Toxicological Evaluations of Nanocomposites with Special Reference to Cancer Therapy

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1 Introduction

Nanotechnology is developing a new era with the development of previously unknown materials and creating possibilities having the profound impact on the economic status, environment, and society. The nanotechnology tool is allowing scientists and manufactures to fabricate materials literally molecule-by-molecule. Properties associated with matter, custom design of previously unexplored structures, devices and unique systems with remarkable properties, like considerably increased strength, significantly decreased weight, much increased electrical conductivity or having the capacity to change shape, colour could be harnessed. Their applications in the field of modern medical and biological research are immense. Though researchers have devised various techniques and well defined intricate strategies to deliver poorly-soluble drugs into the infected tissue or cells, challenges remain to design drug delivery in a target-specific manner without causing the negative impact on the normal cells and tissues. The synthesis of nanoparticles and nanocomposites covering a broad range of metal, metal-oxide, and semiconductors to fabricate nanostructures with varying morphology are now being used in various ongoing research to successfully deal with the challenges and overcome obstacles. Moreover, nanoparticles or nanofibers in fabrics enhance various physical resistance, without increasing weight, thickness or stiffness of the fabric. Water filters that are only 15–20 nm wide can sieve very small particles, including virtually all viruses and bacteria. Hence this method is presently being implemented as a cost-efficient, portable water treatment system, improving the quality of drinking

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Inamuddin et al. (eds.), *Sustainable Polymer Composites and Nanocomposites*,
https://doi.org/10.1007/978-3-030-05399-4_38

water in the developing countries. Not only improving the quality of life, nanoparticles like carbon nanotubes have a number of applications which includes producing strong and lightweight sports good. This proves beyond doubt that nanoparticles have an array of important usages in the modern era. But the goodness of nanoparticles and nanocomposites are not confined in the above- mentioned uses only. They are one of the main targets and hope for the betterment of human health and lifespan in future. The variety of nanotechnology-based platforms has been speculated for use in various biological purposes including improved cancer chemotherapy.

Synthesis of nanocomposites with nanoparticles and various matrix carriers improve the target specificity of the drugs along with their effectiveness in the biological system. The current problem with chemotherapeutic drugs is that they mostly affect the normal tissues along with the cancer ones. The utility of nanocomposites has the potential to address the issue of target non-specificity. Hence, they have gained importance for efficient transport of anticancer agents into the cancerous cells without affecting normal tissues or cells. Unlike the free drugs, which get neutralized in the body within the short time interval, these nanocomposites can also accumulate in the tumours, achieving a cytotoxic load, higher than the rest of the body [1, 2]. The nanocomposites increase the lifetime of a drug preventing their degradation when used in combination. The nanocomposites thus function by increasing the half-life of them in the biological system to a significant amount. Moreover, due to the process of angiogenesis, the accumulation of nanocarriers in the tumour tissues is ensured, which enhance effectivity of these carriers to significantly over free drugs [3, 4]. So, transport of these drugs through the bloodstream is facilitated by increasing half-life of nanocarriers avoiding the action of our body's first line of defence [5].

Different targeting ligands, such as monoclonal antibodies, peptides, antibody fragments, growth factors can be actually tagged to nanocarriers to achieve site-specific active targeting. Moreover, this gives an added advantage to avoid the multiple-drug resistance imparted by passive targeting [6].

But nanocarriers have few drawbacks which are responsible for its clinical failure. After entering into the tumour vasculature, the nanocarriers must reach the cancer cells by overcoming the different barriers. But the endothelial barrier adjacent to cancer cells sometimes act as a real hurdle ensuring the failure of nanocarrier functioning [7]. Moreover, the nanocarriers get attached to the first available receptor, failing to penetrate the other tumours. Also, targeting moieties increase the immunogenicity and plasma protein absorption of the nanocarriers, thereby actually minimizing their half-life in the bloodstream, which was supposed to be enhanced [7], decreasing their targeting capacity.

