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RESEARCH ARTICLE

Nanoemulsion of Dill essential oil as a green and potent larvicide against *Anopheles stephensi*

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Abstract

Indiscriminate use of industrial larvicides causes environment pollution and resistance against the larvicides in mosquitoes. Essential oils (EOs) have many biological activities such as larvicidal effects which have been proposed as new alternatives for industrial ones. Many components of EOs are volatile, thus, should be formulated to retain their activity. Components of Dill EO were identified by GC-MS analysis. Larvicidal activity (LA) of bulk Dill EO (non-formulated) was evaluated against *Anopheles stephensi* in line with WHO guideline for lab tests. For the first time, nanoemulsions of Dill EO were prepared. Various nanoemulsions having fixed amounts of Dill EO 1.2%, comparable with lethal concentration (LC) at 90% of bulk Dill EO, were prepared having tween 20 (5–30%) with/out ethanol (5–30%). LA of two selected nanoemulsions were then evaluated and compared with that of bulk Dill EO. Five ingredients of oil, with high amounts, were identified as p-Cymenealpha (20.81%), alpha-Phellandrene (20.75%), Carvone (10.97%), Dill ether (9.88%), and cis-Sabinol (3.61%). LC of Dill EO at 50 and 90% were found as 38.8 and 65 ppm, respectively, against 3rd and 4th instar larvae of *An. stephensi* (Beech-Lab strain). Particle size (PS) ranges of nanoemulsions were 10.7–1880.0 nm. LA of optimum nanoemulsion (PS: 10.7 nm) was significantly better than that of bulk Dill EO. The preparation showed stability against 200 times dilution during larvicidal tests and performed significantly better than the nanoemulsion which was not stable after dilution. To obtain improved efficiency against larvae using nanoemulsions of EOs, the nanoemulsion should be resistant against dilution. Such a stable and green nanoemulsion may be used as alternative to industrial larvicides.

Keywords Essential oil · Dill · *Anethum graveolens* · Nanoemulsion · Spontaneous method · Larvicidal activity · *Anopheles stephensi*

Introduction

According to a report by WHO, just in 2015, 212 million of new cases of malaria were identified, with 429,000 death caused by the disease around the world (WHO 2016). *Anopheles stephensi* is major vector of spreading malaria, especially in Eastern Mediterranean and South-East Asia regions of WHO (Maheswaran and Ignacimuthu 2015; WHO 2016).

Continuous of applying chemical larvicides for control of mosquito-borne diseases, such as malaria, has led to occurring resistance against the mosquitoes, especially in *An. stephensi*. Environment pollution is a second outcome of this constant use (Poopathi et al. 2002; Soltani et al. 2015; Vatandoost and Hanafi-Bojd 2005; Vatandoost et al. 2005). EOs are naturally extracted aroma compounds, with wide applications such as flavoring additives, medicines, antioxidants, antifungals/bacterials, and larvicides. During the past decade, EO-based larvicides are proposed as suitable alternatives for industrial ones (Donsì and Ferrari 2016; Govindarajan et al. 2017; Keyal et al. 2016; Langeveld et al. 2014; Oliveira Fde et al. 2014; Osanloo et al. 2017b; Pavela 2015).

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To retain their biological activity, vaporization of volatile components of EOs should be prevented; thus, EOs need to be formulated (Bakkali et al. 2008; Buranasuksombat et al. 2011; Osanloo et al. 2017a). Nanoemulsions are fine oil-in-water dispersions, having droplet in the size of < 200 nm, with increased bioactivity, due to subcellular size and better diffusion (Donsì et al. 2012; Esmaeili et al. 2016; Khani et al. 2016; Mishra et al. 2017). From the literature, nanoemulsions of some EOs such as rosemary, eucalyptus, basil, and copaiba have been prepared as larvicides (da Rodrigues et al. 2014; Duarte et al. 2015; Ghosh et al. 2013; Sugumar et al. 2014). In our previous report, by preparation of nanoemulsion of Tarragon EO with PS of ~15 nm, LA significantly improved at 18 ppm, i.e., 83% < 92%, against *An. stephensi* (Osanloo et al. 2017a). In another study, nanoemulsions of Neem EO were prepared with different sizes (i.e., 31, 93, and 251 nm) and showed maximum LA when PS was 31 nm, against *Culex quinquefasciatus* (Anjali et al. 2012).

