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SILVER NANOPARTICLES: NEW DIAGNOSTIC AND THERAPEUTIC APPROACH IN TREATMENT OF ORAL DISEASES

Dr. Satyapal Johaley*[1], Dr. Freny R. Karjodkar[2], Dr. Kaustubh P. Sansare[3], Dr. Sneha R. Sharma[1] and Dr. Mohd Saalim[1]

[1]Postgraduate Student, Department of Oral Medicine and Radiology, Nair Hospital Dental College, Mumbai Central, Mumbai, Maharashtra, India.

[2]Professor and HOD, Department of Oral Medicine and Radiology, Nair Hospital Dental College, Mumbai Central, Mumbai, Maharashtra, India.

[3]Additional Professor, Department of Oral Medicine and Radiology, Nair Hospital Dental College, Mumbai Central, Mumbai, Maharashtra, India.

***Corresponding Author: Dr. Satyapal Johaley**
Postgraduate Student, Department of Oral Medicine and Radiology, Nair Hospital Dental College, Mumbai Central, Mumbai, Maharashtra, India.

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ABSTRACT

Silver nanoparticles (AgNP) have unique properties which help in molecular diagnostic, in therapies, as well as in devices that are used in several medical procedures owing to its potent antimicrobial activity. Silver nanoparticles are nanoparticles of silver which are in the size range of 1 to 100 nm in size. The use of silver nanoparticles is also important as several pathogenic bacteria have developed resistance against various antibiotics. In most of the therapeutic applications, it is the antimicrobial property that is being majorly explored through the anti-viral property has its fair share of applications in dentistry. This paper aims at comprehensive view on the synthesis and applications of nanoparticles in the field of dentistry.

KEYWORDS: Silver Nanoparticles, Nano medicine, Antimicrobial, Oral Cancer.

INTRODUCTION

Silver nanoparticles (NPs), or Nano silver (NS), are clusters of silver atoms that range in diameter from 1-100 nm.[1] The particles with an antimicrobial function have received considerable attention within a range of various fields, together with medicine and dentistry. These include spherical, cubic and needle-like nano scaled particles (5–100 nm) and near-nanoscaled devices (up to micrometers).The medical properties of silver have been known since nineteenth century, silver-based compounds have been used in many antimicrobial applications. Nanoparticles have a greater surface to volume ratio (per unit mass) than the nonnanoscale particles of same material and therefore more reactive.[2] The oral cavity provides habitats for a wide diversity of micro-organisms includes bacteria, yeasts, and viruses, with members of all groups being associated with oral infections.[3] Bacteria are the chief components of this inhabitant microflora, and the diversity of species found in the oral cavity replicates the wide range of endogenously derived nutrients, the various types of habitat for colonisation including surfaces on the teeth, mucosa, and tongue, and the opportunity to survive as a biofilm .However, the relationship between this micro flora and the host can be disturbed in a number of ways, resulting in the development of infection of the oral structures. These are mostly localized and comprise dental caries, gingivitis, periodontitis, candidiasis, endodontic infections, orthodontic infections and peri-implantitis.[3] Use of silver nanoparticles as antimicrobial agents in conjunction with other oral hygiene tools such as Toothpaste, Toothbrush may prevent many oral and dental conditions. Also, application of nanostructures enables faster and easier detection of oral cancers and assessment of the saliva for the presence of viruses, proteins or specific markers. Nano-capsules, Nano-coatings, Nano-antibiotics and Nano robots enable more efficient treatments. This paper reviews the advances of nanotechnology in dentistry.

Nano medicine

Nano medicine uses Nano-sized tools for the diagnosis, prevention, and treatment of disease and to gain better consideration of the complex underlying pathophysiology of the disease. The definitive goal is a better quality of life. The aim of Nano medicine may be broadly defined as the widespread monitoring, repair, and improvement of all human biological systems, working from the molecular level using engineered devices and nanostructures to achieve medical advantage.[5]

Applications of Nanotechnology in Nano medicine

The use of diagnostic tools and devices to bring a better understanding of the molecular basis of disease, patient predisposition and response to therapy, and to permit imaging at the molecular, cellular and patient levels. The design of nano-sized multifunctional therapeutics and drug delivery systems to yield more effective therapies.[5]

- **Medicine**

– Diagnostics
– Drug delivery
– Tissue engineering

- **Chemistry and environment**

– Catalysis
– Filtration

- **Energy**

– Saving of energy consumption
– Increasing the productivity of energy.
– The use of more eco-friendly energy systems
– Recycling of batteries

- **Information and communication**

– Novel semiconductor devices
– Novel optoelectronic devices
– Displays
– Quantum computers

- Heavy industry

– Aerospace
– Refineries
– Vehicle manufacturers
– Consumer goods
– Foods.