These shortcomings are needed to overcome to ensure the success of nanocarriers. The drawbacks and limited versatility of a single nanoparticle led to the use of nanocomposites in different fields as they exhibit cumulatively all the properties of their components, thereby increasing the versatility to a large extent. Moreover, they also show increased biocompatibility and high stability both in the environment and in biological systems. Metallic nanocomposites are useful for their

multifunctional properties and biocompatibility, keeping their own property unhampered. This is the reason why researchers are showing immense interest in the use if nanocomposites for different biomedical applications including drug delivery, imaging, MRI contrast agent, photothermal ablation agents, photoacoustic imaging contrast agents [8–10].

But the researches on the toxicological evaluation of the nanoparticles and nanocomposites are still fragmentary and even contradictory to each other. But evidence severely suggests that metal nanoparticles like gold nanoparticle are involved in showing toxic effects on cellular levels causing size, shape and surface modifications. Though a small group of scientists claimed the use of gold nanoparticles to be essentially non-toxic, various research groups demonstrated their toxicity. The size of the nanoparticles seemed associated with generating toxicity when studied in cell lines like MCF-7 in a time and dose-dependent manner. The small-sized nanoparticles showed lesser toxicity and lesser accumulation of autophagosomes. These toxic effects might be an issue for using these nanoparticles for biomedical therapies as they might affect the healthy cells along the cancerous ones. Hence researchers are in the process of synthesizing nanocomposites to decrease the toxicity associated with the metal nanoparticles.

1.1 Nanocomposite Systems

Since the 1990s, researchers are showing more interest in nanocomposite systems and as a result, the number of publications, including reviews, is continuously increasing. We can define nanocomposites (NC) as multiphase solid materials in which phases must be present with dimensions of less than 100 nm. Nanocomposite systems have two parts: (i) continuous phase and (ii) discontinuous reinforcing phase. Thus, nanocomposite systems can have a combined or have noticeably different electrical, mechanical, electrochemical, thermal, catalytic and optical properties of the component materials [11–14].

1.2 Synthesis of Nanocomposite Systems: Nanocomposite Materials Are Generally Synthesized Using One of the Two Methods

1.2.1 In Situ Method

An effective and simple way to obtain a nanocomposite is to synthesize the nanoparticle in a matrix by an in situ method. The nanocomposite can be synthesized inside the matrix material in this method, from its corresponding precursors. Therefore, this method follows one-step fabrication of nanocomposites,

where prevention of particle agglomeration as well as well spatial distribution in the matrix system both, have occurred simultaneously and these are the best advantages of this method. The disadvantage of this method is that the unreacted reagents of the in situ reaction might influence the properties of the final nanocomposite material.

1.2.2 Ex Situ Method

Ex situ method for synthesizing nanocomposites in another useful method, where the pre-made nanoparticles are directly dispersed into the matrix to form the composite. This method also has advantages and disadvantages. This method is very much advantageous for the large-scale industrial synthesis of nanocomposites than the in situ method, but the major challenge of this method is to prepare highly dispersible and stable nanoparticles. Generally, sonication method is applied to disperse the nanoparticles in the matrix.

1.3 Synthesis of Au/Ag Supported Mesoporous Metal-Oxide Nanocomposites

Mesoporous materials having tunable pore structure and modified framework composition, show various applications in adsorption, catalysis, separation, energy storage, conversion, biological uses etc. [15–17].

Mesoporous silicate particles have drawn a significant interest among the variety of inorganic materials as it possesses ordered porous structure, simple and cost-effective synthetic methods and wide range of applications [18–20] Modification of mesoporous silica surface can be done by various functional groups [21–26] and various metal NPs [27–31] and these modifications made the materials potentially applicable in different biomedical fields [32–34]. It should be noted that the antibacterial activity of Ag NPs depends not only on the size of NPs [35] but also on their shape [36]. Therefore, the main reason for carrying out the antibacterial activity is to synthesize monodispersed stable Ag NPs synthesis with the similar shape of the NPs. Ghosh et al. synthesized mesoporous silica flakes (MSF) using tetraethylorthosilicate (TEOS) as a silica source and CTAB as a structure directing agent in hexane at room temperature. They modified MSF with aminopropyltriethoxyl silane (APTS). The amino group of APTS formed -NH_2CH_2OH group by reacting with formaldehyde and the resulted group acted as reducing as well as the stabilizing agent to form monodisperse Ag NPs [37]. Li et al. [38] synthesized homogenously distributed gold nanoparticles within titania framework via a multi-component assembly approach. In this method, titania, gold building clusters, and surfactant are assembled in a single step process, that is they mixed Pluronic surfactant P123, $TiCl_4$, $Ti(OBu)_4$, and $AuCl_3$ in ethanol. Homogeneous mesostructured nanocomposites were obtained by casting the

