COPPER IMPREGNATED ANTIMICROBIAL TEXTILES; AN INNOVATIVE AND POTENT WEAPON TO FIGHT INFECTION

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A platform technology has been developed in which copper oxide is impregnated or plated into polymeric fibres or cotton fibres, respectively, endowing the fibres with potent broad-spectrum anti-bacterial, anti-viral, anti-fungal and anti-mite properties [1]. This durable platform technology introduces copper oxide-treated fibres and enables the mass production of woven and non-woven fabrics with no requirement for alteration of industrial procedures or machinery. This technology facilitates the production of anti-viral gloves and filters (which deactivate HIV-1 and other viruses); anti-bacterial self-sterilizing fabrics (which kill antibiotic resistant bacteria, including MRSA and VRE); anti-fungal socks (which alleviate symptoms of athlete's foot); anti-dust mite mattress-covers (which reduce mite-related allergies) and gauze (which is highly effective in promoting skin regeneration, closure of chronic wounds and the alleviation of bed sores). This paper will demonstrate the potential use of copper in new applications that address medical issues of the greatest importance such as viral transmissions; nosocomial infections; wound healing and the spread of antibiotic resistant bacteria.

COPPER AS A BIOCIDE

Copper ions have been used for centuries to disinfect fluids, solids and tissues [2,3]. The ancient Greeks (400 BC) prescribed copper for pulmonary diseases and for purifying drinking water. The Celts produced whisky in copper vessels in Scotland around 800 AD, a practice that has continued to the present day. Copper strips were nailed to ship's hulls by the early Phoenicians to inhibit fouling, as cleaner vessels were faster and more manoeuvrable. Gangajal (holy water taken from the Ganges River) has been stored in copper utensils in Hindu households for centuries due to copper's anti-fouling and bacteriostatic properties. By the 18^{th} century, copper had come into wide clinical use in the western world for the treatment of mental disorders and afflictions of the lungs. Early American pioneers moving west across the continent put silver and copper coins in large wooden water casks to provide them with safe drinking water for their long voyage. In World War II, Japanese soldiers put pieces of copper in their water bottles to help prevent dysentery. Copper sulphate is highly prized by some inhabitants of Africa and Asia for healing sores and skin diseases. NASA first designed an ionization copper-silver sterilizing system for its Apollo flights.

Today copper is used as a water purifier, algaecide, fungicide, nematocide, molluscicide, and as an anti-bacterial and anti-fouling agent [4-8]. It is considered safe to humans, as demonstrated by the widespread and prolonged use of copper intrauterine devices (IUDs) by women [9-11]. In contrast to the low sensitivity of human tissue (skin or other) to copper [12], micro-organisms are extremely susceptible to copper. Copper toxicity to micro-organisms, including toxicity to viruses, may occur through the displacement of essential metals from their native binding sites, from interference with oxidative phosphorylation and osmotic balance and from alterations in the conformational structure of nucleic acids, membranes and proteins [13].

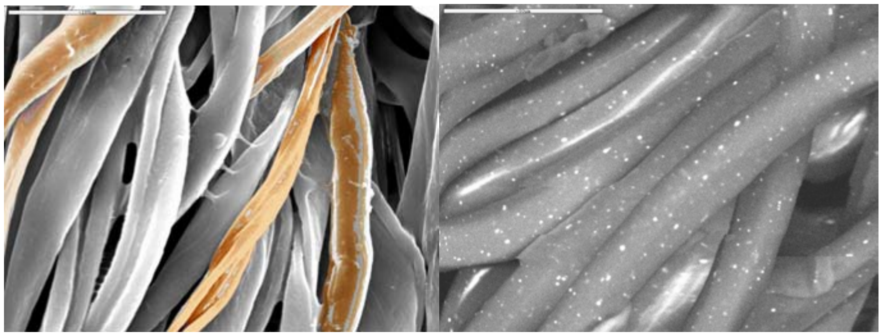

Figure 1. SEM images of cellulose fibres plated with copper oxide (left panel) and polyester fibres containing 3% (w/w) copper oxide particles (right panel).

INCORPORATION OF COPPER OXIDE INTO NATURAL AND SYNTHETIC FIBERS

Utilizing the properties of copper, two durable platform technologies were developed [1,13]: the first one plates cotton fibres with copper oxide (Fig 1, left panel) and the second one impregnates polyester, polypropylene, polyethylene, polyurethane, polyolefin or nylon fibres with copper oxide (Fig 1, right panel). The fibres can be cut into short staple or produced in filament form and texturized, if so desired. The product yielded is a fibre that can be introduced at the blending stage of yarn production or directly into a woven or knit product so that no manufacturing processes are changed. Woven and non-woven fabrics can be produced.