Anethum graveolens (Umbelliferae family), known as Dill, is a widespread plant which is used in foods and pharmaceuticals as an antibacterial, anti-inflammatory, and antifungal agent (Chen et al. 2014; Kumar et al. 2017; Ma et al. 2015; Orhan et al. 2013; Snuossi et al. 2016). EO of Dill has also shown LA against some larvae specious: LC at 50 and 90% against *Aedes aegypti* has been reported as 20.2 and 34.7 μg/mL, respectively (Promsiri et al. 2006). In another report, Dill EO at concentration of 0.1 mg/mL had 90% mortality against *Aedes albopictus* (Seo et al. 2015).

In this study, nanoemulsion was prepared using spontaneous emulsification, which is a mild procedure for preparing nanoemulsions from different oils, including EOs. This method uses optimized amounts of oil, surfactant, and water, and no mechanical force such as homogenizer or ultrasound is employed as they can lead to evaporation of volatile components (Bouchemal et al. 2004; Osanloo et al. 2017a). For the first time, nanoemulsion of Dill EO was prepared and optimized, then, its LA against 3rd and 4th instar larvae of *An. stephensi* (Beech-Lab strain) was compared with its bulk form.

Materials and methods

Materials

Dill EO was purchased from Barij Essence Pharmaceutical Company, (Iran). Tween 20 and ethanol were obtained from Merck chemicals (Germany). Third and fourth instar larvae of *An. stephensi* (Beech-Lab strain) were used in this research, obtained from the Department of Medical Entomology, Tehran University of Medical Sciences. This strain has been maintained in the laboratory without exposure to insecticides for 30 years.

Determining ingredients of EO of dill by GC-MS analysis

The GC-MS Analyses were performed using a 6890 GC system coupled with 5973 network mass selective detector (Agilent Technologies, USA). Separation of the EO components was carried out on an HP-5MS silica fused columns (30-m length, 0.25-mm internal diameter, and 0.25-μM film thickness 5% phenyl-methylpolysiloxane). The GC-MS column temperature was programmed as follows: initial temperature was set at 40 °C and fixed for 1 min, then, increased with rate of 3 °C/min to final temperature of 250 °C and hold for 60 min. Temperature of injection port and detector was fixed at 250 and 230 °C, respectively. Other instrument parameters were set as split flow 25 mL/min, septum purge 6 mL/min, and column flow rate 1 mL/min. Helium gas with purity of 99.99% was used as carrier gas. Mass spectra were taken at full scan mode and 70 eV ionization energy with scanned mass range at 50–350 m/z.

Determination of components of EO was performed by comparing their retention indices (RIs) determined with reference to a homologous series of C9–C24 n-alkanes. Firstly, this was confirmed by chromatographic injection of available analytical standard compounds (C9–C24 n-alkanes) and comparison of their retention times with those obtained for the EO. If standard compounds were not available, the identification was carried out by comparison with traditional retention indices. The identification was also confirmed by comparison of their mass spectra with those stored in the Wiley7n.l MS computer library. The linear temperature-programmed retention indices (RIs) of all the constituents were calculated from the gas chromatogram by interpolation between bracketing n-alkanes (Eq. (1).

$$RI = 100\left[\frac{tR(i)-tR(z)}{tR(z+1)-tR(z)} + z\right] \quad (1)$$

where z is the number of carbon atoms in the smaller n-alkane, and tR(i), tR(z), and t are the retention times of the desired compound, the smaller n-alkane and the larger n-alkane, respectively. In addition, the search match factor (SMF), rank number (RN) in the mass library, and five highest peaks in the mass spectra were prepared and used for identification of the components.