mixture followed by an ageing process. The surfactant P123 was removed by calcining the sample resulting crystalline mesoporous TiO_2 networks embedding gold nanoparticles. On the other hand, the Ag/mesoporous ZnO nanocomposite was synthesized by microwave irradiation route [39]. The reaction was carried out in an argon atmosphere for 15 min with zinc (II) acetate and silver nitrate as precursor salts to synthesize ZnO and Ag NPs respectively. Briefly, zinc (II) acetate and ethylene glycol were added to the aqueous $AgNO_3$ solution in a round-bottomed flask, fitted to the refluxing system inside the microwave oven. The reaction was conducted for 15 min under argon atmosphere. At the end of the reaction, the powder from the liquid was separated by centrifugation with the mother liquid and then washed with water and ethanol. Then the nanocomposite product was dried overnight under vacuum. Chowdhury et al. synthesized Ag-TiO_2 nanocomposite through a green synthetic method. The mesoporous anatase TiO_2 was synthesized by a hydrothermal method where they used titanium (IV) oxysulfate (TIOS) as precursor salt, urea as reducing agent and SDS as the surfactant in aqueous solution. Then the silver nanoparticle doped TiO_2 (Ag–TiO_2) was obtained by an impregnation method. In this method, water dispersible Ag NPs were used which were obtained from green carambola extract at pH 10 [40].

Sinha et al. [41] synthesized mesoscopic manganese oxide/gold nanoparticle composites by mixing $Mn(NO_3)_2 \cdot 6H_2O$ salt solution with a solution of NaOH and an aqueous solution of CTAB at pH 8.0. The resulting gel (pH 10.5) was heated in a closed vessel. The solid product was filtered calcined at 500 °C for 4 h and then it was stirred in aqueous H_2SO_4 solution followed by filtering and washing with water, and finally dried at 105 °C to obtain mesoporous MnO_2 sheets. The Au metal was vaporized from an Au disk to create a plasma by using the second harmonic of an Nd:YAG pulsed laser with a pulse width of 7 ns and energy of 1 J pulse. The supports which were prepared as thin sheets, placed in front of the cluster beam. Then each side of the wafer was exposed to the cluster beam for the same time interval and finally, the metal content in the composite was measured by chemical analysis (inductively coupled plasma).

1.4 Synthesis of Au/Ag Supported Graphene Nanocomposites

Since the experimental existence in 2004, graphene attracts the huge attention of the scientific community in almost all fields of material science applications. This credit goes to the extraordinary properties of graphene-like its high surface area ($\sim$2600 m^2g^{-1}), high thermal and mechanical stability, unique electronic and charge transport properties [42, 43]. Moreover, functionalized graphene nanocomposites show a wide array of applications in different fields such as in chemical and biological sensors, charge storage devices, capacitors, nanoelectronic and nanophotonic devices etc. [44–48]. These applications of graphene like structures may vary depending upon the route of synthesis that includes micro-mechanical

exfoliation, Chemical vapour deposition (CVD), chemical reduction of graphene oxide (GO) etc. [42, 49–51]. In order to produce large-scale graphene, the chemical exfoliation of GO to produce reduced graphene oxide (RGO) is one of the most cost effective and efficient pathways [52].

The modified Hummers method is used to synthesize graphene oxide was from natural graphite. The synthesized GO was dispersed in DI water by sonication and $AgNO_3$ was added as the precursor salt to obtain Ag nanoparticles. Finally, the Ag/graphene composite was prepared by adding sodium borohydride ($NaBH_4$) as the reducing agent. The synthetic pathway of silver loaded graphene (Ag/G) is shown in Fig. 1 [53].

Wadhwa et al. demonstrated the synthesis of reduced graphene oxide silver (RGO-Ag) nanocomposite by using microwave irradiation. Modified Hummers method was also applied here to synthesize graphene oxide followed by microwave-assisted the reduction of GO and silver nitrate ($AgNO_3$) by hydrazine hydrate via in situ method [52].

