In light of these, a be-phase study was performed to examine the diffusion pattern of essential oils from a Gum-karaya patch through the skin. In the first part, two different essential oils, orange and lavender oils, were incorporated into hydrocolloid patches and their penetration through the skin was examined using Franz diffusion cells apparatus. In the second part of the study [*in vivo*] we examined the diffusion of essential oil from the patch and the penetration of its components through the skin to the circulation, using male Sprague-Dawley rats. Understanding the mode of passage and quantifying the penetration rate of essential oil are crucial to design novel practical and commercial approach of patch inserted essential-oil.

Materials and Methodology

Patch preparation

Gum karaya-essential oil patches with or without starch were produced as previously described by Cherebina et al. [19]. Briefly, the first fraction was composed of 13.6 to 23.6% (w/w) distilled water, 21.1% (w/w) glycerol (Sigma Chemical Co., St. Louis, MO), 7.5% (w/w) of either *Lavandula angustifolia* essential oil ("Light of the Desert", Kibbutz Urim, Israel) or Valencia orange oil (Kibbutz Givat Haim, Israel), 1% (w/w) Tween 80 (Sigma) as an emulsifier and, optionally, 10% (w/w) potato starch (Merck, Darmstadt, Germany) as a filler. The second fraction consisted of suspending 20.0% (w/w) bark-free, HPS-grade (hand-picked selected, summer crop, 200 µm) pure Gum-karaya powder (Sigma) in 27.7% (w/w) propylene glycol (Merck). The two fractions, prepared separately, stirred for 5 min at ambient temperature and kept at -20°C for half an hour to slow the gelation reaction. They were then mixed together and quickly poured into a small Petri dish (height 5 mm, diameter 40 mm) or a rectangular mold with dimensions of 11 × 10 × 0.5 cm (length × width × thickness) to form the final solidified patch.

Gas chromatography analysis

Gas chromatography (GC) was performed on an Agilent 7890A gas chromatograph equipped with a split/splitless capillary injector, flame ionization detection (FID) system and GC Chem Station (Version B. 03.01; Agilent Technologies 2007). Chromatography was carried out on a WAX or HP-5 columns. The using of WAX column [30 m × 0.32 mm × 0.25 µm; Agilent] was combined with split injection (1:40) therefore, only part of the absorbed sample reached the column (used for Exp.1). The utilizing of HP-5 column was combined with splitless injection in which the whole absorbed sample reaches the column, thus we could identify more constituents than with the WAX column (used for Exp. 2). The GC operating conditions were: splitless or split 1:40 injector 240˚C, oven 50˚C for 1 min and then 10˚C min^{-1} to 160˚C, then 25˚C min^{-1} to 240˚C and held for 6 min.

In a preliminary examination, Geranyl formate and Linalyl isovalerate were examined as standard. Linalyl isovalerate was found more suitable for our study (data not shown). Standard was prepared from 0.5 ml of blank blood, 10 µl internal standard (0.0026 mg linalyl isovalerate in 25 ml acetonitrile) and an appropriate dilution of lavender oil in 10 µl acetonitrile. Lavender oil was first dissolved in acetonitrile (625 mg L^{-1}) and further diluted with acetonitrile to make intermediate standards (0.5, 1, 5, 25 and 125 mg L^{-1}). The calibration curves were plotted using the peak area ratio of linalool (the main constituent of lavender oil) and linalyl isovalerate *vs.* linalool concentration.

Experimental design

The study composed two experimental models to examine transfer of Gum-karya patches inserted essential oil through the skin. In the first part of the study (Experiment 1) the Franz diffusion cells apparatus was used. In the second part of the study (Experiment 2) an *in vivo* study was performed using male Sprague-Dawley rats.

Examination of essential-oil transfer through the skin by using Franz diffusion cells

The study was performed in Franz diffusion cells (FC) (PermeGear, Hellertown, PA). Frozen Stomach skin pieces (1.2 cm × 1.2 cm) from a male rat were thawed at room temperature and placed in FC glass. The absorption surface area was 0.64 cm^2. The FC was thermoregulated with a water jacket at 32°C. The 4.5 ml volume of the FC chamber was filled with a receptor solution containing 5% (w/v) bovine serum albumin (BSA) diluted with phosphate buffer pH 7.4. Either 0.38 g of patch or almond oil (both containing 7.5% essential oil) was applied to the donor compartment. The receptor solution was continuously agitated with a magnetic stirrer. During the experiments, the donor compartments and sampling arms were sealed to prevent evaporation. The fluid was removed from the receptor chamber after 0, 6, 12, 24, 36 and 48 h and replaced with fresh phosphate buffer solution. Samples were stored at 4°C till GC analysis, using a WAX column.