Synthesis of Silver Nanoparticles

Nanotechnology and contemporary synthetic chemistry have been used to establish a plethora of well-characterized methods for synthesis of silver nanoparticles. All methods have its own advantages and shortcomings. Parameters that are influenced by the synthesis method used include the mean nanoparticle (NP) diameter and size distribution, NP shape, stability, inclusion of ligand shells and capping agents protecting the nanosilver core. Chemical and physical synthesis methods of AgNPs. Biological Synthesis of Silver Nano particles from bacteria, fungus and silver synthesizing Plants, there are various methods for synthesis of NS most commonly; NS is obtained by reduction of silver nitrate using either a reducing agent (e.g. sodium borohydride) or photo reduction via UV light. Capping agents, such as citrate, are used to prevent aggregation and agglomeration of NPs. During chemical reduction, the reducing agent donates electrons to the silver ions ($Ag+$), causing silver to revert to its metallic form ($Ag0$). By controlling the experimental conditions (e.g. Temperature, energy input, presence of capping agents), the reaction kinetics can be manipulated such that clustering silver atoms form NS of Nano scale dimensions.[6]

Effect of size and shape on the antimicrobial activity of nanoparticles

Nanosilver includes nano sized structures made from silver atoms that are metallically bonded together. At nano scale, particles show different physical, optical and chemical properties owing to control of quantum mechanics. The size of nanoparticles implies that larger surface area to come in contact with the bacterial cells and hence, it will have higher percentage interaction than bigger particles. The size of metallic nanoparticles ensures that a significantly large surface area in contact with bacteria. Large contact surface is expected to enhance the extent of bacterial elimination. The nanoparticles smaller than 10nm interact with bacteria and produce electronic effect, which enhance reactivity of nanoparticles .The nanoparticles with different shapes have different effect on bacterial cells. According to Pal et al (2007) truncated triangular nanoparticles show bacterial inhibition with silver content of 1µg. While in case of spherical nanoparticles total silver content of 12.5µg is needed. Rod shaped particles need a total of 50 to 100µg of silver content.[7]

Biological properties of silver nanoparticles

Antibacterial properties

AgNPs have a broad antibacterial effect on an array of Gram-negative and Gram-positive bacteria and antibiotic-resistant bacteria strains.Antimicrobial properties of silver are well known for centuries for the treatment of burns and chronic wounds. The antimicrobial property of silver is related to the quantity of silver and rate of silver released. Silver in its metallic state is inert but it reacts with the moisture in the oral cavity or skin gets ionized. The ionized silver is highly reactive, as it binds to the bacterial cell and brings structural changes in the bacterial cell wall and nuclear membrane leading to cell death.[7] It is supposed that silver ions interact with three main components of the bacterial cell to produce the bactericidal effect: the peptidoglycan cell wall and the plasma membrane; cytoplasmic DNA; and bacterial proteins, especially enzymes involved in the vital cellular process such as the electron transport chain.[6]

Antifungal properties

Nanosilver is an effective antifungal agent against a broad spectrum of common fungi. Kim et al investigated AgNP antifungal properties on a total of forty-four strains of six fungal species and found that AgNPs can inhibit the growth of Candida albicans, Candida glabrata, Candida parapsilosis, Candida krusei, and Trichophyton mentagrophytes efficiently. Specifically, fungal infections are more common in immunocompromised patients because of cancer chemotherapy, or human immunodeficiency virus (HIV) infections.so this can be useful in treatment of oral candidiasis.[8]

