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# Efficient surface functionalization of wound dressings by a phytoactive nanocoating refractory to *Candida albicans* biofilm development

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**Abstract**

The present study reports the fabrication and characterization of a novel nanostructured phyto-bioactive coated rayon/polyester wound dressing (WD) surface refractory to *Candida albicans* adhesion, colonization and biofilm formation, based on functionalized magnetite nanoparticles and *Anethum graveolens* (AG) and *Salvia officinalis* (SO) essential oils (EOs). TEM, XRD, TGA, FT-IR were used for the characterization of the fabricated nanobiocoated WDs. Using magnetic nanoparticles for the stabilization and controlled release of EOs, the activity of natural volatile compounds is significantly enhanced and their effect is stable during time. For this reason the nanobiocoated surfaces exhibited a longer term anti-biofilm effect, maintained for at least 72 h. Besides their excellent anti- adherence properties, the proposed solutions exhibit the advantage of using vegetal natural compounds, which are less toxic and easily biodegradable in comparison with synthetic antifungal drugs, representing thus promising approaches for the development of successful ways to control and prevent fungal biofilms associated infections.

**Keywords:** Biocompatible surfaces, Phytoactive nanosystems, Anti-biofilm strategy

## Background

Surgical associated wound infections (SAWIs) are affecting tissues, organs or spaces, exposed to microbial contamination especially during performance of an invasive procedure. The development of SAWIs is related to four factors: the degree of microbial contamination of the wound during surgery, the duration of the procedure, the host factors, such as chronic diseases and immunologic status [1], and post-operatory wound care.

SAWIs are associated with considerable morbidity and occasional lethality, as well as with substantial healthcare costs and patient inconvenience and dissatisfaction [2]. For these reasons surgeons strive to avoid SAWIs by the use of mechanical, chemical and antimicrobial approaches, or by a combination of these methods. Fungi cause nosocomial infections in surgical patients as a part of polymicrobial infections or fungemia, which could be responsible of aggressive soft tissue infections [1]. Even though the most prevalent microbes involved in SAWIs are bacterial opportunistic pathogens, about 15% of wound infections are produced by *Candida albicans* alone [3], and this percent is continuously growing. *C. albicans* are the most common fungi frequently associated with biofilm-related infections. The most important feature of biofilm growth is the high resistance to antimicrobial agents that can be up to 1000-fold greater than that of planktonic cells [4]. Antifungal drug resistance is a prominent feature, especially in the management of invasive mycoses [5].

Due to the significant increase of actual antifungal drug resistance, new alternative strategies for combating fungal infections are needed. Natural compounds, such as vegetal extracts and (EOs) have proved spectacular antimicrobial traits against different strains, including fungal pathogens [6, 7]. Besides their antimicrobial efficiency, the risk to develop side effects or resistance features to vegetal extracts is very low. However, a real challenge for essential oil applications in the biomedical field is limiting their high volatility and therefore, improving stability [8].

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Magnetite nanoparticles (MNPs) are widely studied for their potential applications in biology and medicine, such as magnetic resonance imaging [9, 10], drug targeting [11, 12], drug delivery [13], stabilization of EOs and inhibition of microbial biofilm development [14], improved surfaces with anti-adherent properties [15], hyperthermia [16] or cancer treatment [17]. Functionalized magnetite particles (FMNPs) are being used in an increasing number of biomedical applications [18, 19], offering chemical groups designed to permit the specific attachment of drugs and to improve their biocompatibility

Recently, a 5 nm average diameter core/shell nanosystem exposing to the surface *Mentha piperita* EO molecules was reported to exhibit anti-adherent and anti-biofilm properties [20].

The combination of the stabilizing carrier properties of MNPs with the antimicrobial features of natural phytocompounds could represent a successful approach for the development of novel materials and surfaces, refractory to microbial biofilms development. Recent studies revealed that WDs nanocoating could prevent wound microbial contamination and subsequent biofilm development on viable tissues or implanted devices [21]. For example, nanobiocoatings based on MNPs and major fractions extracted from EOs (i.e. eugenol and limonene) have improved the resistance of WDs to staphylococcal and pseudomonal colonization.

The aim of this study was to obtain and evaluate a novel nanostructured, biocompatible, phytoactive WD surface, refractory to fungal colonization and biofilm development, with potential application for wound care.