Evaluation of LA

LA of EO was evaluated according to recommended method by WHO, with some modification, against *An. stephensi* (WHO 2005). In brief, solutions (1:200) of different concentrations of bulk Dill EO (EO dissolved in ethanol) or nanoformulations were prepared in containers having no chlorine water. Subsequent to homogenizing them with specific rubber probe, batches of 25 larvae of *An. stephensi* were added

to all containers. After 24 h of exposure, counted dead larvae as well as LC at 50 and 90% were calculated using probit analysis and SPSS software (v22). Tests were repeated 12 times in 3 different replicates in recommended conditions, (25–28 °C and 12 h L: 12 h D photoperiod). For increasing accuracy, the tests were discarded if mortality in control groups (ethanol only added) increased from 5%.

Preparation of nanoemulsions

Many components of Dill EO are volatile; thus, spontaneous method (without using mechanical force) was used for preparation of nanoemulsions. Different amounts of tween 20 (5–30%) with/out ethanol (up to 30%) were mixed by Dill EO (fixed at 1.2%, comparable with calculated LC90%) at

Table 1 Components of Dill essential oil, identified by GC-MS analysis

No	Retention time	Compound	Peak area	%	Retention indices
1	1.441	trans-1,2-Dimethylcyclopropane	11,988,551	0.073	
2	4.923	Heptanal	2,429,513	0.015	
3	6.721	alpha-Thujene	63,233,481	0.383	
4	6.974	alpha-Pinene	324,042,472	1.961	
5	7/421	Comphene	16,357,158	0.099	
6	8.378	Sabinene	110,540,500	0.669	
7	8.88	beta-Myrcene	124,936,564	0.756	601
8	9.727	alpha-Phellandrene	3,428,300,398	20.750	634
9	10.797	p-Cymene	3,438,724,094	20.813	676
10	11.408	beta-Ocimene Y	9,183,810	0.056	700
11	11.771	gamma.-Terpinene	20,875,070	0.126	709
12	12.914	alpha-Terpinolene	88,228,681	0.534	738
13	12.967	Dehydro-p-cymene	47,647,621	0.288	739
14	13.266	Undecane	8,983,283	0.054	747
15	13.896	1-Octen-3-ol, acetate	7,983,100	0.048	762
16	14.45	Delta-3-carene	40,900,376	0.248	776
17	14.81	cis-Limonene oxide	16,022,677	0.097	785
18	15.641	Prehnitene	285,953,663	1.731	805
19	16.649	Borneol	149,698,276	0.906	825
20	17.377	Dill ether	1,632,901,980	9.883	840
21	17.821	cis-Dehydrocarvone	237,664,989	1.438	849
22	18.205	cis-Sabinol	596,248,843	3.609	857
23	19.57	Pulegone	204,614,290	1.238	884
24	20.25	Carvone	1,811,790,818	10.966	898
25	20.503	Propellane	442,769,878	2.680	903
26	26.122	Piperitenone	162,499,567	0.984	1008
27	26.847	Prehnitene	249,036,502	1.507	1022
28	27.038	1,3-Adamantanediol	263,052,370	1.592	1026
29	27.608	1(2H)-Naphthalenone, octahydro-8a-hydroxy	413,770,289	2.504	1037
30	28.128	2-Cyclohexen-1-one, 4-hydroxy-3-methyl-6-(1-methylethyl)-, trans	135,622,795	0.821	1047
31	28.836	Prehnitole	200,209,411	1.212	1060
32	35.184	Dillapiole	47,735,255	0.289	1185
33	35.733	delta-Cadinene	43,956,811	0.266	1196
34	38.029	Octanoic acid, 3-methylbutyl ester	10,344,837	0.063	1242
35	40.804	2-(3′-Methylphenylidene)biphenyl	19,392,530	0.117	1298
36	42.485	Allylchlorodimethylsilane	129,889,941	0.786	1332
37	43.974	8-Acetyl-7-hydroxy-2,2-dimethyl-4-chromanone	92,233,205	0.558	1372
38	46.046	Methyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate	52,895,998	0.320	1421
39	48.814	Hexadecanoic acid	47,761,250	0.289	1485