BIOCIDAL PROPERTIES OF FABRICS CONTAINING COPPER OXIDE

Antibacterial

Exposure of gram positive or gram negative bacteria to fabrics containing copper oxide particles results in potent reduction in their viable titres (Table 1).

Table 1: Antimicrobial properties of copper-oxide impregnated fabrics

Type of Copper Treated Fibres	% of Copper in Fabric (w/w)	Name of Organism Tested	Time (hr) of Exposure	% Reduction of Titre
Plated Cellulose	0.2	Staphylococcus aureus	1	>99.8
	0.2	MRSA	1	>99.5
	0.2	VRE	1	99.5
	0.2	Escherichia coli	1	>99.9
Polyester	1	Staphylococcus aureus	4	>99.9
	1	Listeria	1	>99.8
	1	Salmonella	2	>98.5
	1	Escherichia coli	1	>99.9
Polypropylene	3	Staphylococcus aureus	3	>99.9
	3	Escherichia coli	3	>99.9
	3	Klebsiella pneumoniae	3	>99.9
	3	Enterococcus	3	>99.9
Nylon	0.5	Staphylococcus aureus	2	>99.9
	0.5	Escherichia coli	1	>99.9

Antifungal

Exposure of fungi to fabrics containing copper oxide particles results in potent reduction in their viable titres (Table 2).

Table 2: Antifungal properties of copper-oxide impregnated fabrics

Type of Copper Treated Fibres	% of Copper in Fabric (w/w)	Name of Organism Tested	Time (hr) of Exposure	% Reduction of Titer
Plated Cellulose	0.2	Candida albicans	24	>99.9
Polyester	0.5	Candida albicans	24	>99.9
	1	Tricophyton mentagrophytes	24	>99.9
	1	Tricophyton rubrum	24	>99.9
	1	Aspergillus niger	24	>99.9
Polypropylene	3	Candida albicans	24	>99.9
Nylon	0.5	Candida albicans	24	>99.9

The American Association of Textile Chemists and Colorists (AATCC) Test Method 100-1993 was used to determine the biocidal properties of the fabrics against the bacteria and fungi tested. The initial bacterial or fungal inoculum used varied between $1x10^5$ to $4x10^6$ colony forming units (cfu)/sample. These tests were carried out by independent laboratories: AminoLab Laboratory Services, Weizmann Industrial Park, Nes Ziona 79400, Israel, and Hy Laboratories Ltd., Park Tamar, Rehovot 76325, Israel.

Antiviral

Filters containing copper oxide-impregnated polypropylene fibres can reduce infectious titres of a panel of viruses spiked into culture media (Table 3). Enveloped; non-enveloped; RNA and DNA viruses were affected, suggesting the possibility of using copper oxide-containing devices to deactivate a wide spectrum of infectious viruses found in filterable suspensions. Prolongation of the exposure of these micro-organisms to the copper oxide-containing fibres further reduced their viable titers.

Table 1. Reduction of infectious viral titers by copper-oxide containing filters

Virus	% Infectivity Reduction
HIV-1	>99.99
Punta Toro	>99.99
Rhinovirus 2	99.99
Pichinde	99.99
CMV	99.95
Measles	99.95
Influenza A	99.5
WNV	99.5
Adenovirus	99
RSV	99
Parainfluenza 3	96
Yellow Fever	95
VEE	94
Vaccinia	80

The CMV testing was done at the Ben Gurion University, Beer Sheva, Israel by Dr. Shemer-Avni; HIV-1 and Adenovirus testing was done in Cupron Biosafety Viral Laboratory, Rehovot, Israel. All other viruses were tested at the Institute for Antiviral Research, Utah State University, Utah, USA.

Anti-mite efficacy

Figure 2 shows the result of an experiment in which the effect of two fabrics, one containing 0.4% and one containing 2% copper oxide (w/w), were tested for anti-mite activity. The house dust mite tested was *Dermatophagoides farinae*. While during the first 12 days of the experiment all mites exposed to control fabrics were alive, more than 60% and 100% of the mites exposed to the 2% copper fabric were dead after 1 and 5 days, respectively. Approximately 50% of the mites exposed to the 0.4% copper fabrics died within 12 days of exposure to the fabrics. After 47 days of culture, 86% and 67% of the mites in the absence of any fabric and in the control fabric containers were alive, while all mites exposed to the 0.4% copper fabric were dead.

This and other experiments with mites were conducted under a subcontract agreement by Dr. Kosta Y. Mumcuoglu from the Department of Parasitology, Hebrew University-Hadassah Medical School, Jerusalem 91120, Israel.