In vivo examination of essential-oil transfer inserted Gum-karaya patches through the skin to the circulation

Animals: Male Sprague-Dawley rats, weighing 300-350 g were used in the study (Harlan, Rehovot, Israel). Rats were maintained under specified-pathogen-free (SPF) conditions, acclimated to the environment for at least 7 days before the study started, and housed in an individual cage to prevent contamination of the essential oil between animals. Animals were anesthetized, their stomach fur was shaved and Gum-karaya patches with or without lavender essential oil were applied to their stomach skin (time=0 h). The experimental protocols were approved by the Hebrew University of Jerusalem Committee on the Use and Care of Animals.

Sampling: Before sampling, rats were restrained and the tail was gently massaged to facilitate blood collection from the tail tip. From each animal, blood samples (0.5 ml) were collected at 0, 12, 24, 36, 48 and 60 h, placed in Eppendorf heparin-coated glass vials (Agilent), sealed with septa and screw caps and stored at -80°C till analysis.

Prior to analysis, the blood sample was thawed and 10 µl of internal standards was added to the vial. The vial septum was pre-punctured using a needle and a fiber sheath was inserted and positioned in the center of the headspace. The vial was placed on a heating block to maintain a constant temperature (50°C) and the solid-phase microextraction (SPME) assembly was clamped securely. The absorption time was 30 min and no stirring was required. After absorption, the SPME fiber sheath was immediately transferred to the GC injector for 5 min desorption and analyzed.

Patches were removed from the animals after 60 h and the application site was wiped with 70% alcohol. Animals were then sacrificed and the skin area to which the essential oil patch had been applied was removed and dissected into small pieces. The skin pieces were placed in 1 ml of ethanol containing linalyl isovalerate as internal standard and sonicated for 30 min at 50˚C. A 10 µl aliquot was then injected straight into the gas chromatograph.

Statistical analysis

Statistical analyses were conducted with JMP software (SAS Institute 2007, Cary, NC), including ANOVA and Tukey-Kramer Honestly Significant Difference test for comparisons of means. P ≤ 0.05 was considered significant.

Results and Discussion

Experiment 1

Transdermal delivery of essential-oil components from Gum-karaya patches through the skin was examined, using FCs test. The examination included [1] lavender essential oil, which contains a high proportion of terpenoids and [2] Valencia orange oil, which includes a considerable amount of terpene. Note that all the experiments were conducted at ambient temperature. Earlier study [18] reported a possible transdermal delivery of essential oil into the blood stream, resulted of percutaneous absorption of lavender oil following massage. Therefore, in addition to the traditional FCs test, we performed in the current study another set of examinations in which skin was smeared with a mixture of almond and essential oil to imitate aromatherapy skin massaged. Findings indicated that the inclusion of the essential oil using Gum-karaya patch was similar to that found after by massage-like simulation.

The two main ingredients in lavender oil are the terpenoids linalool and linalyl acetate, which account together about 68.4% of the oil composition. The main ingredient in Valencia orange essential oil is terpene d-limonene. It should be noted however, that higher proportion ingredient does not imply superior transfer abilities through the skin as penetration depends on various factors, some of which were examined here. The components of lavender and orange essential oils found in the current study, in the medium, are presented in Table 1.

Lavandula angustifolia essential oil[z]		Valencia orange essential oil	
Ingredient	**% in oil**	**Ingredient**	**% in oil**
Linalool	36.18	d-Limonene	95.17
Linalyl acetate	32.31	Myrcene	1.86
(E)-Caryophyllene[y]	4.73	α-Pinene	0.42
(E)-β-Farnesene[y]	3.64	Decanal	0.28
Borneol	2.87	Linalool	0.25
(Z)-β-Ocimene[y]	1.61	Sabinene	0.12
Caryophyllene oxide	1.47	β-Pinene	0.12
Hexyl butanoate	1.28	Geranial	0.10
Camphor	1.17	Neral	0.07
α-Santalene	1.01	Dodecanal	0.07
α-Terpineol	0.99	Citronellal	0.05

Table 1: Composition of lavender and orange essential oils. [z]Information was supported by the suppliers of the essential oil, [y]E stands for entgegen, i.e. opposite sides of a double bond; Z stands for zusammen, i.e. same side of a double bond.

Elapsed time (h)	Linalool(mg/L)	Linalyl acetate(mg/L)	Camphor(mg/L)
6	16.49 ± 2.81^a	0.15 ± 0.14^a	0.51 ± 0.33^a
12	34.46 ± 1.20^b	0.26 ± 0.25^a	0.74 ± 0.02^b
24	61.64 ± 3.83^c	0.37 ± 0.01^a	1.53 ± 0.13^c

Table 2: Accumulated concentrations of linalool, linalyl acetate and camphor transferred from gum karaya- *Lavandula angustifolia* essential oil patches. At time zero, no traces of the three components were detected. Results are expressed as mean ± standard error. [a,b,c]Different superscript letters within a column indicate a statistically significant difference at P<0.05.

