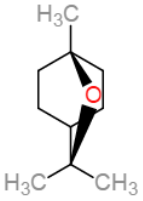
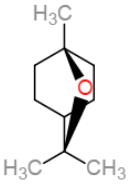
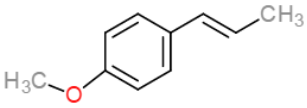
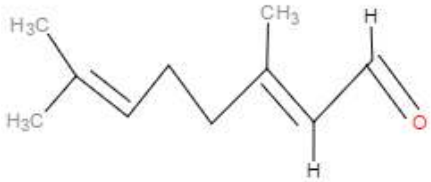
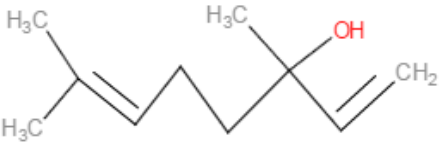
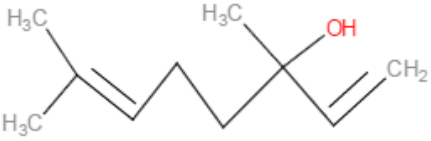
**Table 3 was adapted from Codex Standard for Named Vegetable Oils (CODEX-STAN 210 - 1999) with small modifications*

accurate assessment. Nevertheless, in vitro studies showed the correlation of histamine H1, H4 receptors, activation to itch evocation, thus inferring the role of antihistamines as antipruritic agents, with the postulated superior efficacy of the H4 counterpart [46,47]. Besides, H1 receptor antagonists were also proved to expedite damaged barrier skin regeneration [48], whose effects if unfixed might as well cause dry skin – induced itch. In writing this part of the review, the authors could not search for a substantial amount of direct *in vivo* studies on essential oils alleviating itch by acting as antihistamine, hence replacing them with related evidences. More specifically, as H1, H4 histamine receptors also are present in the lungs, noses and skins, studies on anti-allergic, anti-spasmodic and bronchodilatory oils passed the inclusion criteria. In so doing, the oils of *lippia dulcis* Trev., *carum copticum,* german chamomile flower, lavender, *B. persicum, piper betel, croton nepetaeofolius* were listed for their antihistaminic activities on various experimental designs, all of which antagonize H1 receptors. Of the 6 oils examined *lippie dulcis* Trev. and *carum copticum* were found to largely owe their antihistaminic acitivities to the main constituents, carvacrol and camphor, respectively. On the other hand, although no studies on essential oils exerting H4 antagonisticity were found, their potentials in the field is indispensible as H4 antagonists clearly excel over their H1 counterparts in alleviating itch.

Local anestheticity of the 6 oils examined was assessed by measuring the following physiological parameters: peak-to-peak amplitude (PPA), compound action potential (CAP), chronaxie and rheobase. Strictly speaking, PPA and CAP represent nerve conduction, while the latter stand for nerve excitability. Regardingly, decreasing values of PPA and CAP along with increasing values of chronaxie and rheobase are signs of an anestheticized nerve. Following that logic, rosewood, lavender, EOCz, EOLa, EOAZ, EOCN oils were proved to exert depression on nerve excitability within a pharmacological range and in a concentration-dependent manner. Such activity was postulated to stem from the interference of sodium channel activation, which is a characteristic of local anesthetics drug like lidocaine. In other words, these essential oils not only behave similarly to their synthetic counterparts, but also possess potency at concentrations that are appropriate for human intake, thus might be considered for novel drug synthesis. Of the 6 oils examined, only EOCN and rosewood oils' effects were irreversible after the washout, indicating their impressive potency. Also, a pattern among the aforementioned studies surfaces up when one examines them closely: each essential oil's local anesthetic activity is partially or wholly (in the EOLa's case) linked with its main constituents, which possess similar or stronger potency. Henceforth, although studies of the activity on oils are minor, researchers may extrapolate other potential oils from their accordingly main constitutents. In fact, abundant researches have been carried out to examine these extracts's anestheticity such as linalool, menthol, terpineol, eugenol, cavacrol,

1,8-cineole, estragole, β -carophyllene, etc. Moreover, researchers could as well predict a plant's local anestheticity by examining its analgesic, sedative and antispasmodic effects, as can be inferred from the studies where 6 oils possess similar activities. In addition, Table 4 enlists essential oils and their according main/active constituents in this category.