Antiviral properties

AgNPs are also an antiviral agent against HIV-1, hepatitis B virus, respiratory syncytial virus, herpes simplex virus type 1. It has been observed that AgNPs have higher antiviral activity than silver ions, due to species variance as they dissolve to release Ag0 (atomic) and Ag+ (ionic) clusters, however, silver salts release Ag+ only. Lara found that the anti-HIV mechanism of nanosilver is based on the inhibition of the primary stages of the HIV-1 cycle.[9] AgNPs can bind to glycoprotein gp120, thus prevent a cluster of differentiation (CD) 4 dependent binding, fusion, and contamination. They act as an effective virucide to block HIV-1 cell-free and cell-associated infection. Moreover, AgNPs inhibit post-entry stages of the HIV-1 life cycle. Though the viral-inhibitory mechanism is not yet fully understood, the properties of AgNPs make a potential broad-spectrum agent and not prone to induce and are not prone to develop resistance that could be used preventively against a variety of viral strains.[10]

Anti-inflammatory properties of AgNPs

Various researchers have been performed to explain the possible inflammatory activity of silver nanoparticles in animal models and human. They concluded that anti-inflammatory activity of AgNPs might be mediated by reducing cytokine release, decreasing lymphocyte and mast cell infiltration and inducing apoptosis in inflammatory cells. Matrix metalloproteinases (MMPs) contribute to tissue injury and inflammatory processes and their overexpression is linked with chronic ulcers instead of acute wounds, which suggests that MMPs might contribute to the non-healing nature of chronic ulcers. Nanocrystalline silver dressings significantly reduced MMP-9 levels in a porcine model and improved wound healing. In a human clinical study (n=15), nanocrystalline silver dressings enhance delayed healing of chronic leg ulcers. This might have been attained by decreasing not only the number of bacteria in the wound but also the inflammatory response, as demonstrated by a reduction in neutrophil infiltration during biopsy.[7]

Anti-adhesive AgNPs and inhibition of oral biofilm

Silver nanoparticles are being considered to decrease bacterial and fungal adhesion to oral biomaterials and devices, e.g. amalgamation into denture materials and orthodontic adhesives. The ideal amount of silver nanoparticles used in such polymers will be of critical importance to prevent an adverse effect upon their physical properties. The study by Ahn et al. reported that experimental composite adhesives (ECAs) had rougher surfaces than conventional adhesives due to the addition of silver nanoparticles, although bacterial adhesion to ECAs was shown to be less than that to conventional adhesives and was not influenced by saliva. Biofilm progression is known to contribute to secondary caries and the failure of resin-based dental composites. Concerning dental implants, several companies market novel synthetic hydroxyapatite (HA) materials as the ‘optimal’ osteoconductive implant coating available, and some companies have developed nanoscaled varieties. These comprise an HA material available in nanophase and a nanocrystalline silver-based antimicrobial coating that should reduce the possible for biofilm formation. The antibacterial properties of an amorphous carbon film incorporating silver nanoparticles in a 40–60 nm size range and deposited onto a standard titanium material have been evaluated.[11]

Nanosilver in diagnostic imaging and therapeutics of Oral Cancer

The application of AgNPs in cancer is divided into diagnostic and therapeutic purposes. Few researchers have reported the development of the therapeutic use of AgNPs as nanocarriers for targeted delivery, chemotherapeutic agents, and as enhancers for radiation and photodynamic therapy. The capability of AgNPs in cellular imaging in vivo could be very valuable for studying inflammation, tumors, immune response, and the effects of stem cell therapy, in which contrast agents were conjugated or encapsulated to nanoparticles through surface modification and bioconjugation of the nanoparticles. Silver plays an important role in imaging systems due to its plasmonic properties. AgNPs, due to their smaller size, are mainly used in diagnostics, therapy, as well as combined therapy and diagnostic approaches by increasing the acoustic reflectivity, ultimately leading to an increase in brightness and the creation of a clearer image.[12]

AgNP as Biosensors in the examination of p53 protein in serum of head and neck squamous cell carcinoma (HNSCC) patients