## Methods

### Materials

All chemicals were used as received. $FeCl_3$, $FeSO_4 \cdot 7H_2O$, $NH_4OH$ (25%), and $CH_3OH$ were purchased from Sigma-Aldrich ChemieGmbh (Munich, Germany). General-use 10 × 10 mm rayon/polyester based wound dressings were provided from Doctor Anghel's Medical Center.

### Synthesis of FMNPs

Magnetite was prepared by wet chemical precipitation from aqueous iron salt solutions by means of alkaline media [22-24]. Briefly, 500 mg of palmitic acid ($C_{16}$) and 8 mL of $NH_4OH$ (25%) were added in 200 mL deionized water under vigorous stirring. Then, 0.65 g of $FeCl_3$ and 1 g of $FeSO_4 \cdot 7H_2O$ were dissolved in 400 mL of deionized water and $Fe^{+3}/Fe^{2+}$ solution was dropped into the basic solution of $C_{16}$. After precipitation, functionalized magnetite crystals were repeatedly washed with methanol, separated with a strong NdFeB permanent magnet. In the same way there were prepared MNPs ($Fe_3O_4$ without organic shell $C_{16}$), used as control. The major difference between FMNPs ($Fe_3O_4$@$C_{16}$) and MNPs ($Fe_3O_4$) is that FMNPs ($Fe_3O_4$ coated with organic shell $C_{16}$) are soluble, while MNPs ($Fe_3O_4$ without any coating agent) are insoluble in chloroform.

### Extraction of EOs

EOs were extracted from *Anethum graveolens* (AG) and *Salvia officinalis* (SO) dried plants by microwave assisted extraction, using a Neo-Clevenger type apparatus. The extraction was performed for 30 minutes and the chemical composition of the EOs was settled by GC-MS analysis according to our previously published protocols [25, 26].

### Fabrication of FMNP-SO and FMNP-AG

FMNPs (100 mg) were solubilized in 2 mL of $CHCl_3$ and oriented in magnetic field and 100 μL of AG and respectively, SO were added and mixed until complete evaporation of chloroform. This step was repeated three times for the uniform loading of AG and SO in the MNPs. After 72 h the as prepared FMNPs-SO and FMNPs-AG were analyzed by TGA to estimate the amount of essential oils entrapped into the FMNPs.

### Fabrication of phytoactive nanobiocoated wound dressings

After 72 h of drying at room temperature, FMNPs-EO were solubilized with chloroform by a ratio FMNPs-EO:$CHCl_3$ = 1 mg/mL. Sterile WD pieces (10 × 10 mm) were introduced in FMNPs-AG or FMNPs-SO for achieving the nanophytoactive layer. Coated WD pieces have been extemporaneously dried at room temperature. The rapid drying was facilitated by the convenient volatility of chloroform [27].