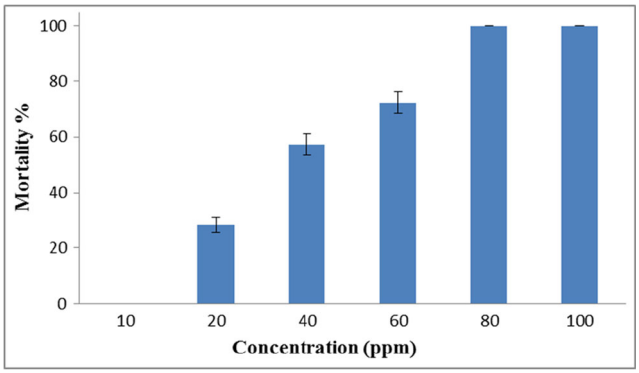


Fig. 1 Evaluation of larvicidal activity of bulk Dill EO against *An. stephensi*

600 rpm and room temperature. Then, deionized water was added gradually up to 5 mL and stirred for 15 min, for preparation of nanoemulsions.

Analyzing PS of nanoemulsions

PS and PSD (particle size distribution) of prepared nanoemulsions were determined using DLS (dynamic light scattering, scatteroscope, K-ONE.LTD, Korea) and confirmed by TEM (transition electron microscopy, LEO 906E, Zeiss, Germany). PSD was calculated using Eq. 2.

$$\mathrm{PSD} = \sqrt{d(75\%)/d(25\%)} \quad (2)$$

d median diameter of particles (percent of cumulative).

For evaluation of physical stability, optimum formulation (F9) was ultra-centrifuged in 25,000 rpm at specific temperatures (i.e., 4 °C and room temperature). In another test, the nanoformulation was stored at mentioned temperatures for 30 days, then, visually checked for any creaming, precipitation, or phase inversion.

Comparison of larvicidal activity of Dill EO vs. selected nanoemulsions

Nanoemulsions with PS < 20 nm and PSD < 2 were selected (i.e., F2 and F9) and their LA was compared with similar concentration of bulk Dill EO (1.2% dissolved in ethanol). By adding 1 mL from each sample to test containers, concentration of oil was eventually fixed at 60 ppm. Two control groups were also considered: nanoformulations without Dill EO (i.e., micelles of tween) and ethanol only. For comparing the LA of nanoemulsions with bulk Dill EO, SPSS software and ANOVA with 95% confidence intervals were used.

Results and discussion

Determining ingredients of Dill by GC-MS analysis

In total, 39 components for the EO were identified by GC-MS analysis (see Table 1). Five ingredients with high amounts were detected: p-Cymenealpha (20.81%), alpha-Phellandrene (20.75%), Carvone (10.97%), Dill ether (9.88%), and cis-Sabinol (3.61%).

Evaluation of LA of Dill EO

Results of LA of bulk Dill EO at different concentrations (10–100 ppm) against *An. stephensi* are demonstrated in Fig. 1. LA appeared from 20 ppm and increased by arising concentration of EO. Calculated LC50 (38.8 ppm) and LC90 (65.0 ppm) and probit equation are given in Table 2.

In the literature, LA of many EOs against *An. stephensi* can be found. For instance, LC50 of EOs of *Citrus aurantium*, *Citrus paradise*, and *Nigella sativa* are reported as 31.20, 35.71, and 53.9 ppm, respectively (Raj et al. 2015; Sedaghat et al. 2016).