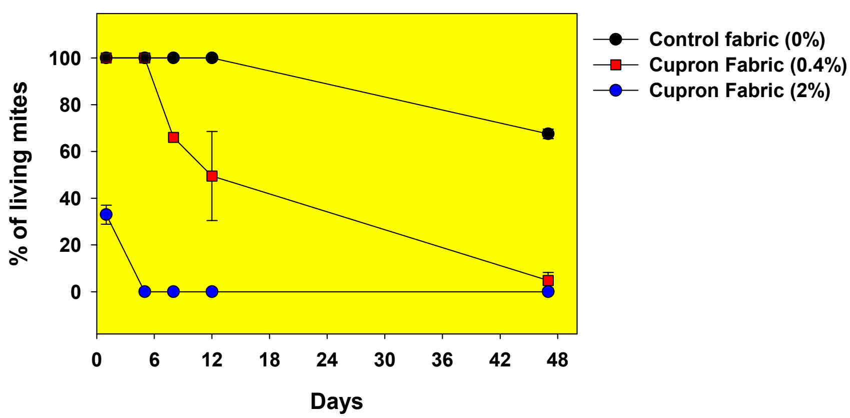

Figure 2. Anti-mite activity of fabrics containing 0.4 and 2% copper oxide (w/w)

CLINICAL STUDIES

Athlete's foot efficacy

Fifty six individuals suffering from athlete's foot (*tinea pedis*) were given socks containing 1% copper-oxide in the soles of the socks. The individuals were asked to wear the copper-socks on a daily basis. During this period the individuals did not receive any local or systemic anti-fungal treatment and their feet were monitored by a podiatrist.

The following measures were studied: erythema, burning and itching, oedema, scaling, vesicular eruptions and fissuring. In all attributes there was a significant improvement or resolution of the attributes studied in an average follow up of 9 days (Fig 3).

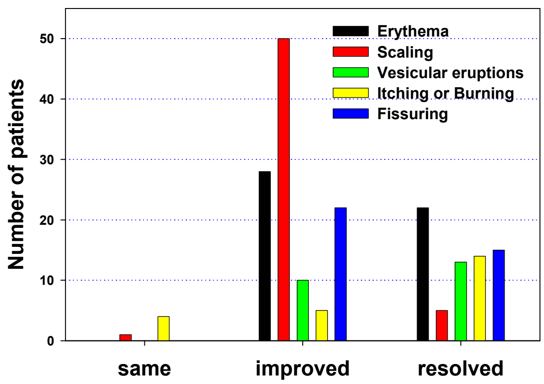

Figure 3. Treatment of Tinea Pedis with Socks Containing Copper Impregnated Fibres

Healing of Diabetic Ulcers

Copper is a key player in many of the complicated processes that together comprise the wound repair mechanism. For example, copper stimulates the formation of new capillaries in the skin via induction of vascular endothelial growth factor (VEGF), copper stabilizes fibrinogen [14,15] and collagen and copper modulates integrins expressed during the final healing phase [16].

Thus, taking together the potent biocidal activities of copper [13], the very low risk of adverse skin reactions associated with copper [12,17], and its roles in the wound healing process, strongly support the notion that the addition or application of copper or copper containing products, such as band aids and gauze containing copper, to wounds may significantly enhance the wound healing process. Indeed, in preliminary data demonstrate that treating chronic diabetic ulcers, which failed or responded poorly to conventional treatments, with copper oxide containing pads, results in significant closure and resolution of the chronic ulcers. One such example is shown in Figure 4.

