การประยุกต์ใช้อนุภาคนาโนของเงินทางการแพทย์
Application of Silver Nanoparticles in Medicine

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บทคัดย่อ

ปัจจุบันมีการพัฒนาประยุกต์ใช้นาโนเทคโนโลยีต่างๆ เช่น ทอง เงิน ไทเทเนียม มาประยุกต์ใช้และก่อประโยชน์นานับประการ อนุภาคนาโนของเงินเป็นอีกอนุภาคหนึ่งที่มีบทบาทที่นำ มาพัฒนาแพร่หลาย โดยเริ่มจากการพัฒนาในขบวนการอุตสาหกรรมการผลิตอาหาร เครื่องดื่ม การบรรจุ หีบห่อ การทำความสะอาด เพื่อป้องกันแบคทีเรีย และ อื่นๆ รวมทั้งอนุภาคนาโนของเงินมีบทบาท ที่สำคัญในทางการแพทย์ เช่น การนำอนุภาคนาโนของเงิน ติดตามยาเพื่อการรักษาในผู้ป่วย โรคมะเร็ง (Drug delivery), การนำพิษของนาโนเพื่อป้องกันเชื้อโรคชนิดต่างๆ และสิ่งแปลกปลอมเข้าสู่ร่างกาย, การนำมาพัฒนาช่วยอ่านผลวิเคราะห์ตรวจวินิจฉัยโรค ติดเชื้อ และโรคทางพันธุกรรมด้วยตาเปล่า เป็นต้น

นอกจากนี้อนุภาคนาโนของเงินยังก่อโทษเช่นกัน มีการศึกษาที่รายงานถึงพิษเกี่ยวข้องกับอันตรายที่นำมาใช้ โดยต้องคำนึงถึงจำนวนปริมาณ, ขบวนการสังเคราะห์ และขนาดอนุภาค รูปร่างของนาโนที่เหมาะสมในการนำมาใช้ในงานที่เกี่ยวข้องโดยเฉพาะคุณประโยชน์ที่แอบแฝงด้วยพิษร้ายแรงต่อมนุษย์ พบว่า อนุภาคนาโนของเงินจะส่งผลทำลายการทำงานของระบบหายใจ ผิวหนัง รวมทั้งระบบ ทางเดินอาหารอีกด้วย

ผลของกลไกการทำงานอนุภาคนาโนของเงินจะส่งผลต่อหน้าที่การทำงานของไมโตคอนเดรียภายในเซลล์ของสิ่งมีชีวิต และส่งผลให้เกิดการตายของเซลล์ดังกล่าว (Apoptosis) ทำให้เปลี่ยนแปลงรูปร่างขนาด สอดคล้องกับการผลิตอนุมูลอิสระที่เกิดขึ้นภายในเซลล์ Reactive oxygen species (ROS) ส่งผลให้สูญเสีย หน้าที่การทำงานภายในเซลล์ต่อระบบต่างๆ ในร่างกาย รวมทั้งสิ่งมีชีวิตในสิ่งแวดล้อมด้วย อย่างไรก็ตาม การพัฒนานาโนเทคโนโลยีด้วยอนุภาคของเงิน รวมทั้งโลหะต่างๆ ยังต้องการพัฒนาค้นคว้าอย่างต่อเนื่อง ทั้งประโยชน์-โทษที่จะได้รับ โดยวิทยาการดังกล่าวยังเป็นองค์ความรู้ใหม่ที่นำมาประยุกต์ใช้ และยังขาดข้อมูลที่แน่ชัดทั้งต้องอาศัยนักวิจัยรุ่นใหม่ที่สร้างสรรค์ผลงานเกี่ยวกับนาโนเทคโนโลยีให้มากขึ้น

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Abstract

Nanotechnology is a multidisciplinary field: examples are food packaging materials and food supplements. In medical was an application such as diagnosis, monitoring, therapy and kill the bacteria fungi and virus.

The toxicity of nano-silver were respiratory system, skin and gastro-intestinal tract in the cellular of man and nanotechnology is the ability to work at the atomic, molecular and supra molecular levels also.

The mechanisms of silver nanoparticles the cellular responses apoptosis of cell morphology. It has been well established that dysfunction of mitochondria is a key step towards apoptosis and increased ROS was found in association with mitochondrial. However, the research of advantage and disadvantage of silver and metal nanoparticles should be further study amongst new scientists generation.