Table 2 presents the accumulated concentrations of linalool, linalyl acetate and camphor that were transferred from the patch through the skin. While at time 0 ingredients were not found in the medium, an increased concentration of ingredient was observed through the examined time (i.e., 6, 12 and 24 h), in particular, that of linalool and camphor. Figure 1 presents representative profile of permeation from the patch, through the skin into the medium of d-limonene, a Valencia-orange essential oil component. The steady-state flux was calculated from the slope of the linear portion of the curve, which expressed accumulated amount of essential oil per unit area *vs.* time.

The calculated steady flux for d-limonene was 1.9×10^{-4} mg·cm^{-2}h^{-1} and that for linalool and camphor were 0.018 and 4.3×10^{-4} mg·cm^{-2}h^{-1}, respectively (curves are not shown). When ingredients were transferred through the skin by rubbing, the calculated steady flux was 0.027 and 5.7×10^{-4} mg·cm^{-2}h^{-1} for linalool and camphor, respectively. In light of these findings we suggest that after the first compression to the skin, the soft Gum karaya patch fits itself neatly to the skin's curvatures [20] which in turn enable a homogeneous and isotropic distribution of essential oil droplets and diffuse transformation.

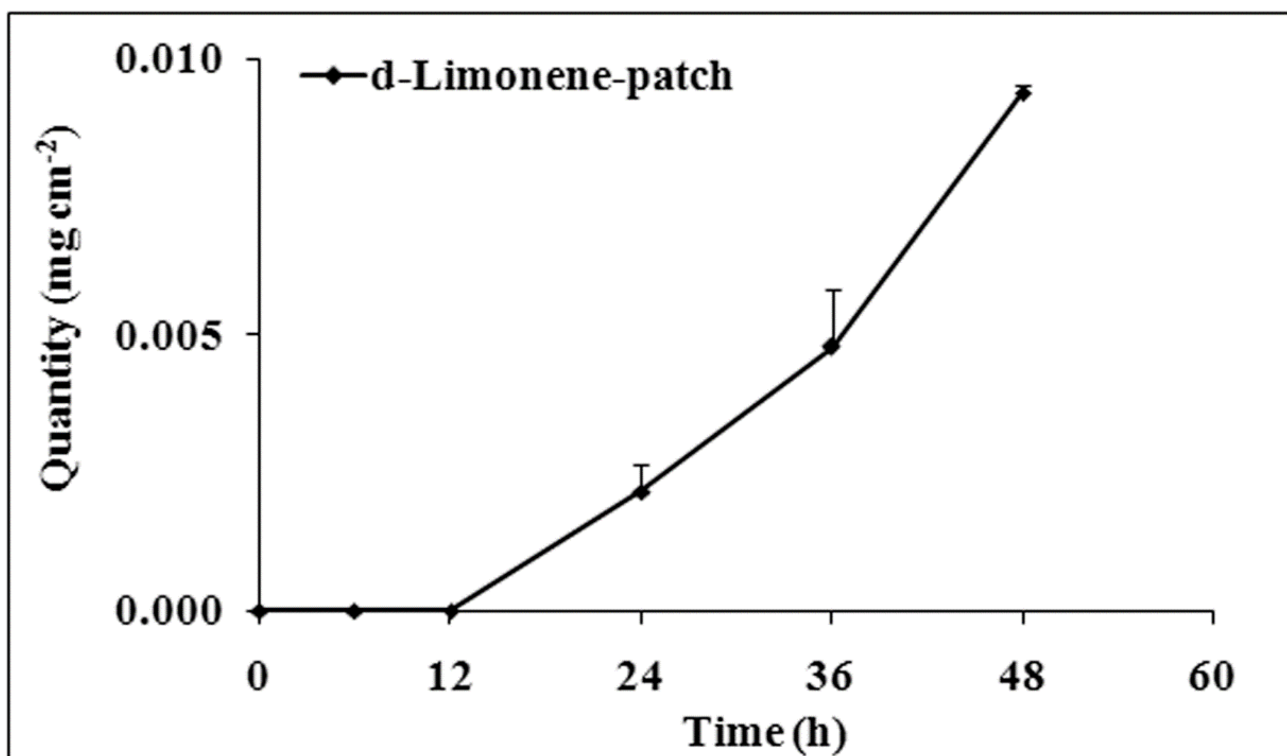

Figure 1: Transdermal delivery of essential-oil components from Gum-karaya patches through the skin, using Franz diffusion cells test. Presented is a permeation profile for d- Limonene, a representative component of Valencia orange essential oil.

Table 3 presents the accumulated concentrations of linalool, linalyl acetate and camphor, transferred through the skin after massage-like simulation. While not significant, an increased concentration was observed during the experiment. In particular, the diffused camphor amounts that accumulated in the medium were found to be higher after for 6h. Note that for massage, the coefficient of variance was very high, presumably due to uneven distribution of the essential oil on the skin. Nevertheless, rubbing with a mixture of almond and which essential oil, done in the current study, is not identical to the conventional massage procedure in which systematic heating of the skin is performed.