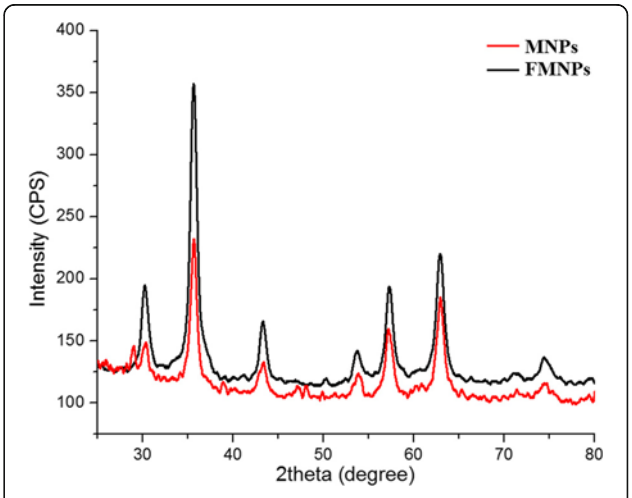


**Figure 1** XRD patterns of MNPs and FMNPs.

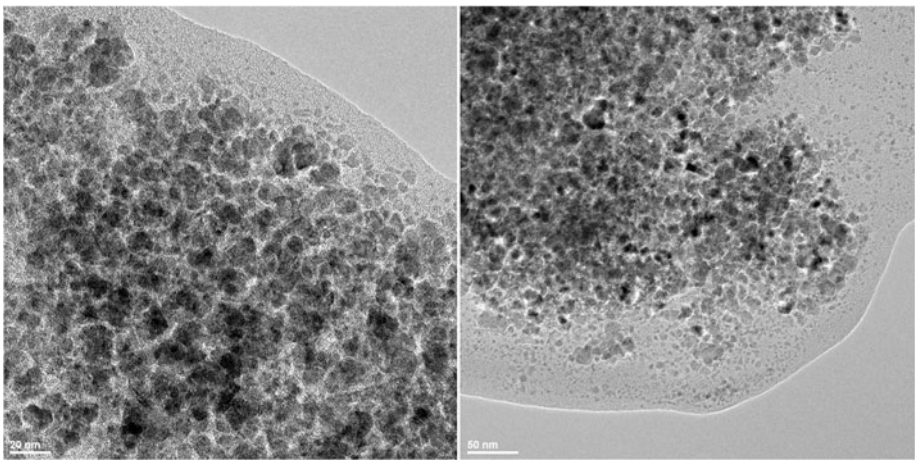


**Figure 2** TEM images of FMNPs.

The WD@FMNPs-AG and WD@FMNPs-SO specimens were sterilized by ultraviolet irradiation for 20 min.

## Characterization

### *TEM*

The transmission electron microscopy (TEM) images were obtained on finely powdered samples using a Tecnai™ G2 F30 S-TWIN high resolution transmission electron microscope from FEI Company (OR, USA). The microscope was operated in transmission mode at 300 kV with TEM point resolution of 2 Å and line resolution of 1 Å. The fine powder was dispersed into pure ethanol and ultrasonicated for 15 min. After that, diluted sample was placed onto a holey carbon-coated copper grid and dried before TEM analysis.

### *FT-IR*

A Nicolet 6700 FT-IR spectrometer (Thermo Nicolet, Madison, WI) connected to the OMNIC operating system software (Version 8.2 Thermo Nicolet) was used to obtain FT-IR spectra of the hybrid materials. The samples were placed in contact with attenuated total reflectance (ATR) on a multibounce plate of ZnSe crystal at controlled ambient temperature (25°C). FT-IR spectra were collected in the frequency range of 4,000–650 $cm^{-1}$ by co-adding 32 scans and at a resolution of 4 $cm^{-1}$ with