Repellency activity of Dill EO against different specious of mosquitoes (such as *Ae. aegypti*, *An. stephensi*, and *Cx. quinquefasciatus*) has been evaluated (Amer and Mehlhorn 2006b). LA of 41 herbal EOs, including Dill EO, has been reported against *Ae. aegypti*, *An. stephensi*, *and Cx. quinquefasciatus*, with LC50 of ~100 ppm against *An. stephensi* (Amer and Mehlhorn 2006a). However, we could not find a comprehensive

Table 2 Results of probit analysis for larvicidal activity of Dill EO against *An. stephensi*

EO name	Probit equation	LC50 (ppm)	LC90 (ppm)	Chi-square (df)[4]	Sig
Dill	$Y^{1} = 0.049X^{2} - 1.901$	38.8 (21.1–57.9)[3]	65.00 (49.4–126.3)[3]	74.817 (3)	0.150 > sig[5]

[1] Mortality

[2] Concentration of Dill

[3] Confidence interval 95%,

[4] Degree of freedom

[5] Since the significance level is less than 0.150, a heterogeneity factor is used in the calculation of confidence limits.

Table 3 Components ratio of prepared nanoemulsions of Dill essential oil (EO was fixed at 1.2%, distilled water was added to all the samples up to desired volume of 5 mL)

Formulation	Particle size (nm)		
	Tw (Eth) %	PS	PSD
F1	5	211 ± 9	1.9
F2	5 (5)	17.1 ± 4	1.4
F3	10	213 ± 10	1.3
F4	10 (10)	18.8 ± 5	8.2
F5	15	668 ± 21	1.3
F6	15 (15)	15.9 ± 4	6.1
F7	20	1880 ± 56	1.3
F8	20 (20)	18.6 ± 3	8.1
F9	25	10.7 ± 3	1.4
F10	25 (25)	15.6 ± 8	5.8
F11	30	10.8 ± 5	2.4
F12	30 (30)	19.5 ± 9	7.2

Tw Tween 20, *Eth* ethanol, *PS* particle size, *PSD* particle size distribution

report showing LC50 and LC90 and concentration with perfect effect of Dill EO against *An. stephensi*.

Vatandoost et al. (Vatandoost et al. 2012) classified EOs into 5 groups according to larvicidal properties. LA of bulk Dill EO lies in active group of this classification, thus, has merits for further investments, such as preparing its nanoformulation.

Preparation of nanoemulsion of Dill EO

Based on the LA studies of Dill EO, developing a nanoformulation from Dill EO has the potential to improve its efficacy, without observing environmental pollution. Components ratio and size of various prepared nanoemulsions of Dill EO are depicted in Table 3. PS and PSD ranged 10.7–1880 nm and 1.3–8.2, respectively. By increasing concentration of tween (without ethanol) from 5 to 20%, PS increased (i.e., 211–1880 nm, see samples F1, F3, F5, and F7). However, by further increasing the concentration of tween to 30% (i.e., samples F9 and F11), PS decreased. Interestingly, at 30% tween concentration, PSD increased which is probably due to formation of micelles without oil in core of the particles. Above 30% tween concentration, a gel-like preparation was prepared (i.e., very high viscosity), thus, preparing nanoemulsions with higher concentrations of tween was not performed.

Ethanol as co-surfactant helps improved dispersion of tween and oil; thus, by adding ethanol to the formulations, PS suddenly decreased (e.g., PS of F1 (211 nm), decreased to 17.1 nm (i.e., F2)). A balance between ingredients is necessary for obtaining smallest PS and PSD values in nanoemulsions. In previous researches, nanoemulsion with smaller size showed better larvicidal activity (Anjali et al. 2012; Osanloo et al. 2017a). Also, smaller PSD values are often preferred to improve physical stability (Esmaeilzadeh-Gharehdaghi et al. 2014; Sattler 2010), performance (Akbarzadeh et al. 2012; Cui et al. 2009), and loading capacity