Elapsed time (h)	Linalool (mg L^{-1})	Linalyl acetate (mg L^{-1})	Camphor (mg L^{-1})
6	31.07 ± 36.72^a	2.30 ± 2.24^a	0.01 ± 0.03^a
12	48.34 ± 50.41^a	3.33 ± 3.23^a	0.89 ± 0.98^a
24	94.78 ± 0.19^a	5.62 ± 4.10^a	1.78 ± 0.06^a

Table 3: Accumulated concentrations of linalool, linalyl acetate and camphor diffused from rubbing a mixture of *Lavandula angustifolia* essential oil and almond oil on the skin. Results are expressed as mean ± standard error. ^{a}Different superscript letters within a column indicate a statistically significant difference at $P<0.05$.

The results depicted in Tables 2 and 3, explored the transferal ability of several essential oil constituents through the skin. The, transfer is affected by three main factors: (1) the constituent molecular weight; (2) the relative solubility in water; and (3) the logarithm of its partition coefficient (Log P) [21]. In that respect, lavender and Valencia orange essential oils have a similar molecular masse, ranged between 136 and 196 Da and both successfully penetrated the skin. On the other hand, their solubility differs, being relatively high for linalool and camphor and relatively low for linalyl acetate and limonene. Log P value between 2 and 3 is considered an optimal for transferring ingredients

with a molecular mass of ~250 Da through the skin [21]. In the current study, the Log P for linalyl acetate and limonene was ~4, while that for linalool and camphor was ~3, which associated with its higher transfer. In addition, both limonene and linalyl acetate are lipohilic materials and characterized by lower solubility in water, which enable passage through the lipophilic epidermal skin layer, but not the dermis. In contrast, linalool and camphor are moderately lipophilic and can be soluble in water, therefore able to pass through the epidermis as well as the dermis. Taken together, these features might explain the relatively good transfer and diffusion rate of the linalool and camphor in comparison to that of linalyl acetate and d-limonene.

Table 4 presents the accumulated concentrations of limonene diffused from the Gum karaya-Valencia orange essential oil patches. Limonene was not detected 12 h, but an increased concentration of 0.31 mg L^{-1} was detected after 24 h, which further accumulated and was 4.3-fold higher at 48 h of the treatment. In comparison, the calculated steady-state flux for linalool and camphor was higher relative to that calculated for the other ingredients (Tables 2 and 3). On the other hand, the limonene flux was lower relative to that calculated for linalyl acetate and camphor, which might explain in part its' low accumulation and magnitude (Table 2). Moreover, no limonene was detected in the medium when the skin was massaged with an almond-Valencia oil mixture.

Elapsed time (h)	d-Limonene (mg L^{-1})
0 to 12	0.00 ± 0.00^a
24	0.31 ± 0.07^b
36	0.68 ± 0.16^c
48	1.34 ± 0.02^d

Table 4: Accumulated concentrations of limonene diffused from gum karaya-Valencia orange essential oil patches. Results are expressed as mean ± standard error. ^{a,b}Different superscript letters within a column indicate a statistically significant difference at P<0.05.

Table 5 summarizes the proportion of linalool, linalyl acetate and camphor that were transferred through the skin during 24 h of treatment. The proportion was calculated relative to the initial amount of patch-entrapped essential oil. The lowest proportion of transfer was noted for linalyl acetate (~0.01%), and the highest for linalool (3.93%), suggesting that the entrapped essential oil is an "infinite" dose and can last for long period. In support of this assumption, less than 5% of the patch content diffused through the skin during 60 h of the experiment. These results are in line with the diffusion rates presented earlier.

Component Elapsed time (h)	Diffused linalool (%)		Diffused linalyl acetate(%)		Diffused camphor (%)	
	La patch	Ao-La mixture	La patch	Ao-La mixture	La patch	Ao-La mixture
0	0.00^a	0.00^a	0.00^a	0.00^a	0.00^a	0.00^a
6	0.73 ± 0.16^b	1.29 ± 1.53^a	0.008 ± 0.011^a	0.107 ± 0.150^a	0.70 ± 0.04^b	0.01 ± 0.01^a
12	1.53 ± 0.03^c	2.01 ± 2.09^a	0.013 ± 0.018^a	0.153 ± 0.216^a	1.02 ± 0.01^c	1.15 ± 1.26^a
24	2.74 ± 0.31^d	3.93 ± 0.01^a	0.009 ± 0.001^a	0.246 ± 0.344^a	2.10 ± 0.32^d	2.28 ± 0.08^a

Table 5: Percentages of diffused linalool, linalyl acetate and camphor vs. elapsed time from *Lavandula angustifolia* (La) essential oil patches and a mixture of almond oil-*Lavandula angustifolia* (Ao-La) essential oil rubbed into the skin. ^{a,b,c}Different superscript letters within a column indicate a statistically significant difference at P<0.05. Results are expressed as mean ± standard error.