Introduction

Nanoparticles particularly use in medical applications such as diagnosis and therapy, which the later demonstrates an example of adding silver nanoparticles to socks to kill the bacteria associated with foot odor. Also, it has been known that silver and its compounds have strong inhibitory and bactericidal effects as well as a broad spectrum of antimicrobial activities for bacteria, fungi and virus since ancient time (Lok et al., 2006: 916-24; Cho et al,. 2005: 956-60; Silver, 2003: 341-53) Drosophila melanogaster, (Ahamed et al., 2009: 363-9), zebrafish (Asharani et al., 2008: 25; Barllan et al.,:1897-910; Griffitt 2008: 1972-8), oyster embryos (Ringwood et al., 2009), Daphnia pulex (Griffitt et al., 2008: 1972-8) and Caenorhabditis elegans were pass cell membranes in C. elegans by silver. However, the potential toxicity of gold nanoparticles is still not completely understood. In the past few years, the toxicity of nanomaterials, such as nanoparticles, quantum dots, nano wires, and nanotubes was reported. (Chen Z et al., 2006: 109-20; Cho EC et al., 2009: 517-22; Sayes CM2 et al., 2007: 163-80; Kim JS et al., 2006: 338-47; Yang ST et al., 2008: 940-4).

Nanotechnology is the ability to work at the atomic, molecular, and supramolecular levels (on a scale of ~ 1-100 nm) in order to understand, create, and use material structures,. devices, and systems with fundamentally new properties and functions resulting from their small structure. Nanotechnology is a multidisciplinary field, which involves of the primary and applied sciences such as physics, chemistry, biology, medicine, and engineering.

Because of all natural and man-made systems have the first level

of company at the nano scale. Therefore, nanotechnology has validated a remarkable in clinical and medical uses because nano materials are generally in the similar size range with biological entities for example cells, organelles, DNA, and proteins. Nanotechnology provides the promising tools and technology platforms for the investigation of biological systems. The development and engineering of small devices have already demonstrated promising results in medical diagnosis, monitoring and therapy.

Nano materials are defined as materials produced such as unique mechanical, optical, chemical, electrical and magnetic properties. The unique properties of nanomaterial directly depend on their size and structure. Nanoparticles ease to modify because they are often stabilized with a weakly binding layer of charged ligands (e.g. citrate) that can be replaced with molecules with chemical functionalities that bind more strongly (e.g. thiols, amines, and disulfides) to their surface than these ligands.

Nevertheless, nanoparticles are concerned due to their extremely high surface areas and increased reactivity. Because of these unique physical and chemical properties, nanoparticles can potentially impact the health of those exposed to them during industrial manufacturing and production. Silver at the nanoscale, nano-silver is nowadays used in an increasing number of consumer and medical products. Because silver is a soft white lustrous element, an important use of silver nanoparticles is to give products a silver finish. Still, the remarkably strong antimicrobial activity is the major direction for development of nano-silver products. Of the more than 800 consumer products that contain nanomaterials, roughly 30 % are claimed to contain silver particles (Susan W P. Wijnhoven, 2009).

Examples are food packaging materials and food supplements, odor resistant textiles, electronics and household appliances, cosmetics and medical devices, water disinfectants, and room sprays. Some of the applications of nano-silver have resulted in the concern of governments and discussions among the public. An example is the addition of silver nanoparticles to socks to kill the bacteria associated with foot odor. Technologies of nanoparticles are being used in food production. The way nanotechnology is expended within the food production leads to a first estimate of potential consumer exposure and thus can be used as a ranking of risks. Nanotechnology used for food production without introducing/adding nano scale products or compounds in the food can be considered as low risk for the consumer. On the other hand, the ultimate direct consumer exposure can

be expected when nanoparticles are included into food directly. The use of nano-silver includes the processing, conservation and consumption phase of the food production chain (Table below). For food supplements with nano sized silver also statements about the function like 'Purifying and conservation of unknown targets. Supporting the immune system' and 'Helpful against severe illness's have been put on products. Since these statements have not been evaluated by, for instance, the European Medicines Evaluation Agency (EMEA), the European Food Safety Authority (EFSA) or the US Food and Drug Administration (FDA), the products are not medical products and are not intended to diagnose, treat, cure or prevent any disease. The category Food and Beverages in the product inventory was split up into four sub-categories, and contained 27 different products with nano- silver found on the global market representing different applications. Furthermore, also relevant in the storage of food are two refrigerators found in the consumer products category. Already mentioned earlier, consumer exposure is expected to be high when nanoparticles are included in food, as is the case for the nano-silver supplements. With regard to the major use of nano-silver in coatings to prevent bacterial growth, the actual exposure of humans is hard to estimate. The expected consumer exposure remains low as long as the inert nano-silver particles are bound in the packaging materials or in the coatings on surfaces of packaging materials and food preparation devices. When nano-silver particles are bound to other materials, exposure to nano-silver is only expected to occur when there is a risk of wear off or migration of nano-silver particles in the free or aggregated form into the food. However, there can be release of Ag^+ otherwise there may not be desired antimicrobial effect and no information is available on the release of nano-silver ions taking (Susan W P. Wijnhoven, 2009).