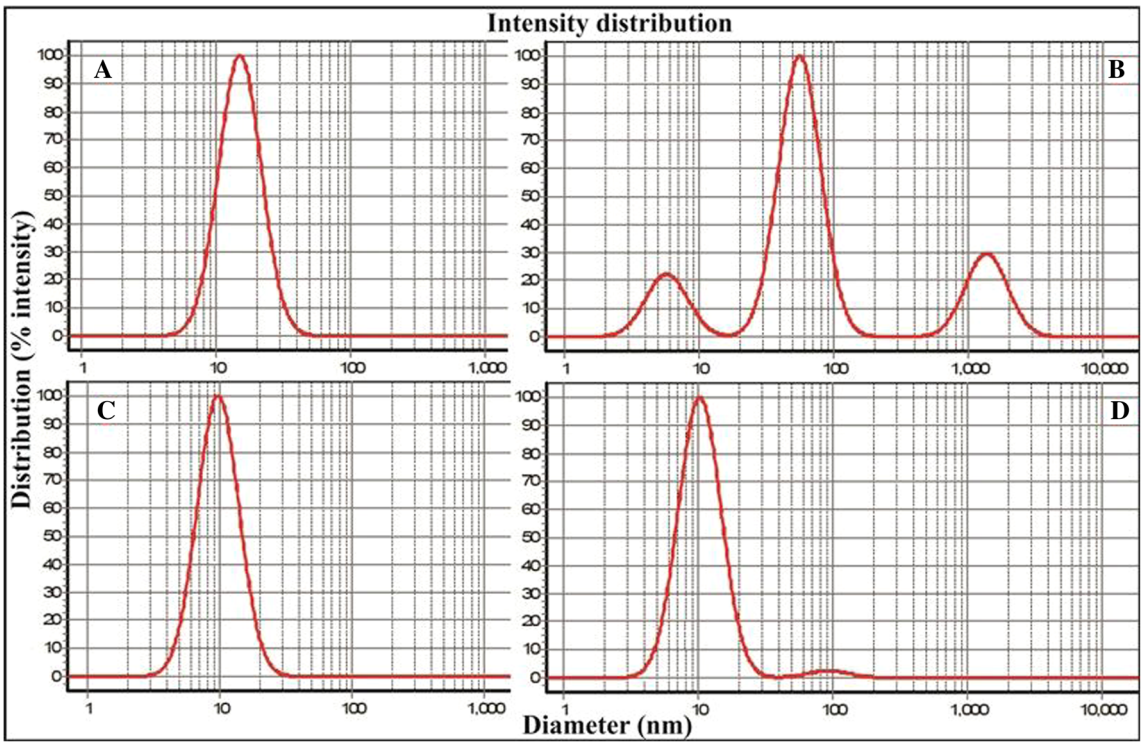


Fig. 2 **a** F2 formulation before dilution. **b** F2 formulation after dilution. **c** F9 formulation before dilution. **d** F9 formulation after dilution

(Sinko 2006). Thus, in this study, nanoemulsions with smallest PS (i.e., < 20 nm) and PSD (i.e. < 2) were selected for investigation of their larvicidal activity (i.e., F2 and F9).

Comparison of LA of bulk Dill vs. selected nanoemulsions

DLS results of undiluted form of the selected nanoemulsions (i.e., F2 and F9) are illustrated in Fig. 2a, c . The results after 200 folding dilution during LA tests are also depicted in Fig. 2b, d). PS of F2 and F9 after dilution were 57.7 and 12.8 nm, respectively, with PSD of 4.3 and 2.4, respectively. As the details show, F2 appears to be substantially influenced by dilution, while negligible changes are observed in F9 after dilution.

Comparison between LA of Dill EO and the two selected nanoemulsions (F2 and F9) are depicted in Fig. 3. Samples without oil had no larvicidal effect (data not shown). LA of F9 was significantly better than the other two samples while no significant difference was observed between bulk Dill EO and F2.