Table 4. Essential oils and their main/active constituents having local anestheticity

Essential oils	Main/active constituents	References
Alpinia zerumpet	1,8-cineole (20.57%) 	[27]
Croton nepetaefolius	1,8-cineole (24,98%) 	[31]
Croton zethneri	Anethole (85.7%) 	[32]
Lippia alba	Citral (75%) 	[33]
Lavandula augustifolia	Linalyl acetate (43.6%) Linalool (31.5%) 	[34]
Rosewood oil	Linalool (87.7%) 	[35]

**All the images of Table 3 were drawn using ChemDoodle 2D sketcher*

Being a prospective therapy, studies on ligands of cannabinoid receptors not only showed improved results in itch-relating diseases [49,50] but also generated no observed side effects. Its mechanism has not been officially agreed upon, yet many are convinced that small particles agonizing CB1/CB2 receptors may be the protagonists. Fortunately, aromatic oils with their tiny molecular components excel in targeting channels or other parts that are impenetrable to normal oils, and CB1/CB2 receptors stand as no exceptions. In fact, classes of phytocannabinoids and noncannabinoid plant constituents have been categorized in the last few years as prospective ligands of the said receptors. Since limited researches on phytocannabinoid's antipruritic effect are present, the authors opted for studies concentrating on essential oils that contain the reported constituents and exert antinoiciceptive and/or anti-inflammatory potency, which share related pathway with pruritus. In so doing, the essential oils of *Ocimum basicilum* L., *Farfugium japonica, Bupleurum fruticescens, Cordia verbenacea* and *Echinacea purpurea* L. were enlisted in this category since they produce anti-inflammatory effects and bear α-amyrin, β-caryophyllene and alkylamides as their main constituents, respectively. These nano-sized molecules, as aforementioned, can act as full CB_1/CB_2 agonists. Although studies on phytocannabinoid and non-cannabinoid plant constituents have recently been robust, its essential oil aspect and topical therapeutic effects have not been deeply delved into. Largely, researchers take their interests in treating retroperitoneal inflammation [51,52] or the efficacy of the plants' ether extracts. This, however, sets more opportunities for researchers to elucidate on the potential effects of CB2/CB1 agonists contained in essential oils for the alleviation of itch.

5. CONCLUSION

This review offers a novel approach to alleviating pruritus concerning herbal medicine. As noted, itch poses as a challenging predominant symptom of skin diseases that calls for the attention of specialists. Among the alternatives to treatments, plant oils have proved its efficacy in alleviating pruritus. To be more specific, the use of plant oils as moisturizers has been recognized in this reviewed as the most promising among the 4 therapies mentioned. The rests, antihistamine, topical neuromodulators and cannabinoid require further research to confirm their practicality in the matter.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Ikoma A, Steinhoff MS, Ständer S, Yosipovitch G, Schmelz M. The neurobiology of itch. Nat Rev Neurosci. 2006;7(7):535–47.
2. Patel KN, Dong X. An itch to be scratched. Neuron. 2010;68:334–9.
3. Elmariah SB, Lerner EA. Topical therapies for pruritus. Seminars in Cutaneous Medicine and Surgery. 2011;30:118–26.
4. Gehring W, Wenz J, Gloor M. Influence of topically applied ceramide/phospholipid mixture on the barrier function of intact skin, atopic skin and experimentally induced barrier damage. Int J Cosmet Sci. 1997;19(4):143–56.
5. Varothai S, Nitayavardhana S, Kulthanan K. Moisturizers for patients with atopic dermatitis. Asian Pac J Allergy Immunol [Internet]. 2013;31:91–8. Available:http://www.ncbi.nlm.nih.gov/pubmed/23859407
6. Okada K, Matsumoto K. Effect of skin care with an emollient containing a high water content on mild uremic pruritus. Ther Apher Dial. 2004;8(5):419–22.
7. Wright S. Essential fatty acids and the skin. Prostaglandins, Leukot Essent Fat Acids. 1991;38(4):229–36.
8. Mao-Qiang M, Elias PM, Feingold KR. Fatty acids are required for epidermal permeability barrier function. J Clin Invest [Internet]. 1993;92(2):791–8. (Cited 2016 Dec 14) Available:http://www.ncbi.nlm.nih.gov/pubmed/8102380
9. Evangelista MTP, Abad-Casintahan F, Lopez-Villafuerte L. The effect of topical virgin coconut oil on SCORAD index, transepidermal water loss, and skin capacitance in mild to moderate pediatric atopic dermatitis: A randomized, double-blind, clinical trial. Int J Dermatol. 2014; 53(1):100–8.