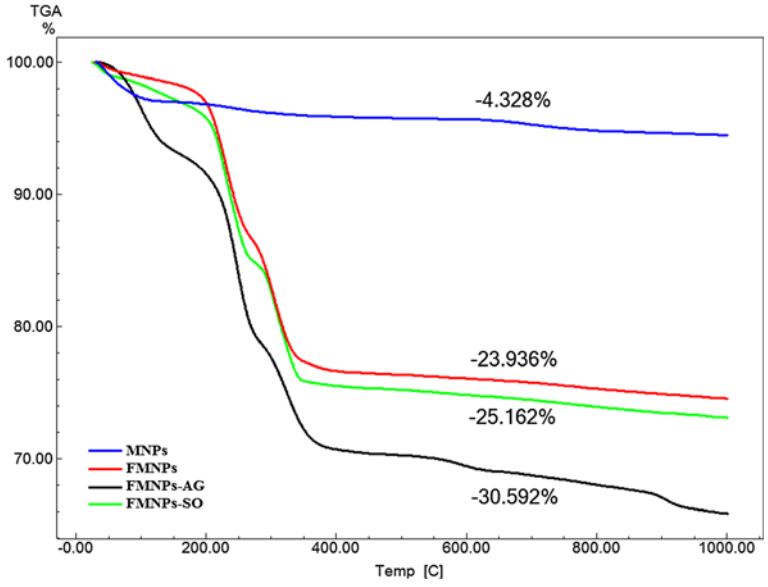


**Figure 3** TGA analysis of MNPs, FMNPs, FMNPs-SO and FMNs-AG.

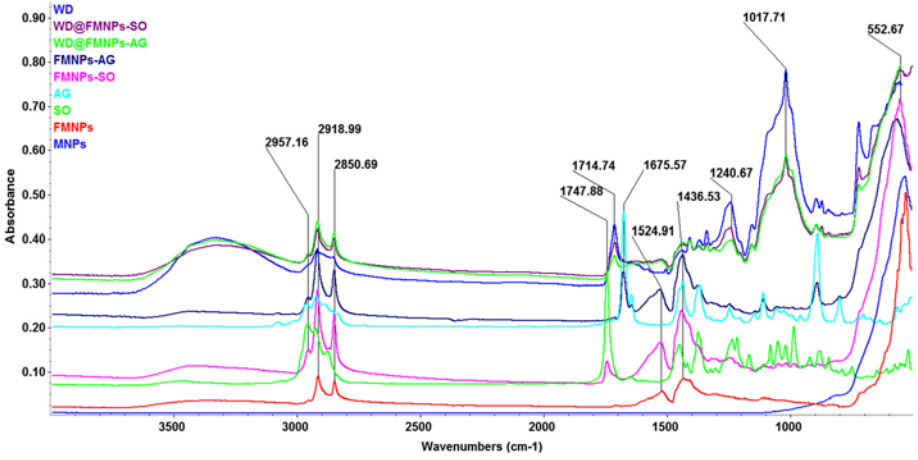


**Figure 4** FT-IR spectra of WD, WD@FMNPs-SO and WD@FMNPs-AG.

strong apodization. All spectra were ratioed against a background of an air spectrum. After every scan, a new reference air background spectrum was taken. The plate was carefully cleaned by wiping with hexane twice followed by acetone and dried with soft tissue before filling in with the next sample. The spectra were recorded as absorbance values at each data point in triplicate.

### *TGA*

The thermogravimetric (TG) analysis of the MNPs, FMNPs, FMNPs-SO and FMNPs-AG was assessed with a Shimadzu DTG-TA-50H instrument. Samples were screened to 200 mesh prior to analysis, were placed in alumina crucible, and heated with 10 $K \cdot min^{-1}$ from room temperature to 800°C, under the flow of 20 $mL \cdot min^{-1}$ dried synthetic air (80% $N_2$ and 20% $O_2$).

### *XRD*

X-ray diffraction analysis was performed on a Shimadzu XRD 6000 diffractometer at room temperature. In all the cases, Cu Kα radiation from a Cu X-ray tube (run at 15 mA and 30 kV) was used. The samples were scanned in the Bragg angle 2θ range of 10–80 degree.

### *Strains and culture conditions*

*C. albicans* ATCC 10231 strain was purchased from ATCC (American Type Culture Collection) and cultured using Sabouraud Chloramphenicol Agar and Sabouraud broth (Acumedia). Fungal inoculum was grown overnight in Sabouraud broth and diluted ~ 1000 times in the same medium, for reaching a density of $10^2$-$10^3$ CFU/ml.

### *Biofilm development assay*

Biofilm formation was assessed in 6 multi-well plates (Nunc), using a static model for monospecific biofilms development. WD and WD@FMNPs-EO pieces were distributed in 6 multi-well plates (one per well). Two mL of *C. albicans* inoculum with standardized density were added in each well, to completely cover the WD pieces. Samples were incubated for 24 h at 37°C. Biofilms were analyzed after 24 h, 48 h and 72 h by viable count assay and SEM.

### *Viable cell counts*

Viable cell counts analysis of microorganisms grown in biofilms was assessed following an adapted, previously described protocol [28]. Briefly, after 24 h incubation the culture medium was removed and the WD pieces washed with sterile PBS (phosphate buffered saline), in order to remove unattached bacteria. WD samples were placed in fresh medium and incubated for other additional 24 h, 48 h and 72 h. After the incubation period WD pieces were gently washed with sterile PBS for not disturbing the biofilm and placed in 1.5 ml Eppendorf tubes containing 750 μL PBS. Samples were vigorously mixed by vortexing for 30 seconds and sonicated for 10 seconds in order to disperse biofilm cells into the suspension. Serial ten-fold dilutions were achieved and plated on Sabouraud Chloramphenicol Agar for viable cell counts assay. Experiments were performed in triplicate and repeated on three separate occasions.

### *SEM analysis*

After 24 h, 48 h, 72 h incubation period, WDs were washed gently with sterile PBS, for not disturbing the biofilm, and fixed by immersing each sample in methanol for 5 seconds. After fixation, samples were allowed to air dry and SEM analysis was performed on a HITACHI S2600N electron microscope, at 15 and 25 keV, in primary electrons fascicle, on samples covered with a thin silver layer.

### *Statistics*

Data were analyzed using GraphPadInStat and Prism softwares, by applying One-way Analysis of Variance (ANOVA) test. P values lower than 0.05 were considered significant.