It thus appears from the FCs experiments that terpenoids (linalool, linalyl acetate and camphor) penetrate the skin barrier better than terpene (limonene). The rate of transfer of lavender oil from the patch was similar to that transferred by massage. On the other hand, limonene, was only detected while using patch.

Experiment 2

Examining the patch location- abdominal vs back skin: The animal skin is not homogeneous in composition, roughness, topography or the amount of hair follicles per unit area. These factors might influence the patch adhesion and the transfer of essential-oil constituents through the skin. In light of these, patches containing 7.5% lavender essential oil were adhered to the back or abdomen skin of live rat. In addition, massage-like simulation was carried out using a mixture of almond and lavender oils. Note that a similar concentration inserted into in the patch was used for massage. Blood analysis was conducted by GC using the WAX column, and accumulated concentration of linalool (mg L^{-1}) was calculated for each location (i.e., back *vs.* abdomen) and for each method (i.e., patch *vs.* massage; Figure 2). For all treatments, the concentration of linalool was higher than in the control group, i.e. blank patch without lavender oil. These higher values are thought to be related to the direct transfer of linalool through the skin. Nevertheless, a concentration of 0.11 ± 0.03 mg·L^{-1} was recorded for the control (Figure 2A) most likely due decomposition of the internal standard, linalyl isovalerate. Such a reaction can occur as a result of enzyme (esterase) activity in the blood or of the blood's oxidation-reduction ability [22]. In support of this assumption, food and water consumed by the animals were examined and found to be clean of linalool (data is not shown) thus, external contamination of the samples should have ruled out.

Citation: Roth Z, Shcherbina Y, Nussinovitch A (2017) Transdermal Delivery of *Lavandula angustifolia* and Valencia Orange Essential Oils Using Gum-karaya Patches. Med Aromat Plants (Los Angles) 6: 291. doi:10.4172/2167-0412.1000291

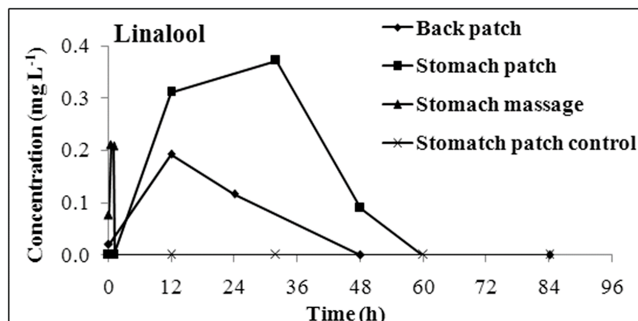

Figure 2A: *In vivo* examination of essential-oil transfer from Gum-karaya patches through the skin to the circulation. Patch with or without lavender essential oil was adhered (time =0) to the abdomen or the back skin of the animal for 60 h. Blood samples were collected from the tail tip every 12 h and analyzed by GC using a WAX column and split injection. Presented is concentration of linalool, components of lavender oil, in the blood.

A higher level of linalool was recorded in the blood samples when patches were adhered on the abdomen, relative to the back skin. Linalool in the blood was also evident after rubbing the skin with the almond-essential oil mixture, with the highest concentration (0.32 $mg \cdot L^{-1}$) 30 min after the administration started. This concentration was similar to that recorded (0.48 $mg \cdot L^{-1}$) 36 h after adhering the patch to the abdomen area. Similarly, to the levels reported here, traces of linalyl acetate and linalool have been detected in the blood of mice exposed to pure linalyl acetate via breathing [23,24]. Application of a lavender oil patch on the back or abdomen resulted in a similar level of camphor (Figure 2B). On the other hand, camphor was not detected in the blood when blank patch or rubbing with the oil mixture was performed. Higher concentration of linalyl acetate was detected in the blood when abdomen rather back-adhered patch was used. Linalyl acetate was not detected when the blank patch or massage was performed.

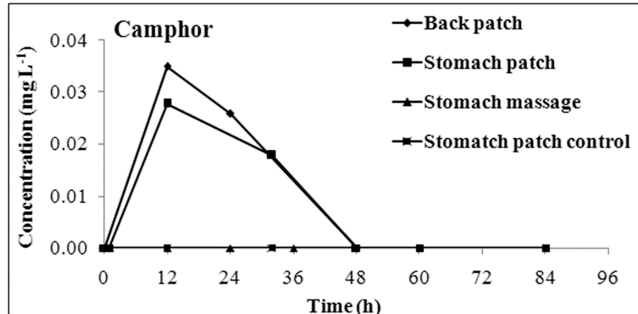

Figure 2B: *In vivo* examination of essential-oil transfer from Gum-karaya patches through the skin to the circulation. Patch with or without lavender essential oil was adhered (time =0) to the abdomen or the back skin of the animal for 60 h. Blood samples were collected from the tail tip every 12 h and analyzed by GC using a WAX column and split injection. Presented is concentration of Camphor, components of lavender oil, in the blood.