The strong reducing agents like hydrazine and sodium borohydride can be used to synthesize metal nanoparticles very easily, but the main drawback of these reducing agents is that they are toxic and hazardous to the environment. To avoid

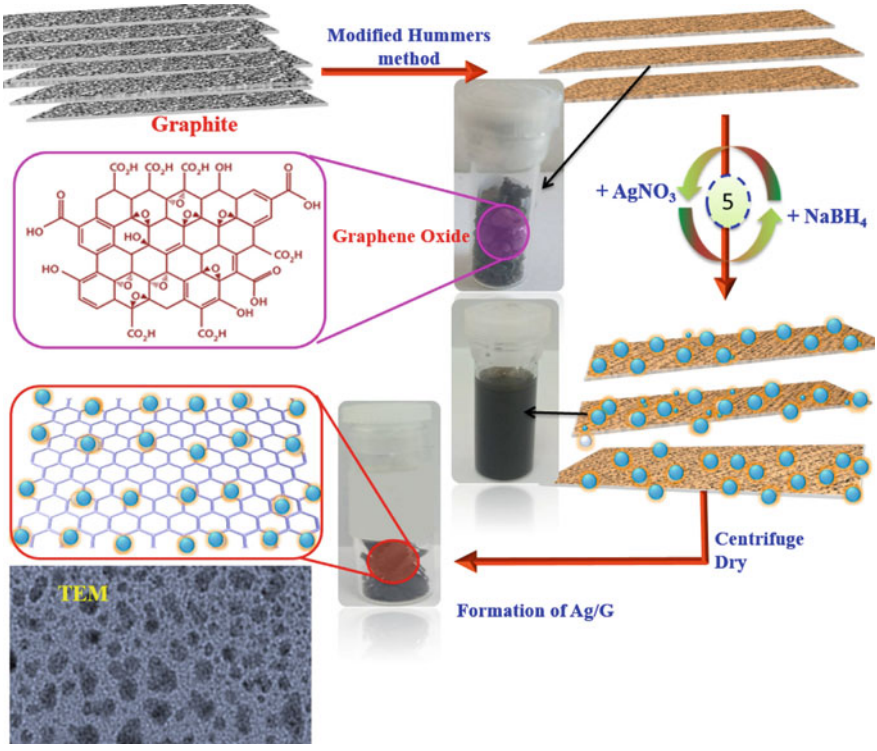


Fig. 1 Schematic representation of the synthesis of silver loaded graphene (Ag/G) composite [53]

such detrimental effects, researchers are recently using a green and inexpensive chemical synthesis approach. silver nanoparticle (AgNPs)–graphene oxide (GO) composite was also synthesized by the green synthetic approach where beta cyclodextrin used as a stabilizing agent and ascorbic acid act as reducing agent [54].

Ju and Chen demonstrated a green and simple in situ approach to synthesize Au nanoparticles on nitrogen-doped graphene quantum dots (Au NPs–N-GQDs). The composite was obtained by simple refluxing of the nitrogen-doped graphene quantum dots and $HAuCl_4 \cdot 4H_2O$ as the precursor salt of Au NPs without using any other reductant and surfactant [55].

1.5 Synthesis of Au/Ag Supported Polymer Nanocomposites

Usually, the nanoparticles tend to aggregate in the polymer matrix and thus the dispersion of nanoparticles in polymer matrices is challenging. This kind of problems of nanoparticles usually results in poor processability of composites and a high defect density [56, 57]. The composite material's physical properties are very much dependable on particle dispersion within the nanocomposite [58]. Toor and Pisano adopted ex situ approach to synthesize nanocomposite material. They prepared PVP coated gold nanoparticles in the form of a dried powder and this powder was dispersed in dimethylformamide (DMF) solvent. On the other hand, the polymer solution was prepared by them where the PVDF in pellets form was mixed with the DMF solvent at 100 °C with continuous stirring. This particle solution was mixed with the polymer solution in various concentration under sonication to prepare the nanocomposite suspension [59] (Fig. 2).