The p53 protein is a 53-kDa nuclear tumor suppressor protein present in humans and is encoded by the *TP53*gene. When tumors develop, point mutations in the *TP53* gene can lead to overexpression of p53 proteins, which contribute to continuous cell division and leads to cancer. Overexpression of p53 has been stated in 60% of laryngeal carcinomas, 37% of hypo pharyngeal carcinomas, and 52% of tongue carcinomas.[13] With the mortality and breakdown of tumor cells, p53 protein released from tumor cells will enter into the circulation. It was stated that 68 out of 75 patients (91%) with head and neck squamous cell carcinoma (HNSCC) had noticeable serum p53 protein in the preoperative blood.[14-15] The detection of serum p53 protein might play a significant role in the serological analysis of a tumour, including HNSCC. The serum p53 protein level can be examined mostly by enzyme-linked immunosorbent assay (ELISA). ELISA has advantages of sensitivity, reproducibility, and stability. Its applications are controlled for high-titer anti-p53 antibody interference of some noncancer patients and it is a time-consuming, complicated and inconvenient procedure.[15] Biosensors using plasmonic nanostructures localized surface plasmon resonance (LSPR) are advantageous over commercial, thin, plasmonic, continuous films(surface plasmon resonance). The localized surface plasmon resonance (LSPR)-based nanobiosensor is a new type of optical biosensor technique that combines nanotechnology with optical biosensor technology. LSPR is one of the unique characteristics of metallic or metalized nanostructured materials, such as noble metal nanoparticles. It can be excited when the incident photon frequency is resonant with the collective oscillation of the conduction electrons.[17] The developed LSPR biosensor based on the triangular silver (Ag) nanoparticles can be used for the detection of p53 protein levels in patients with Head and Neck Squamous cell carcinoma.[16-17]

Nanosilver in therapeutics

In cancer treatment the Magnetic Fluid Hyperthermia (MFH) is a favorable technology because with the magnetic Nanoparticles is more specific to cancer cells and more destructive. Typically, gold NP is used as they are relatively less toxic than Nanosilver. The plasmonic properties of Nanoscale silver particles enable them to be used as an in vivo therapeutic tool. Plasmonic particles are conjugated to biological targets such as cancer cells or tissues and are used to absorb light and convert it into thermal energy. This destroys the targets by thermal ablation; tumor which has taken up these particles, will not be able to get rid of them.This means if the tumor cells grow between treatment, their daughter cells will have some of these nanoparticles inside them. This means that only one dose needs to be administered, and future applications of AC magnetic field will affect the daughter cells. This is favorable treatment of cancer as allowing such particles to be used in non-invasive treatment of Cancer.[18]

Potential applications of Nanosilver Particles in Dentistry

Prevention of dental caries and restorative dentistry

Dental caries is most common and widespread oral disease, acidic attack from cariogenic bacteria being the main etiologic agent, such as Streptococcus mutans and Lactobacillus spp. It has been shown that there is microleakage on restoration margins, and these gaps can be colonized by oral bacteria, causing secondary caries. In order to prevent or to diminish biofilm accumulation over restoration and in its margins, restorative materials have been modified, especially through the incorporation of AgNPs to composite resins due to its antimicrobial properties and AgNP prevent biofilm formation.[19]

Based on the researches it is possible to say that the antibacterial effects of AgNPs-containing restorative materials might reduce the progress of recurrent caries, to increase the durability of restorations, and to be effective in decreasing the formation of bacterial biofilms on teeth and restorations, without compromising mechanical properties and cytotoxicity of composite resins and adhesive systems.

Treatment of Denture stomatitis

The treatment of denture stomatitis is based on topical or systemic antifungal drugs, for example, fluconazole and nystatin. Though, this infection is often persistent, since antifungal resistance has been reported in Candida biofilms.[20] Moreover, it has been observed that Candida species present in biofilms are less susceptible to antifungal drugs than planktonic cells. Denture stomatitis represents a challenge for dentistry, and methods for its prevention should be encouraged. The novel acrylic resin incorporated with AgNPs could be developed as a denture base to prevent denture stomatitis due to antimicrobial properties of AgNPs.[20]

Endodontics

Various studies have proved that bacteria are the main etiologic agent of pulpal infection and periapical lesion formation. The microbiota of diseased root canals is polymicrobial and is conquered by Gram-negative anaerobes. It has been confirmed that the presence of residual bacteria in the root canal is linked with considerably higher rates of treatment failure. Since the eradication of bacteria in root canals is the key to treatment success, endodontic materials should ideally provide some antimicrobial activity, in order to improve the prognosis of endodontically treated teeth. Outcomes of researches have shown that AgNPs-containing MTA holds higher antimicrobial effect against Enterococcus faecalis, Candida albicans, and Pseudomonas aeruginosa, compared to unmodified MTA. AgNPs solution at lower concentration possesses the same bactericidal effect as 5.25% NaOCl; hence, it could be used as a new intracanal irrigant.[21]