The findings of this experiment explored the therapeutic potential of using patches contained essential oil. A better transfer of lavender essential-oil components was found when patches were adhered to the abdomen skin. Thus, in in the next experiment we used abdominal rather back patches to investigate the essential-oil components transferring.

***In vivo* examination of essential-oil transfer from Gum-karaya patches through the skin to the circulation:** Patch contained lavender essential oil was adhered to the abdomen skin of the animal for 60 h. Blank patches, without entrapped oil, served as control. Blood samples were taken every 12 h and tested by GC with a WAX column combined with split injection. Figure 3 presents the concentrations of linalool, linalyl acetate and camphor in the blood. A similar pattern was observed for linalool and camphor, expressed by increased concentration between 12 and 36 h, followed by a significant decrease till 60 h. In general, camphor levels ranged between 0.020 and 0.025 $mg \cdot L^{-1}$ and that of linalool between 0.105 and 0.114 $mg \cdot L^{-1}$. In the control animals, camphor was not detected whereas a constant level of 0.11% linalool was recorded. This level is mostly related to the decomposition of the standard linalyl acetate as previously discussed. Accordingly, the linalool value found in control samples was subtracted from that recorded for the treated group. An increase in linalyl acetate concentration was recorded after 12 h, followed by a decrease during the next 24 h.

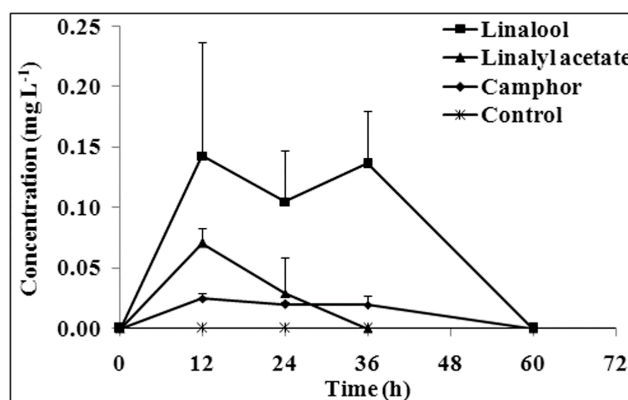

Figure 3: Transfer of lavender essential oil components from Gum-karaya patches through the skin to the circulation. Patch with or without lavender essential oil was adhered (time=0) to the abdomen skin of the animal for 60 h. Blood samples were collected from the tail tip every 12 h and analyzed by GC using WAX column combined with split injection. Presented are the concentrations of Linalool, Linalyl acetate and Camphor in the blood.

Determining terpene levels in the blood is a complicated issue due to their tendency to undergo isomerization, or decomposition in weak acidic solutions such as blood. In addition, terpenes can serve as enhancers for other terpenes and thus their level might affect the results [25]. Moreover, chemical analyses performed with WAX or HP-5 columns might yield different results. Therefore, additional study was performed, in which patches containing lavender essential oil were adhered to the abdomen area for 60 h and GC-analysis was done using HP-5 column. Detection under splitless conditions facilitated the detection of linalyl acetate, linalool and camphor, similar to that found with WAX column. However, two additional constituents, borneol and

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α-terpineol were detected with HP-5 columns. In particular, concentrations of linalool, borneol and camphor were higher relative that of terpeneol and linalyl acetate. Moreover, a significant difference was found between linalool levels relative to that of camphor and borneol 12 h of the experiment. Linalool reached its highest value (0.099 $mg{\cdot}L^{-1}$) after 24 h and then decreased significantly to 0.053 $mg.L^{-1}$ during the following 36 h. Camphor and borneol reached their highest level after 12 h (0.083 and 0.061 $mg{\cdot}L^{-1}$, respectively). Borneol level decreased during the next 12 h to the same level of camphor, which remained constant. After 60 h, both Borneol and camphor decreased to 0.035 and 0.031 $mg{\cdot}L^{-1}$, respectively. In general, α-Terpineol concentration did not significantly differ from that of linalyl acetate. α-Terpeneol level increased after 12 h to a level of 0.005 to 0.009 $mg{\cdot}L^{-1}$, where it stayed for the next 48 h. Linalyl acetate showed a similar pattern, increasing to levels of 0.006 to 0.009 $mg{\cdot}L^{-1}$ after 12 h. It is important to note however, that in contrast to the values recorded for WAX columns, no component of the essential oil fell to a value of zero after 60 h, when HP-5 columns were used (Figure 4).