10. Agero AL, Verallo-Rowell VM. A randomized double-blind controlled trial comparing extra virgin coconut oil with mineral oil as a moisturizer for mild to moderate xerosis. Dermatitis [Internet]. 2004;15(3):109–16. Available:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15724344
11. Darmstadt GL, Mao-Qiang M, Chi E, Saha SK, Ziboh VA, Black RE, et al. Impact of topical oils on the skin barrier: Possible implications for neonatal health in developing countries. Acta Paediatr [Internet]. 2002;91:546–54. Available:http://sig.biostr.washington.edu/~raven/darmstadt2002.pdf
12. Piccardi N, Piccirilli A, Choulot J, Msika P. Sunflower oil oleodistillate for atopy treatment: An *in vitro* and clinical evaluation. Google Scholar. J Invest Dermatol [Internet]. 2001;117(2):418–418. (Cited 2016 Dec 13) Available:https://scholar.google.com.vn/scholar?hl=vi&q=Sunflower+oil+oleodistillate+for+atopy+treatment%3A+an+in+vitro+and+clinical+evaluation.&btnG=
13. Eichenfield LF, McCollum A, Msika P. The benefits of sunflower oleodistillate (SOD) in pediatric dermatology. Pediatric Dermatology. 2009;26:669–75.
14. Lubbe A, Verpoorte R. Cultivation of medicinal and aromatic plants for specialty industrial materials. Industrial Crops and Products. 2011;34:785–801.
15. Vermaak I, Kamatou GPP, Komane-Mofokeng B, Viljoen AM, Beckett K. African seed oils of commercial importance - Cosmetic applications. South African J Bot. 2011;77(4):920–33.
16. Dal'Belo SE, Rigo Gaspar L, Maia Campos PMBG. Moisturizing effect of cosmetic formulations containing *Aloe vera* extract in different concentrations assessed by skin bioengineering techniques. Ski Res Technol. 2006;12(4):241–6.
17. Kim JH, Choi DK, Lee SS, Choi SJ, Kim CD, Yoon TJ, et al. Enhancement of keratinocyte differentiation by rose absolute oil. Ann Dermatol. 2010;22(3): 255–61.
18. Schempp CM, Windeck T, Hezel S, Simon JC. Topical treatment of atopic dermatitis with St. John's wort cream--a randomized, placebo controlled, double blind half-side comparison. Phytomedicine [Internet]. 2003;10(Suppl 4):31–7. Available:http://www.ncbi.nlm.nih.gov/pubmed/12807340
19. Görnemann T, Nayal R, Pertz HH, Melzig MF. Antispasmodic activity of essential oil from *Lippia dulcis* Trev. J Ethnopharmacol. 2008;117(1):166–9.
20. Boskabady MH, Shaikhi J. Inhibitory effect of *Carum copticum* on histamine (H1) receptors of isolated guinea-pig tracheal chains. J Ethnopharmacol. 2000;69(3): 217–27.
21. Boskabady MH, Ramazani M, Tabei T. Relaxant effects of different fractions of essential oil from *Carum copticum* on guinea pig tracheal chains. Phyther Res. 2003;17(10):1145–9.
22. Kobayashi Y, Takahashi R, Ogino F. Antipruritic effect of the single oral administration of *German chamomile* flower extract and its combined effect with antiallergic agents in ddY mice. J Ethnopharmacol. 2005;101(1–3):308–12.
23. Kim HM, Cho SH. Lavender oil inhibits immediate-type allergic reaction in mice and rats. J Pharm Pharmacol [Internet]. 1999;51(2):221–6. Available:http://www.ncbi.nlm.nih.gov/pubmed/10217323
24. Boskabady MH, Moghaddas A. Antihistaminic effect of *Bunium persicum* on guinea pig tracheal chains. Iran Biomed J. 2004;8(3):149–55.
25. Hajare R, Darvhekar VM, Shewale A, Patil V. Evaluation of antihistaminic activity of *Piper betel* leaf in guinea pig. J Pharm Pharmacol. 2011;5:113–7.
26. Leal-Cardoso JH, Lahlou S, Weinreich D, Caldas Magalhães PJ. The essential oil of *Croton nepetaefolius* selectively blocks histamine-augmented neuronal excitability in guinea-pig celiac ganglion. J Pharm Pharmacol. 2010;62(8):1045–53.
27. Leal-Cardoso JH, Moreira MR, da Cruz GM, de Morais SM, Lahlou MS, Coelho-de-Souza AN. Effects of essential oil of *Alpinia zerumbet* on the compound action potential of the rat sciatic nerve. Phytomedicine [Internet]. 2004;11(6):549–53. Available:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15500268
28. Zalachoras I, Kagiava A, Vokou D, Theophilidis G. Assessing the local anesthetic effect of five essential oil constituents. Planta Med. 2010;76(15): 1647–53.