Kanahara et al. [60] prepared amino-terminated polymer particles using the SORP technique. The solution of each polymer in THF was prepared at a certain concentration. Membrane-filtered water was slowly added to the polymer solution in a glass bottle with constant stirring and the resulting mixture was then allowed to stay uncovered at ambient temperature to evaporate the THF. An opaque dispersion of polymer particles in water was obtained after complete evaporation of the THF. Then the aliquot of the aqueous dispersion of polymer particle was mixed with an

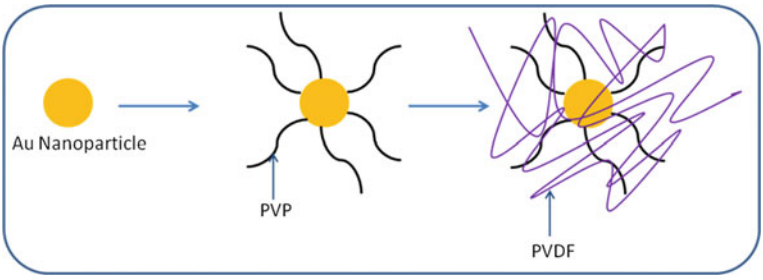


Fig. 2 PVP coated gold nanoparticles are blended with the PVDF polymer

aqueous dispersion of Au NPs and an aqueous PEG solution in a microtube, where PEG was used as a stabilizing agent that can prevent the agglomeration of polymer particles. These composite particles were then separated out by centrifugation followed by washing with water.

Cucurbit [8] uril was used to prepare a gold nanoparticle-polymer composite material, which acts as a supramolecular "handcuff" to grip together with the functionalized gold nanoparticles and acrylamide copolymer. The AuNPs must be functionalized by a water-soluble SAM yet remain accessible for CB [8] host-guest binding, as water solubility is a must for CB [8] ternary system. Water-soluble functionalized-AuNP 3 with a neutral (major) ligand tri (ethylene glycol)-1-butanethiol (EG_3-C_4-SH; 1) and a viologen-containing (minor) ligand, 1-methyl-4,40-bipyridinium-dodecanethiol bisbromide ($[MV^{2+}$-C_{12}-SH] · $2Br^-$; 2) were prepared by a mixed self-assembled monolayer (mSAM) approach. AuNPs with a diameter of roughly 5 nm were prepared and functionalised with varying ligand mixtures of 1 and 2 leading to the AuNP 3 as depicted in Fig. 3. Another NP control was prepared in a similar manner with a SAM consisting of solely EG_3 (EG_3-AuNP 4) [61] (Fig. 4).

1.6 Synthesis of Au/Ag Supported Dendrimer Nanocomposites

Silver-dendrimer nanocomposites were synthesized by mixing dendrimers and silver nitrate solution to obtain Ag^+/dendrimer complex at pH 7.0. Sodium

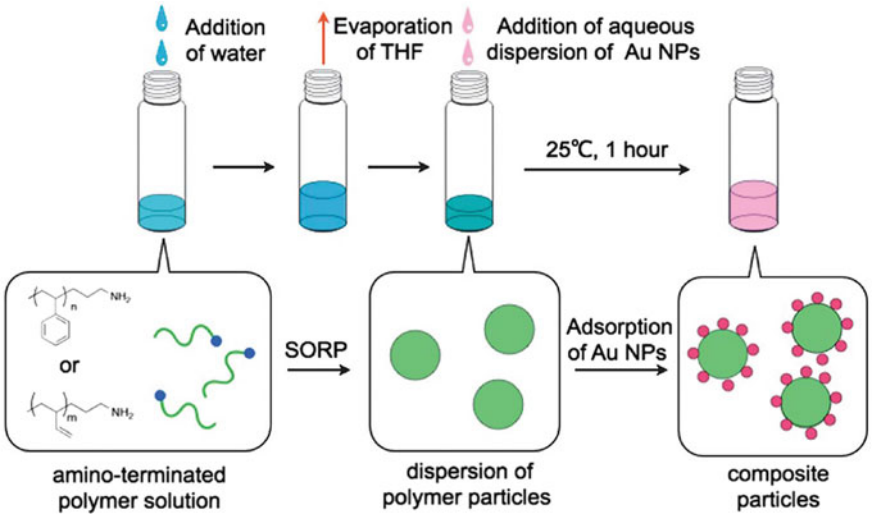


Fig. 3 Schematic illustration of the preparation of composite particles [60]