## Results and discussion

Innovative functionalization techniques are critical steps needed to optimize the use of magnetic nanoparticles for medical applications [29-31], in order to improve their stability in different environments.

Here, we report the fabrication of a modified phytoactive nanobiocoated WD, able to prevent *in vitro C. albicans* biofilm development.

The extracted EOs proved to contain high amounts of certain phytoactive compounds previously reported as exhibiting antimicrobial effects [32, 33]. AG essential oil proved to be rich in limonene 56.53%, carvone 39.56% and α-phellandrene 1.11%. As for the total area, monoterpenic hydrocarbons accounted for 58.01%, while ethers fraction (dill ether, myristicine and dillapiole) for 0.09% [26].

The SO essential oil proved to be rich in cis-thujone (29.8) and eucalyptol (24.7), followed by substantial amounts of α,β-pinene (6.49% and 4.49%) and camphene (7.33%) [25]. For the main constituents identified in the EOs, the obtained concentrations were similar to that obtained by other authors [34].

XRD patterns of MNPs and FMNPs are represented in Figure 1. The XRD patterns of MNPs and FMNPs have six characteristic peaks at 30.57°(220), 35.9°(311), 43.5°(400), 53.9°(422), 57.3°(511) and 63.1°(440), which matched well with the standard pattern of $Fe_3O_4$ (JCPDS 89–4319) [35, 36]. No diffraction peaks other than those of $Fe_3O_4$ were observed, indicating that highly phase-pure $Fe_3O_4$ particles were obtained.

The morphology and size distribution of magnetite nanoparticles were examined by TEM. Typical TEM images of the as-synthesized nanopowders are shown in Figure 2. The products are nearly of spherical shape. The average diameter of the FMNPs particles was 15 ±2 nm, as estimated by the TEM image.

The TGA thermograms show a continuous weight loss in the temperature range 50–600°C, which is just the range of decomposition temperature for $C_{16}$ and essential oils (Figure 3). The weight losses in this temperature range are 4.32%, 23.93%, 25.16% and 30.59%, corresponding to MNPs, FMNPs, FMNPs-SO and FMNPs-AG. The results further confirmed the attachment and stabilization of the volatility of the essential oils on FMNPs surface. $C_{16}$ content was estimated as the difference between weight loss for the region at approximately 600°C for MNPs and FMNPs, and it is approximately 19.6%. The essential oils (AG and SO) content was estimated following the same pattern and the percentages obtained are 1.22% for SO and 6.65% for AG.

The FT-IR analysis identified the organic coating agent ($C_{16}$) on the surface of the FMNPs compared with MNPs (Figure 4). Two sharp bands at 2918 and 2850 $cm^{-1}$ were attributed to the asymmetric $CH_2$ stretching and the symmetric $CH_2$ stretching, respectively. The 1440 $cm^{-1}$ band is assigned to the anti-symmetric $CH_3$ deformation vibration. FT-IR peak of the FMNPs, recorded at 1701 $cm^{-1}$ revealed the C = O stretching vibration of fatty acid. All the above mentioned peaks can be easily identified for the FMNPs-AG, FMNPs-SO, WD@FMNPs-AG and WD@FMNPs-SO. The band observed at 1675 $cm^{-1}$ is assigned to the C = O bond stretching of the carbonyl group from carvone [37], the major component of the AG essential oil. This band is also observed in the FT-IR spectrum of FMNPs-AG. The band observed at 1747 $cm^{-1}$, is assigned to the C = O bond stretching of the carbonyl group from thujone, one of the major component of the SO essential oil. This result is also supported by FT-IR spectrum of FMNPs-SO. FT-IR