Implantable Materials[23]

Silver impregnated nanomaterials can be used in the following procedures:

- Tissue repair and replacement in periodontal surgeries
- Tissue regeneration scaffolds
- Bone repair and osteoinduction
- Graft materials and membranes
- Diagnostics and Medical therapeutics devices
- Implant materials

AgNP coated Titanium Implants

Titanium (Ti) implants, broadly used in dentistry, frequently present infection around their surface, which remains one of the chief complications in Implantology. Numerous measures have been suggested to evade bacterial contamination, such as implant disinfection and aseptic surgical protocols; however, bacterial invasion often take place after surgery.[22]

In order to avoid biofilm formation over implant surface, antibacterial coatings have been developed; nevertheless, most of them present poor long-term antibacterial action and also the possibility of generating resistant strains after persistent use. AgNPs incorporation to implant surface has been recommended since it would be possible to produce coatings with long-term antibacterial properties by monitoring Ag release. Lu et al.[24] have tested Ti implants incorporated with different concentrations of AgNPs (0.5, 1, 1.5, 2 M).They concluded that AgNP coatings with a low concentration of silver were more favorable for osteoblast growth.

Regenerative Periodontal Surgeries

The capability of silver nanoparticles to prevent the biofilms formations in the oral cavity, as a result of their antibacterial action, has led to their use in prosthetic device coatings, as topical agents, and in dental materials. Numerous devices have recently been proposed for use in the fields of dental implantology, periodontal and alveolar bone regenerative surgeries. The inhibition of dental implant contamination by bacteria and the necessity for biocompatible scaffolds or membranes for use in bone grafts with antibacterial properties (attained by including silver particles in the scaffold, while preserving its structure and features) appear to be interesting applications of Ag NPs. Barrier membranes are devices used in Guided Tissue Regeneration (GTR) /Guided bone regeneration (GBR) techniques to prevent the rapid ingrowth of fibroblasts and/or epithelial cells in a bony defect where slower-growing bone tissue is preferred. Barrier membranes thus prevent the unwanted soft tissues and provide an isolated space into which osteogenic cells can migrate and aid in new bone formation.[25]

Nanosilver toxicity: a need for concern?

The use of silver nanoparticles has been severely limited by the toxicity of silver ions to humans. However; nanotechnology has facilitated the production of smaller silver particles with: Increasing large surface area to volume ratios, Greater efficacy against bacteria and, Lower toxicity to humans. Toxicity from silver is observed in the form of Argyria, only when there is long-term exposure. There are no regular reports of silver allergy.[4]

CONCLUSION

A nanotechnology is a new approach to dentistry. By providing novel methods, it increases efficacy, accuracy, and speed of treatment while decreasing costs. However, similar to other technologies, nanotechnology can cause problems as well if not appropriately employed. Silver in its metallic state is inert, but it reacts with the moisture in the skin/oral mucosa gets ionized. The ionized silver is highly reactive. Thus, it can be used for rapid healing of ulcers or wound in an area with excessive salivation and difficult to retain the medication. The current review shed light on the potentials and capabilities of Silver nanoparticles in diagnosis and treatment of oral disease. In near future, this technology may become the core of dental and medical science and accurate programming in this regard can bring about favorable social and economic outcomes.