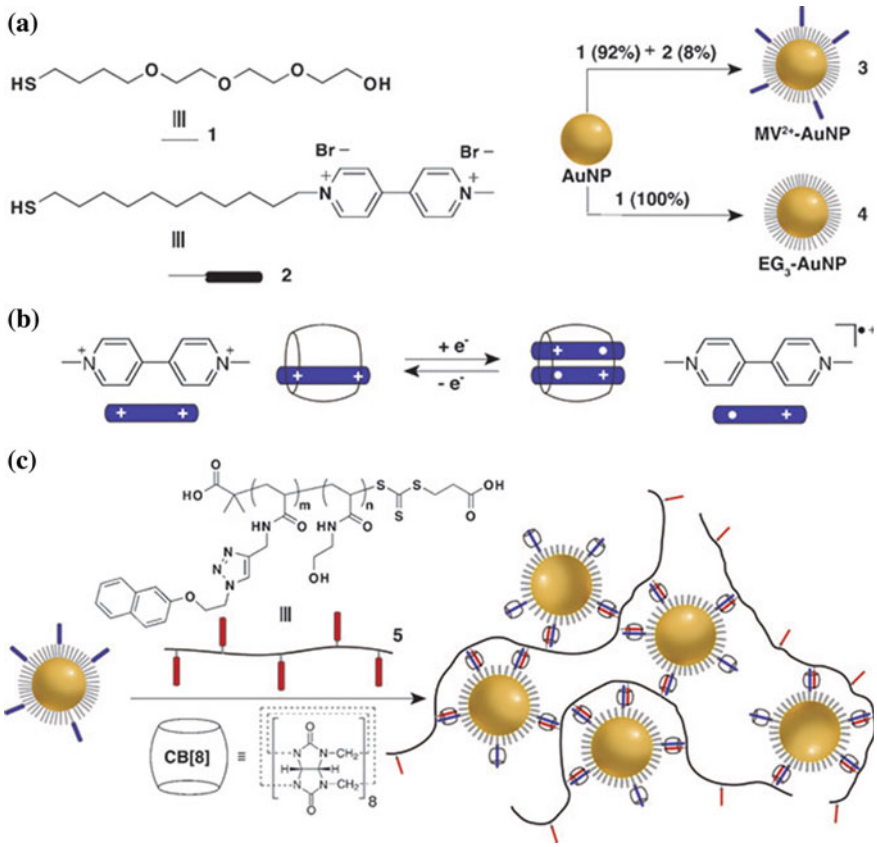


Fig. 4 Schematic representation of **a** preparation of MV^{2+}-AuNP 3 and EG_3-AuNP 4, **b** formation of a 2: 1 $(MV^{+})_2$ CB [8] inclusion complex upon reduction and **c** the noncovalent functionalization of MV^{2+}-AuNP 3 with CB [8] and multivalent Np-copolymers 5 [61]

borohydride was added to the mixture as a reducing agent to reduce Ag^{+} to Ag^{0} and Silver-dendrimer nanocomposite was formed [62]. Zhang et al. showed a simple method of fabrication of thin film composite (TFC) where the silver–polyethylene glycol PEGylated dendrimer nanocomposite is used. They stirred poly (ethylene glycol) methyl ether acrylate (PEGMEA) with the $AgNO_3$ aqueous solution and exposed to the light for several hours to prepare the silver nanocomposite membrane [63] (Fig. 5).

Stable gold-dendrimer nanochains were synthesized in aqueous media without using any templates or organic solvents by regulating the density of dendrimers (Fig. 6). In this approach polyamidoamine (PAMAM) dendrimers self-assembled with gold nanoparticles to obtain one-dimensional nanochains [64].