Table 1. Summary of applications of nano-silver in the food production chain (Susan W P. Wijnhoven, 2009: 109-138)

Chain Phase	Application	Nanotechnology	Function
Processing of food	Food preparation equipment	Incorporated nanosized silver particles	Anti-bacterial coating of food handling devices
Conservation	Refrigerators Storage containers	Incorporated nanosized silver particles	Anti-bacterial coating of storages devices
	Food products	Nanosized silver sprays	Antibacterial action
	Packaging materials	Incorporation of active nano-silver particles	Oxygen scavenging, prevention of growth of bacteria
Food consumption	Supplements	Colloidal metal nanoparticles	Claimed to enhance desirable uptake

Table 2. Applications of nanoparticles in biology and medicine (OVSalata)

Company	Major area of activity	Technology
Advectus Life Science Inc.	Drug delivery	Polymeric nanoparticles engineered to carry antitumor drug across the blood-brain-barrier
Alnis Biosciences, Inc.	Bio-Pharmaceutical	Biodegradable polymeric nanoparticle for drug delivery
Argonide	Membrane filtration	Nanoporous ceramic materials for endotoxin filtration, orthopedic and dental implants, DNA and protein separation
BASF	Toothpaste	Hydroxyapatite nanoparticles seems to improve dental surface
Biophan Technologies, Inc.	MRI shielding	Nonmagnetic/carbon composite materials to shield medical devices from RF fields
Capsulation NanoScience AG	Pharmaceutical coatings to improve solubility of drugs	Layer-by-layer poly-electrolyte coatings, 8-50 nm
Dynal Biotech		Magnetic beads
Eiffel Technologies	Drug delivery	Reducing size of drug particles to 500-100 nm
EnviroSystems, Inc.	Surface disinfectant	Nanoemulsions
Evident Technologies	Luminescent biomarkers	Semiconductor quantum dots with amine or carboxyl groups on the surface, emission from 350 to 2500 nm
Immunicon	Tacking and separation of different cell types	Magnetic core surrounded by a polymeric layer coated with antibody for capturing cells

Table 2. Applications of nanoparticles in biology and medicine (OVSalata), (Continue)

Company	Major area of activity	Technology
KES Science and Technologies, Inc	AiroCide filters	Nano-TiO2 to destroy airborne pathogens
NanoBio Cortporation	Pharmaceutical	Antimicrobial nano-emulsions
NanoCarier Co., Ltd	Drug delivery	Micellar nanoparticles for encapsulation of drugs, proteins, DNA
NanoPharm AG	Drug delivery	Polybutilcyanoacrylate nanoparticles are coated with drugs and with surfactant, can go cross the blood-brain barrier
Nanoplex Technologies, Inc	Nanobarcodes for bioanalysis	
Nanoprobes, Inc.	Gold nanoparticles for biological markers	Gold nanoparticle bio-conjugates for TEM and/or fluorescence microscopy
Nanoshpere, Inc.	Gold biomarkers	DNA barcode attached to each Nano probe for identification purposes, PCR is used to amplify the signal; also catalytic silver deposition to amplify the signal using surface Plasmon resonance
NanoMed Phamaceutical, Inc.		Nanoparticles for drug delivery
Oxonica Ltd	Drug delivery Sunscreens	Doped transparent nanoparticles to effectively absorb armful UV and convert it into heat
PSiVIda Ltd	Tissue engineering, implants, drugs and gene delivery, bio-filtration	Exploiting material properties of nanostructured porous silicone
Smith & Nephew	Acticoat bandages	Nanocrystal silver is highly toxic to pathogens
QuantumDoc Corporation	Luminescent biomarker	Bioconjugated semiconductor quantum dots

Table 3. Number of Food and Beverages products per subcategory.* (Susan W P. Wijnhoven, 2009)

Subtype of product	Matrix	No.	Example
Cleaniing	Fluid/ spray	1	Sterilizing spray
Cooking utensils, coatings	Coatings	6	Cutting and chopping boards, kitchen-and tableware, baby bottle brush
Storage	Solid	8	Fresh boxes, storage bafs and tableware, baby bottle brush
Supplements	Fluid	12	Silver particles in water

*Categories and subcategories were modified from the database of the Woodrow Wilson International Centre of Scholars.

Exposure via medical products

Sliver has been known for decades for its antimicrobial properties in curative and preventive medicine. However, nano-silver into medical products has been of great interest in recent years. Properties of nano-structured silver can be controlled and tailored in a predictable manner and impart them with biological properties and functionalities that can bring new and unique capabilities to a variety of medical applications ranging from implant technology and drug delivery, to diagnostics and imaging.