29. Moreira-Lobo DCA, Linhares-Siqueira ED, Cruz GMP, Cruz JS, Carvalho-de-Souza JL, Lahlou S, et al. Eugenol modifies the excitability of rat sciatic nerve and superior cervical ganglion neurons. Neuroscience Letters. 2010;472.

30. Moreira MR, Cruz GM, Lopes MS, Albuquerque AA, Leal-Cardoso JH. Effects of terpineol on the compound action potential of the rat sciatic nerve. Brazilian J Med Biol Res Rev Bras Pesqui Medicas e Biol Soc Bras Biofisica Al [Internet]. 2001;34(10):1337–40.
Available:http://www.ncbi.nlm.nih.gov/pubmed/11593310

31. Lima-Accioly PM, Lavor-Porto PR, Cavalcante FS, Magalhães PJC, Lahlou S, Morais SM, et al. Essential oil of *Croton nepetaefolius* and its main constituent, 1,8-cineole, block excitability of rat sciatic nerve *in vitro*. Clin Exp Pharmacol Physiol. 2006;33(12):1158–63.

32. Da Silva-Alves KS, Ferreira-Da-Silva FW, Coelho-De-Souza AN, Albuquerque AAC, Do Vale OC, Leal-Cardoso JH. Essential oil of *Croton zehntneri* and its main constituent anethole block excitability of rat peripheral nerve. Planta Med. 2015;81(4): 292–7.

33. Sousa DG, Sousa SD, Silva RE, Silva-Alves KS, Ferreira-da-Silva FW, Kerntopf MR, et al. Essential oil of *Lippia alba* and its main constituent citral block the excitability of rat sciatic nerves. Braz J Med Biol Res [Internet]. 2015;48(8):697-702.
Available:http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1414-98932008000300002

34. Ghelardini C, Galeotti N, Salvatore G, Mazzanti G. Local anaesthetic activity of the essential oil of *Lavandula angustifolia*. Planta Med. 1999;65(8):700–3.

35. De Almeida RN, Araújo DAM, Gonçalves JCR, Montenegro FC, de Sousa DP, Leite JR, et al. Rosewood oil induces sedation and inhibits compound action potential in rodents. J Ethnopharmacol. 2009;124(3): 440–3.

36. Bromma B, Scharein E, Darsow U, Ring J. Effects of menthol and cold on histamine-induced itch and skin reactions in man. Neurosci Lett. 1995;187(3):157–60.

37. Galeotti N, Ghelardini C, Di L, Mannelli C, Mazzanti G, Baghiroli L, et al. Menthol is present in the volatile oil of several species of mint plants such as peppermint. Planta Med. 2001;67:174–6.