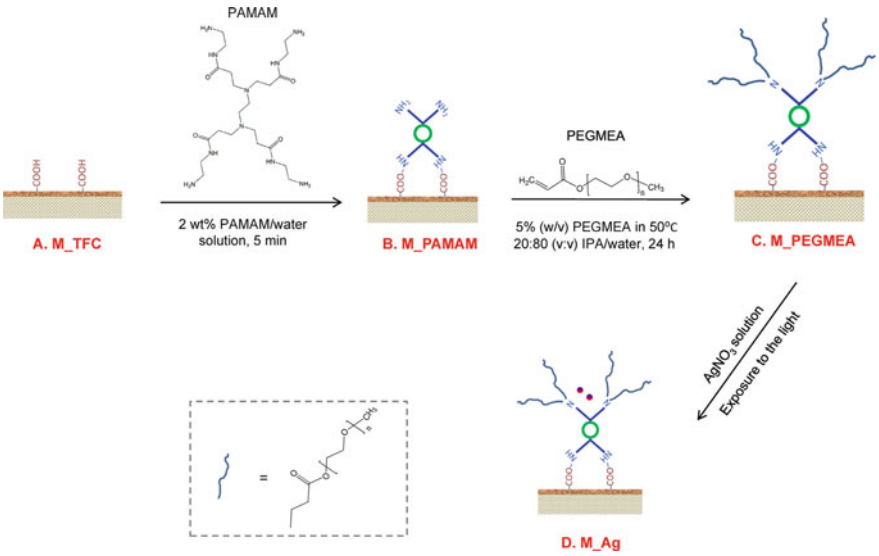


Fig. 5 Schematic diagram of the synthesis of silver–PEGylated dendrimer nanocomposite on the thin film composite membranes [63]

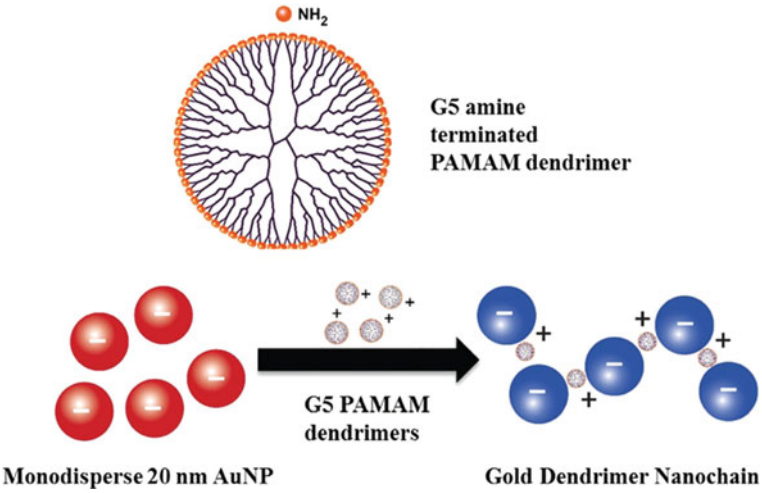


Fig. 6 Schematic representation of the chemical structure of a Generation 5 PAMAM dendrimer and the plausible mechanism of self-assembly of gold nanoparticles (20 nm) with dendrimers to produce electrostatic interactions driven one-dimensional 'nanochains' [64]

2 Applications and Toxicological Evaluations of Gold Nanocomposites

Recently, the use of gold nanoparticles to synthesize different biocompatible nanocomposites has provided various new ways of treatment of different diseases. In cancer, the use of such nanocomposites is becoming popular day by day. In present times, the use of anisotropic gold in the form of nanoparticles has generated much interest amongst scientists all over the world because of the particles' unique properties such as optical, electronic, size- and shape-dependent, and chemical properties, which are completely different from those in bulk and elemental form [65–67]. Moreover, gold nanoparticles (AuNPs) has the potential to act as a photothermal agent [68–70].

2.1 Silica-Based Gold Nanocomposite

The conventional photo-absorbing agents, which are essential for converting radiation energy to heat, have many limitations due to their lack of stability and absorption of radiation. But the use of novel nanostructures has provided the way to overcome such limitations of the conventional agents. The silica-gold-silica (SiO_2–Au–SiO_2) nanocomposite has demonstrated a relatively broad extinction in the NIR region, which is significant for its photothermal effect [71]. Researchers have explored its potential as a photothermal therapy material in vitro in various cell lines of mammalian origin. Researchers have also used Au–SiO_2 nanocomposites for the detection of human ovarian cancer cells (HOC) [72]. By analyzing the optical absorption spectra, it was observed that the treatment of HOC with Au–SiO_2 nanocomposites made them susceptible to change the absorption spectrum in comparison with the control cells. For these reasons, the potential of clinical applications of AuNPs is presently an intense subject for research [73]. Current researchers also indicated that mesoporous silica-coated gold nanocomposites have a strong potential to diagnose and treat breast cancer. They seemed to be potent cytotoxic agents affecting triple negative breast cancer cell line like MDA-MB-231. But toxicological implications of these composites are yet to be evaluated. Questions still remain about whether these can be used in humans with little no side effects on humans and the environment.