Table 4. Emerging applications of nano-silver in medical products. (Susan W P. Wijnhoven, 2009)

Medical domains	Examples	References
Anesthesiology	Coating of breasting mark	Patent
	Coating of endotracheal tube for mechanical ventilator support	-
Cardiology	Coating of driveline for ventricular assist devices	-
	Coating of central venous catheter for Monitoring	-
Dentistry	Additive in polymerizable dental materials	Patent
	Sliver-loaded SiO2 nanocomposite resin filler	Jia et al. (2008)
Drug delivery	Remote laser light-induced opening of microcapsules	Skirtach et al. (2006)
	Coating of contract lens	Weisbarth et al. (2007)
Eye care	Coating of catheter for cerebrospinal fluid drainage	Bayston et al. (2007)
Neurosurgery	Superabsorbent hydrogel for incontinence material	Gailano et al. (2007)
	Additive in bone cement	Lee et al. (2007)
Patient care	Coating of implant for joint replacement	Alt et al. (2004)
	Orthopedic stockings	Chen et al. (2006)
Orthopedics	Treatment of dermatitis	Pohle et al. (2007)
	Inhibition of HIV-1 replication	Bhol et al. (2004)
	Treatment of ulcerative colitis	Bhol and Schechter (2005)
Pharmaceutics	Treatment of acne	Bhol and Schechter (2007)
	Coating of hospital textile (surgical gowns, face mark)	Patent
Surgery	Coating of surgical mesh for pelvic	Li et al. (2006)
Urology	reconstruction	Cohen et al. (2007)
Wound care	Hydrogel for wound dressing	Yu et al. (2007)

Nanosilver's interactions with tissues and routes of exposure

1. Respiratory system

A major portal of nanoparticle was the respiratory system. The pathologies resulting from airborne particle materials, e.g. quartz, asbestos and carbon, have long been topics thoroughly researched in occupational and environmental medicine. Particles less than 2.5 μm can get down to the alveoli. The deposition of inhaled ultrafine particles (diameter <100 nm) mainly takes place in the alveolar region. The effect of nanoparticle occurred ROS production, which are related with toxicity of silver nanoparticle. It is sound to assume, that in such a highly pro-oxidative environment as the intra alveolar space, the enormous surface area of silver nanoparticles may serve as an efficient facilitator of generation of radicals and ROS (Limbach et al., 2007). Addition, a key component of the clearance mechanisms were alveolar of the macrophages. The phagocytosis of macrophages activated and release of chemokines, cytokines, ROS, and other mediators that may result in sustained inflammation and epithelial of respiratory damage. In the other, the silver nanoparticles can detected in blood, heart, liver, kidney and brain from inhaled of the nanoparticle. In the liver could play a major role in clearance of circulatory silver nanoparticle.

2. Skin

Intradermal of silver nanoparticles could enter subcutaneous lymphatic, increase in circulation although dermal toxicity. Nano silver crystallizes released from a commercially available dressing were found to be toxic to both keratinocytes and fibroblasts, and fibroblasts appeared to be more sensitive to silver than keratinocytes. Nano scale Titania, have been shown to have toxically effects on epidermal keratinocytes and fibroblasts or be capable of altering their gene/protein expression.

3. Gastrointestinal tract

All materials given orally are in close contact with the gastrointestinal tract (GIT) which has an overall surface area up to 200 m2 for nutrient exchange. Gastrointestinal ingestion is probably the most common voluntary route of exposure for nano silver since numerous colloidal silver nanoparticle products are publicly peddled as so called "health maintainers" or "immuno boosters"; most of them are used orally. Particles once in the submucosal region are able to enter both lymphatics and capillaries. Lymphatic absorption may give rise to immune response, for instance the mucosal secretory immune function may probably be affected and silver nanoparticle was toxic in the liver also. However, systemic toxicity of ingested nanosilver is scarcely seen. This situation may probably be

accounted for by the presence in the GIT of a complex mixture of compounds including ingested food, digestive enzymes,electrolytes, and intestinal microbial flora, etc. Ingested nanoparticles can have interactions with these compounds, which might change reactivity and toxicity of the particles. Apart from that, GIT ingested particles will undergo sequential pH stress from gastric acid and intestinal fluid. Micro or nano of the silver in livers and kidneys and colon tissues affected by cancer, will be cause Crohn's disease.

Possible mechanisms of cytotoxicity of silver nanoparticles

Silver nanoparticles significantly decreased the function of mitochondria. This is a shared characteristic of cellular responses, and apoptosis or apoptosis-like change of cell. It has been well established that dysfunction of mitochondria is an early and key step towards apoptosis and increased ROS was found in association with mitochondrial perturbation, suggesting that oxidative stress might mediate the cytotoxicity of silver nanoparticles.

However, the research of advantage and disadvantage of silver and metal nanoparticles should be further study amongst new scientists generation.

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