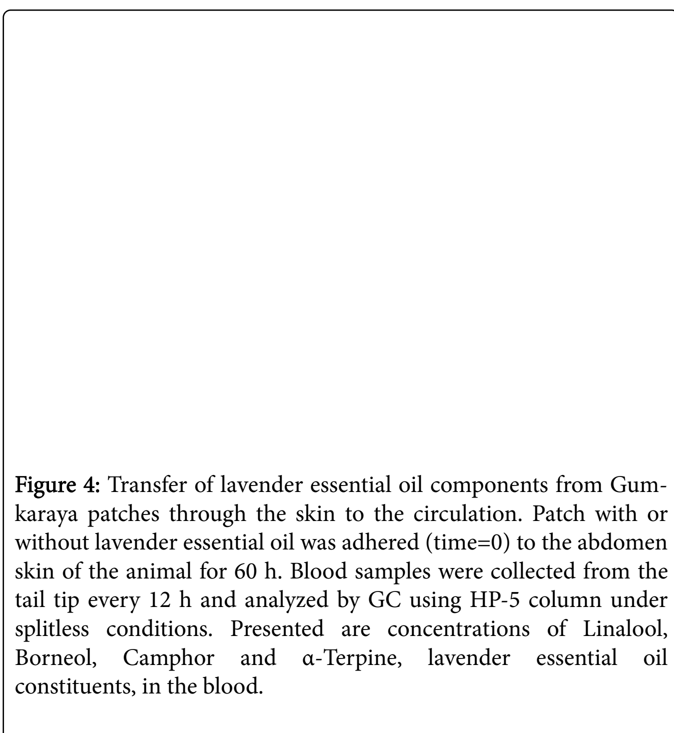

Figure 4: Transfer of lavender essential oil components from Gum-karaya patches through the skin to the circulation. Patch with or without lavender essential oil was adhered (time=0) to the abdomen skin of the animal for 60 h. Blood samples were collected from the tail tip every 12 h and analyzed by GC using HP-5 column under splitless conditions. Presented are concentrations of Linalool, Borneol, Camphor and α-Terpine, lavender essential oil constituents, in the blood.

Extraction of lavender essential oil from the skin: Skin to which patches with or without lavender essential oil were adhered and sampled for extraction. Average skin weight was ~3.1 × 10^{-4} kg and its average thickness was ~965 μm. In contrast to the findings recorded for the blood, the internal standard linalyl isovalerate did not decompose thus, lavender essential oil constituents, linalool and linalyl acetate, were not detected in the control samples. Figure 5 demonstrates the concentrations of the constituents extracted from the skin. The concentration of linalyl acetate was higher than that of linalool (0.241 $mg{\cdot}L^{-1}$ *vs.* 0.062 $mg{\cdot}L^{-1}$, respectively), expressing an opposite pattern to that recorded in the blood (0.009 $mg.L^{-1}$ *vs.* 0.099 $mg{\cdot}L^{-1}$ for linlyl acetate and linalool, respectively). In addition, other constituents of lavender essential oil, such as α-santalene, caryophyllene, β-farnesene and α-trans-bergamotene, were identified in the skin, but not in the blood.

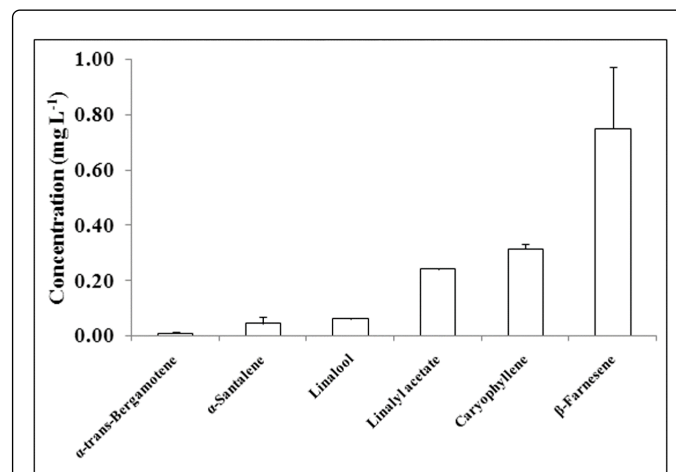

Figure 5: Extraction of lavender essential oil from the skin. Skin pieces, to which patches were adhered, were sampled at the end of the experiment (60 h), extracted and analyzed by GC using HP-5 column under splitless conditions. Presented are concentrations of lavender essential oil constituents extracted from the skin.