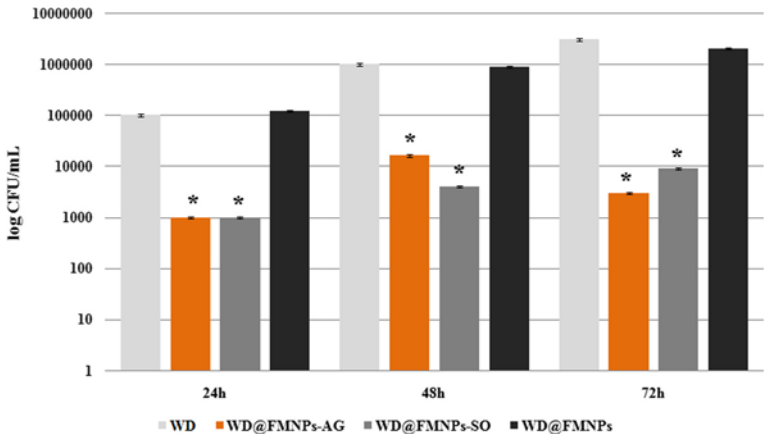


**Figure 5 Graphic representation of viable cell counts analysis after removing *C. albicans* biofilm embedded cells at 24 h, 48 h and 72 h post infection.** *P < 0.05 samples vs. WD uncoated control.

spectra of all tested magnetite-derived nanosystems (MNPs, FMNPs, FMNPs-AG, FMNPs-SO, WD@FMNPs-AG and WD@FMNPs-SO) exhibit a characteristic broad peak of magnetite at about 552 $cm^{-1}$ due to Fe-O stretching [38, 39].

The modified nanophytoactive coated WDs were tested *in vitro* for their antibiofilm activity, using both qualitative (SEM examination) and quantitative (viable cells embedded in biofilm) assays. Due to their antiseptic properties and low side effects SO and AG essential oils have proved to be excellent alternatives for developing antimicrobial strategies [27]. Our data demonstrated that absorbing EOs on FMNPs derived nanosystems could represent an efficient strategy for stabilizing highly volatile natural compounds and to control their release. Viable cell counts assay revealed that both WD@FMNPs-AG and WD@FMNPs-SO have a significant anti-biofilm potential, as demonstrated by the significant decrease in *C. albicans* biofilm embedded viable cell counts, recovered from the fungal biofilms of 48 and 72 h (Figure 5). The obtained results revealed that the nanobiocoatings preferentially inhibit the early stages of biofilm formation (after 24 h), but also reduce the formation and development of mature biofilms.

While the inhibitory effect of AG seems to reach the maximum intensity on 48 h biofilms, the anti-biofilm effect of SO is gradually increasing with the biofilm age. The maximum efficiency of the AG at 48 h and of SO at 72 h could be explained by the different release rate of the two phytocompound from the nanoparticle carrier. However, both nanophytosystems increased the resistance of the functionalized WD to fungal colonization on the entire duration of the experiment comparing with control WDs. The antibiofilm effect of nanophytoactive coated WDs is due to the presence of EOs, since WD@FMNPs have not revealed a significant antibiofilm activity in our experiments. The prolonged anti-fungal effect could be due to the fact that the highly volatile EOs are stabilized by the