REFERENCES

1. Chaloupka K, Malam Y, Seifalian AM. Nanosilver as a new generation of nanoproduct in biomedical applications. Trends Biotechnol, Nov, 2010; 28(11): 580-8.
2. García-Contreras R et al. Perspectives for the use of silver nanoparticles in dental practice. Int Dent J., Dec, 2011; 61(6): 297-301.
3. Allaker RP, Memarzadeh K. Nanoparticles and the control of oral infections. Int J Antimicrob Agents, Feb, 2014; 43(2): 95-104.
4. European Science Foundation (ESF) Nanomedicine: forward look on nanomedicine, October 5, 2011.
5. Chaloupka K, Malam Y, Seifalian AM. Nanosilver as a new generation of nanoproduct in biomedical applications. Trends Biotechnol, Nov, 2010; 28(11): 580-8.
6. Rai M, Yadav A, Gade A. Silver nanoparticles as a new generation of antimicrobials. Biotechnol Adv, Jan-Feb, 2009; 27(1): 76-83.
7. Kim KJ, Sung WS, Moon SK, Choi JS, Kim JG, Lee DG. Antifungal effect of silver nanoparticles on dermatophytes. J Microbial Biotechnol, 2008; 18(8): 1482–1484.
8. Lara HH, Ayala -Nuñez NV, Ixtepan-Turrent L, Rodriguez-Padilla C. Mode of antiviral action of silver nanoparticles against HIV-1. J Nanobiotechnology, 2010; 8: 1.
9. Galdiero S, Falanga A, Vitiello M, Cantisani M, Marra V, Galdiero M. Silver nanoparticles as potential antiviral agents. Molecules, Oct 24, 2011; 16(10): 8894-918.
10. Allaker RP, Memarzadeh K. Nanoparticles and the control of oral infections.Int J Antimicrob Agents, Feb, 2014; 43(2): 95-104.
11. Zhang X-F, Liu Z-G, Shen W, Gurunathan S. Silver Nanoparticles: Synthesis, Characterization, Properties, Applications, and Therapeutic Approaches. Yan B, ed. International Journal of Molecular Sciences, 2016; 17(9): 1534.
12. Maestro R, Dolcetti R, Gasparotto D, et al. High frequency of p53 gene alterations associated with protein overexpression in human squamous cell carcinoma of the larynx. Oncogene, 1992; 7(6): 1159–1166.
13. Frank JL, Bur ME, Garb JL, et al. P53 tumor suppressor oncogene expression in squamous cell carcinoma of hypopharynx. Cancer, 1994; 73(1): 181–186.
14. Leedy DA, Trune DR, Kronz JD, et al. Tumor angiogenesis, the p53 antigen, and cervical metastasis in squamous cell carcinoma of the tongue. Otolaryngol Head Neck Surg, 1994; 111(4): 417–422.
15. Chow V, Yuen AP, Lam KY, Ho WK, Wei WI. Prognostic significance of serum p53 protein and p53 antibody in patients with surgical treatment for head and neck squamous cell carcinoma. Head Neck, Apr, 2001; 23(4): 286-91.

16. Zhao J, Zhang X, Yonzon CR, Haes AJ, Van Duyne RP. Localized surface plasmon resonance biosensors. Nanomedicine (Lond), Aug, 2006; 1(2): 219-28.
17. Shenava A, Sharma S M, Shetty V, Shenoy S. Silver nanoparticles: A boon in clinical medicine. J Oral Res Rev., 2015; 7: 35-8.
18. L. Cheng, M. D. Weir, H. H. K. Xu et al., "Effect of amorphous calcium phosphate and silver nanocomposites on dental plaque microcosm biofilms," Journal of Biomedical Materials Research Part B: Applied Biomaterials, 2012; 100(5): 1378–1386.
19. Rowan R, McCann M, Kavanagh K. Analysis of the response of Candida albicans cells to Silver(I). Med Mycol, May, 2010; 48(3): 498-505.
20. M. Lotfi, S. Vosoughhosseini, B. Ranjkesh, S. Khani, M. Saghiri, and V. Zand, "Antimicrobial efficacy of nanosilver, sodium hypochlorite and chlorhexidine gluconate against Enterococcus faecalis," African Journal of Biotechnology, 2011; 10(35): 6799–6803.
21. J. Hardes, H. Ahrens, C. Gebert et al., "Lack of toxicological side-effects in silver-coated megaprostheses in humans," Biomaterials, 2007; 28(18): 2869–2875.
22. Kanaparthy R, Kanaparthy A. The changing face of dentistry: nanotechnology. Int J Nanomed, 2011; 6: 2799–804.
23. X. Lu, B. Zhang, Y. Wang et al., "Nano-Ag-loaded hydroxyapatite coatings on titanium surfaces by electrochemical deposition," Journal of the Royal Society Interface, 2011; 8(57): 529–539.
24. Stefano Sivolella, Edoardo Stellini, Giulia Brunello, et al., "Silver Nanoparticles in Alveolar Bone Surgery Devices," Journal of Nanomaterials, 2012; Article ID 975842, 12.