This is for the first time that a nanoemulsion of Dill EO is reported and its LA is compared with its bulk form against one of the main malaria vectors, *An. stephensi*. Interestingly, LA of nanoemulsion which suffered negligible changes in structure after dilution (F9) showed significantly better LA compared with the other nanoemulsion (F2) with mortality %: 88.1 vs. 73.4. It is arguable that after dilution, by breaking nanostructure of F2, practically, no difference may be determined between F2 and bulk EO. Thus, similar LA is expected for F2 and bulk EO (see Figs. 2 and 3). However, in the case of F9, small size of the nanoemulsion (even after dilution) has caused a significant improvement in the efficacy. We believe this is the reason for the fact that in the literature only LA of nanoemulsions of EOs has been reported, and no comparison has been made between LA of nanoemulsions with that of bulk essential oil (da Rodrigues et al. 2014; Duarte et al. 2015; Oliveira et al. 2016). In other words, to prove the superior efficacy of nanoemulsions as larvicides, the effect of dilution on structure of nanoemulsion should be considered: a fact that appears to be neglected.

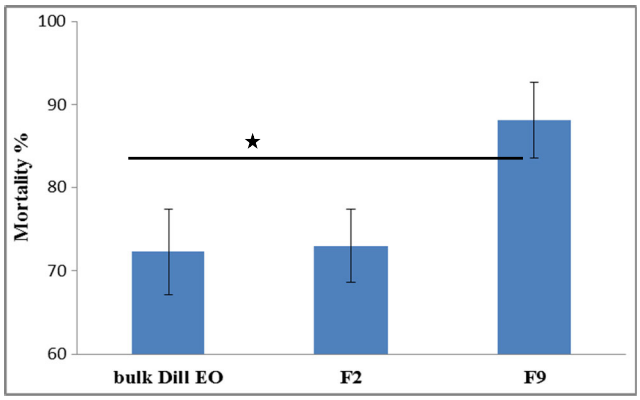
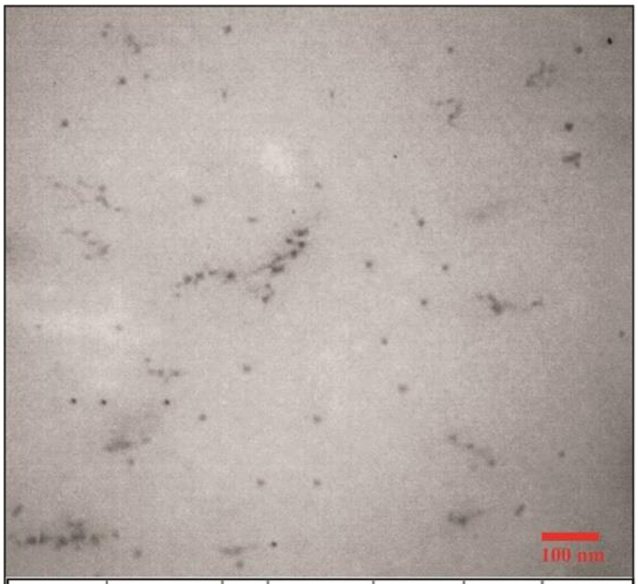


Fig. 3 Comparison of larvicidal activity of bulk Dill EO vs. its nanoemulsions (F2: unstable nanoemulsions after 200 times dilution during larvicide test, F9: stable nanoemulsion)



Tool	Measure	n	Mean	SD	Min	Max
Length	Length	50	11.1	1.2	8.3	13.7

Fig. 4 TEM image of undiluted form of F9 formulation

Characterization of selected nanoemulsion

Considering LA results, F9 was chosen as the optimum formulation. For investigation of its physical stability, the sample was stored at 4 °C and room temperature, for 30 days. No creaming or phase separation occurred, even after centrifugation at 25000 rpm. These results suggest proper stability for the preparation. TEM image of undiluted form of F9 is illustrated in Fig. 4. Its particles appear to be spherical with PS of ~11.1 nm.

Conclusion

To obtain a nanoemulsion from essential oils with proper LA, concentration of the ingredients should be optimized to maintain structural stability of the nanoemulsion after 200-times dilution. Such a nanoemulsion is expected to show higher LA compared with bulk essential oil. This formulation can be suggested as low-cost, environment friendly larvicide, with activity comparable to industrial larvicides. The optimum formulation obtained in our work (i.e., F9) was a preparation with appropriate activity against larvae of *An. stephensi* with no minimum environmental effect.

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