38. Green BG, Schoen KL. Thermal and nociceptive sensations from menthol and their suppression by dynamic contact. Behav Brain Res. 2007;176(2):284–91.

39. Silva J, Abebe W, Sousa SM, Duarte VG, Machado MIL, Matos FJA. Analgesic and anti-inflammatory effects of essential oils of Eucalyptus. J Ethnopharmacol. 2003; 89(2–3):277–83.

40. Okoye FBC, Obonga WO, Onyegbule FA, Ndu OO, Ihekwereme CP. Chemical composition and anti-inflammatory activity of essential oils from the leaves of *Ocimum basilicum* L. and *Ocimum gratissimum* L. (Lamiaceae). Int J Pharm Sci Res IJPSR. 2014;5(6):2174–80.

41. Sharma C, Sadek B, Goyal SN, Sinha S, Kamal MA, Ojha S. Small molecules from nature targeting G-protein coupled cannabinoid receptors: Potential leads for drug discovery and development. Evidence-based Complementary and Alternative Medicine. 2015 Vol. 2015.

42. Kim JY, Oh TH, Kim BJ, Kim SS, Lee NH, Hyun CG. Chemical composition and anti-inflammatory effects of essential oil from *Farfugium japonicum* flower. J Oleo Sci. 2008;57(11):623–8.

43. Martin S, Padilla E, Ocete MA, Galvez J, Jimenez J, Zarzuelo A. Anti-inflammatory activity of the essential oil of *Bupleurum fruticescens*. Planta Med. 1993;59(6):533–6.

44. Passos GF, Fernandes ES, da Cunha FM, Ferreira J, Pianowski LF, Campos MM, et al. Anti-inflammatory and anti-allergic properties of the essential oil and active compounds from *Cordia verbenacea*. J Ethnopharmacol. 2007;110(2):323–33.

45. Yu D, Yuan Y, Jiang L, Tai Y, Yang X, Hu F, et al. Anti-inflammatory effects of essential oil in *Echinacea purpurea* L. Pak J Pharm Sci. 2013;26(2):403–8.

46. Bell JK, McQueen DS, Rees JL. Involvement of histamine H4 and H1 receptors in scratching induced by histamine receptor agonists in Balb C mice. Br J Pharmacol [Internet]. 2004; 142(2):374–80.
Available:http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1574944&tool=pmcentrez&rendertype=abstract

47. Zampeli E, Tiligada E. The role of histamine H_4 receptor in immune and inflammatory disorders. Br J Pharmacol [Internet]. 2009;157(1): 24–33.
Available:http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed9&AN=2009549401\nhttp://sfx.leidenuniv.nl:9003/sfx_local?sid=OVID:Embase&issn=0007-1188&isbn=&volume=157&issue=1&spage=24&date=2009&pid=%3Cauthor%3EZampeli+E.%3C%2author%3E
48. Ashida Y, Denda M, Hirao T. Histamine H1 and H2 receptor antagonists accelerate skin barrier repair and prevent epidermal hyperplasia induced by barrier disruption in a dry environment. J Invest Dermatol [Internet]. 2001;116(2):261–5.
Available: http://dx.doi.org/10.1046/j.1523-1747.2001.01238.x
49. Manuscript A. Novel perspectives and therapeutic opportunities. 2009;30(8): 411–20.
50. Hernandez F, Chandra S. The current state and potential direction of cannabis research. J Exp Integr Med [Internet]. 2016;6(1):44.
Available:http://www.scopemed.org/?mno=219500
51. Oliveira FA, Vieira-Júnior GM, Chaves MH, Almeida FRC, Florêncio MG, Lima RCP, et al. Gastroprotective and anti-inflammatory effects of resin from Protium heptaphyllum in mice and rats. Pharmacol Res. 2004;49(2):105–11.
52. Otuki MF, Vieira-Lima F, Malheiros Â, Yunes RA, Calixto JB. Topical antiinflammatory effects of the ether extract from *Protium kleinii* and α-amyrin pentacyclic triterpene. Eur J Pharmacol. 2005;507(1–3):253–9.

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