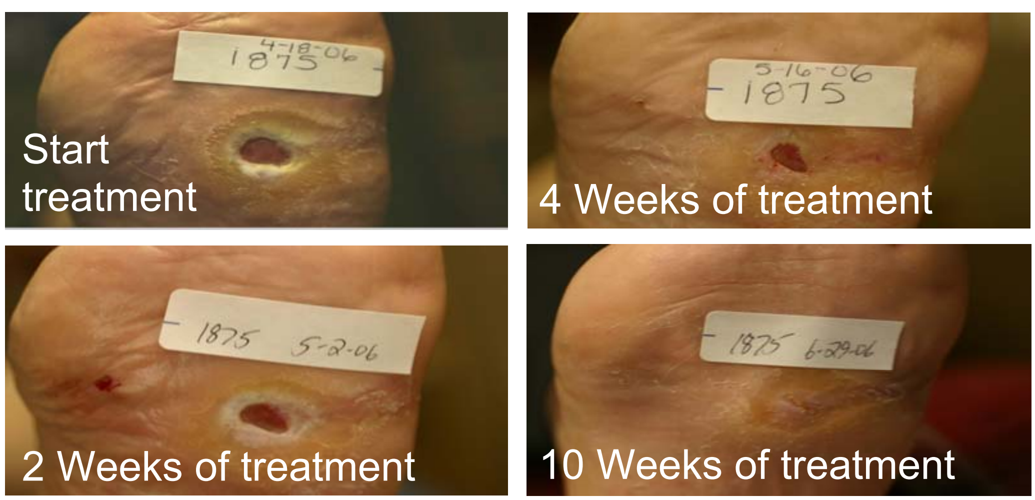

Figure 4. Healing of a chronic ulcer in the foot of a 71 years old diabetic patient. The wound did not close even when treated for 9 months by conventional treatment (oral antibiotics, Acticoat Absorbent, Allevyn, Apligraf and sharp debridement).

DISCUSSION

Permanent or durable binding of inorganic compounds to organic substrates is extremely difficult, especially for mass production processes. By utilizing the properties of copper, two inexpensive platform technologies were developed which permanently bind copper to textile fibres from which woven and nonwoven fabrics can be produced. The introduction of copper oxide at the early stages of the production cycle enables the use of the copper-treated fibres in many manufacturing processes without altering manufacturing procedures or equipment, allowing for rapid and simple production of fabrics with potent biocidal qualities.

Animal studies demonstrated that the copper treated fibers do not possess skin sensitizing properties [1,18]. Furthermore, no individual who used socks containing copper-impregnated fibres to alleviate their athlete's foot conditions reported any negative effects caused by the socks [18,19]. Similarly, none of 100 patients, who slept on sheets containing copper treated fibres, reported any adverse effects [18]. These findings are in accordance with the very low risk of adverse skin reactions associated with copper [12].

The possibility of introducing copper oxide into fabrics may have significant ramifications. One example is the reduction of nosocomial infections in hospitals. Although the contribution of airborne transmission of pathogens to nosocomial infections has been controversial, much data is accumulating in support of the notion that airborne transmission of bacteria contributes significantly to hospital acquired infections (reviewed in Ref [20]). Airborne transmission is known to be the route of infection for diseases such as tuberculosis and aspergillosis. Recently it has been implicated in nosocomial outbreaks of MRSA [21,22], *Acinetobacter baumannii* [23] and *Pseudomonas aeruginosa* [24]. It was found that 65% of the nurses who performed activities on patients with MRSA in wounds or urine, contaminated their nursing uniforms or gowns with MRSA [20]. Hospital ventilation systems have also been implicated with nosocomial MRSA outbreaks [20].

Importantly, it has been demonstrated that sheets which are in direct contact with the patient's skin and its bacterial flora are an important source of airborne bacteria [25,26], including MRSA [27]. Activities, such as bed-making, have been shown to release large quantities of micro-organisms into the atmosphere, only to fall back to background levels 30 minutes after bed-making. The data for the hallway also revealed that the bed-making process dispersed micro-organisms around the building [28]. In an ongoing study at the Barzilai Hospital in Israel, bacterial colonization of sheets, including MRSA, has been found in 22 out of 30 sheets examined (Dr. Y. Mishal, personal communication and Ref [18]). MRSA spread also occurs though indirect contact by touching objects such as towels, sheets, wound dressings and clothes contaminated by the infected skin of a person with MRSA (CDC, Fact Sheet. 7 March 2003. http://www.cdc.gov/ncidod/hip/Aresist/mrsafaq.htm).

We submit that the use of self-sterilizing fabrics, such as pyjamas, sheets and pillow covers, in a hospital setting, will significantly reduce the airborne and indirect contact dissemination of bacteria and other micro-organisms in hospital wards, thus reducing the rate of nosocomial infections. Indeed, preliminary data with 30 patients, who slept overnight on regular sheets and then overnight on sheets containing 90% regular cotton fibres and 10% copper oxide-impregnated fibres, demonstrate a statistically significant lower bacteria colonization on copper oxide-containing sheets than on regular-sheets [18], strongly supporting our hypothesis.

House dust mites (HDM) are considered to be an important source of allergen implicated in allergic asthma, rhinitis, conjunctivitis and dermatitis [29]. By using copper oxide containing fibres in fabrics, the HDM population can be controlled and, if enough copper is present in the fabric, the mites can be eliminated entirely.

In conclusion, this paper presents potential uses of copper in new applications that address medical concerns of the greatest importance. Implementation of even a few of the possible applications of this technology may have a major effect on the lives of many.

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