Summary

The findings of the current study shade light on the mechanism underlying the delivery of essential-oil components, from either patches or by massaging, through the skin to the circulation. Based on findings two different approaches (i.e., FCs and *in-vivo* models) we suggest that a specific essential oil should be consider as a mixture of ingredients rather one component; some of which penetrate the skin while other not. In addition, the penetration of essential oil components is multifactorial in nature. Factors include: molecular weight, solubility, partition coefficient log, skin temperature, energy invested during skin massaging, and other parameters associated with the patch such as adhesion to the skin, topography and physical or chemical properties. Moreover, the essential oil ingredients may remain in the patch, or alternatively be accumulated in the skin and will not further penetrate the skin thus, will not reach to the blood. In that respect, it should be noted that in contrast to the SPME method used for the blood analysis the extracted solution collected from FCs medium was injected directly into the GC.

Taking together the current findings extended the understanding on the passage pattern of essential oil through the skin. A suggested mechanism is presented in Figure 6. Moreover, the findings explore the potential of using Gum-karaya patches of essential-oil for practical and commercial use.

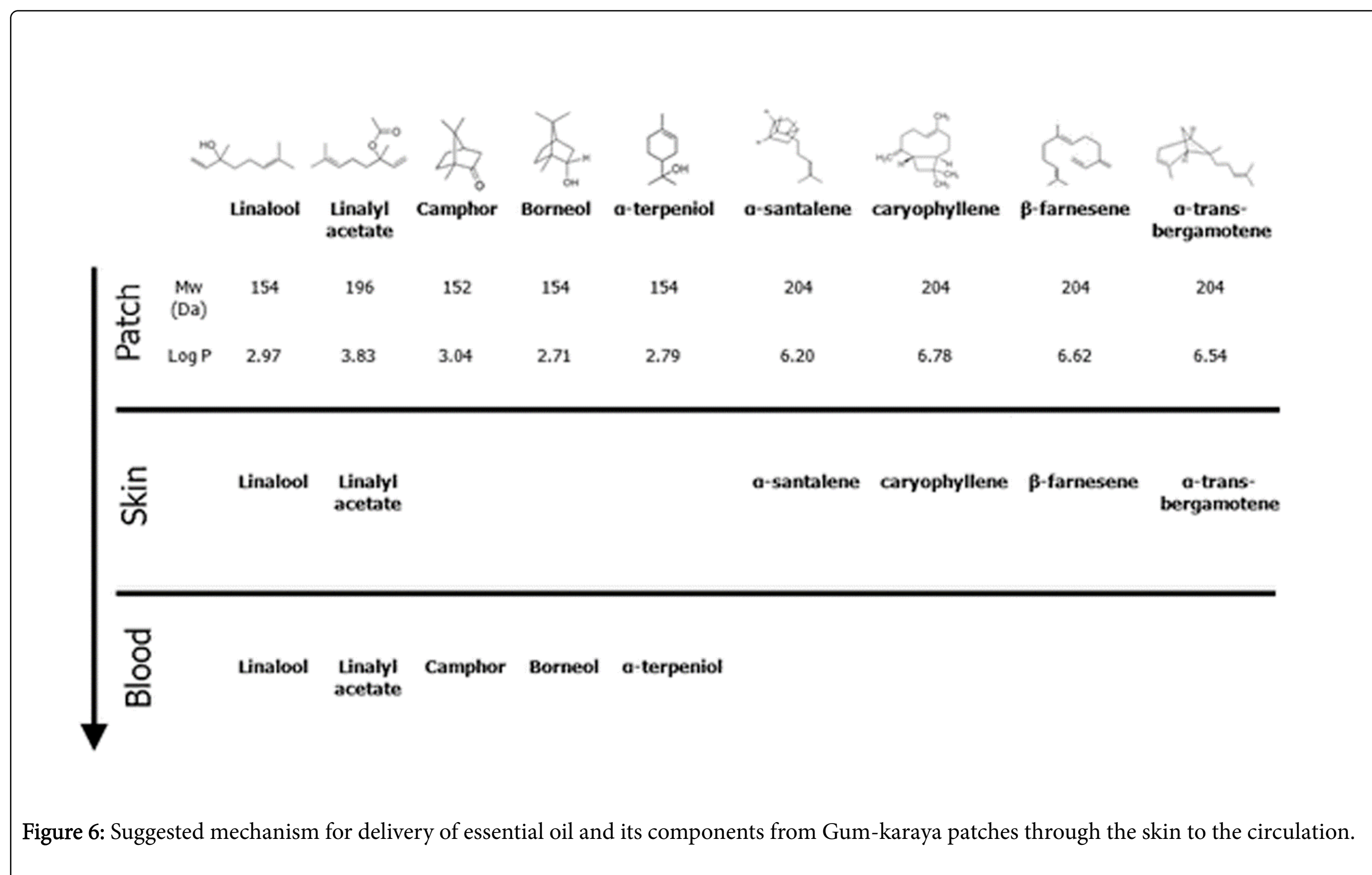

Figure 6: Suggested mechanism for delivery of essential oil and its components from Gum-karaya patches through the skin to the circulation.

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