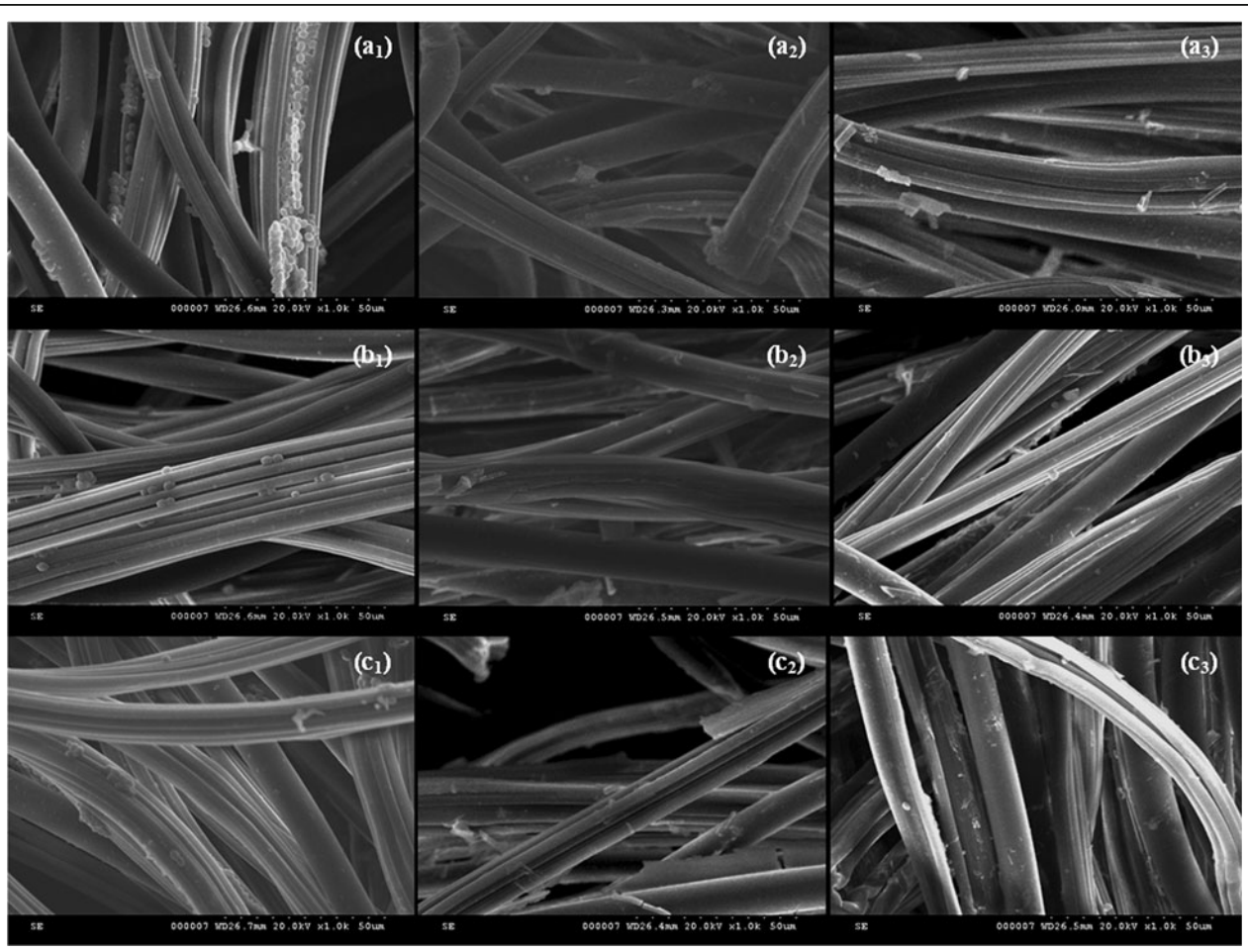


**Figure 6** SEM micrographs indicating the development of *C. albicans* biofilms on control WDs (after 24 h = $a_1$, 48 h = $b_1$ and 72 h = $c_1$ incubation) and on FMNPs-EOs coated WDs (WD@FMNPs-AG after 24 h = $a_2$, 48 h = $b_2$, and 72 h = $c_2$ incubation; WD@FMNPs-SO after 24 h = $a_3$, 48 h = $b_3$, and 72 h = $c_3$ incubation).

functionalized magnetite nanoparticles, which are thus acting as efficient carriers and also ensuring a controlled release of the active phytocompounds, coupled with lower cytotoxicity and biodegradability.

SEM results support CFU data and demonstrate that *C. albicans* grew and developed normal biofilms on the surface of control WDs, but biofilm formation is significantly impaired when using FMNPs-EOs coated surfaces. Normal biofilm development is compromised since its initiation because adherence and first stage biofilm development are inhibited, as revealed by the results observed after 24 h (Figure 6). Both WD@FMNPs-AG and WD@FMNPs-SO coated WDs are efficient against biofilm formation by inhibiting its initialization and further development.

## Conclusions

Here we report a novel nanostructured phyto-bioactive coated rayon/polyester wound dressing surface refractory to *C. albicans* adhesion, colonization and biofilm formation. Using magnetic nanoparticles for the stabilization and controlled release of essential oils, the activity of natural volatile compounds is significantly enhanced and their effect is stable during time, being maintained for at least 72 h. Besides their excellent anti- adherence properties, the proposed solutions exhibit the advantage of using vegetal natural compounds, which are less toxic and easily biodegradable in comparison with the synthetic antifungal drugs, representing thus promising approaches for the development of successful ways to control and prevent fungal biofilms associated infections.

#### Competing interests

The authors declare that there are no conflicts of interest.

#### Authors' contributions

IA provided the wound dressings, designed the study; AMH performed the microbiological assays and analyzed the obtained results, drafted the manuscript; EA conceived the study and supervised the physico-chemical experiments; AMG obtained and performed the physico-chemical characterization of the hybrid nanoparticles, drafted the manuscript; MCC conceived the study, interpreted the microbiological assays results, revised the manuscript. All authors read and approved the final manuscript.

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