2.2 Lipid-Coated Gold Nanocomposite

Liposomal nanoparticles are made up of natural lipids having the potential to encapsulate both water-soluble and insoluble drugs in their core. Their design is for controlled delivery of therapeutic agents enhancing therapeutic efficacy minimizing

side effects. Encapsulation or coating of metallic nanoparticles especially Au with lipids is a useful non-covalent approach to stabilize surface chemistry and to increase the compatibility of lipid-coated nanohybrids loaded with drugs at biological level [74–79]. In a study by Kang et al. it has been shown that the administration of docetaxel (DTX) in a lipid bilayer on the nanoparticles leads to the reduction of its side effects, thereby increasing its efficacy. DTX, an anti-cancer drug showed to effectively increase its intracellular delivery and therapeutic efficacy when administered with nanoparticles [80]. The uptake of drugs by the cells was significantly enhanced by this formulation and it also enhanced cytotoxicity compared to uncoated AuNPs and the free drug. The above-mentioned effects were because of cell-cycle arrest in the G_2/M phase of skin melanoma cell line B16F10 and breast cancer cell line MCF-7 cells with the increased population of sub-G_1 phase apoptotic cells. Thus drug-encapsulated lipid-coated nanoparticles have a scope to be used as a promising nanocarrier system for significantly enhanced cancer chemotherapy.

2.3 Manganese Oxide-Based Gold Nanocomposites

Macrophages and monocytes, two of the key components of host response to tumor cells, augments cell proliferation in the tumor microenvironment and in case of infections [81], along with the hypoxic condition, which is also very essential for the survival of tumors and this hypoxic condition can be clearly noticed in case of inflammation or solid tumor formation [82]. Suppression of the hypoxic condition by modulating the signalling pathways of Hypoxia Inducing Factor (HIF) with the use of gold-manganese oxide nanocomposite induces the subset of macrophages to revert back to a cytotoxic and anti-tumorigenic form [83]. This strategy of reversing hypoxic condition of the tumour microenvironment, through their effect on Tumor-Associated Macrophages, can be utilized as a mechanism to combat cancer. Moreover, broad near-infrared absorption of porous gold nanoparticle-manganese monoxide nanocomposites effectively increase the diagnostic time and also provides deeper photoacoustic imaging depth [84], which can be used to perform more accurate MR/Photoacoustic/CT tumour imaging in the human body.

2.4 Chitosan-Based Gold Nanocomposite

A group of researchers used Chitosan, a non-toxic biopolymer, along with gold nanoparticles to develop a nanocomposite that shows properties like the high current response intensity, a high electrocatalytic tendency towards H_2O_2 reduction, high stability, and good biocompatibility. Immunosensors prepared from this gold/chitosan nanocomposite can be used for high-throughput biomedical sensing and clinical applications, such as for the detection of prostate cancer using PSA

biomarker, without any sophisticated and complicated fabrication procedure [85]. Nanocomposite, constructed with gold nanoparticles (AuNPs), Carbon nano-onions (CNOs), single-walled carbon nanotubes (SWCNTs) and chitosan (CS) (AuNPs/CNOs/SWCNTs/CS) have been used to develop high-sensitivity electrochemical immunosensor that can detect carcinoembryonic antigens (CEA), which is a clinical tumor marker [86]. Along with the high sensitivity and excellent stability in the biological system, this immunosensor also provides excellent selectivity due to the property of resistance to interference in the presence of other antigens in the serum. Moreover, this platform can be utilized to design various highly selective and sensitive immunosensors to detect important biomarkers such as ciprofloxacin and immunoglobulin A (Fig. 7).

Apart from great application benefits, this type of nanocomposites also offers some health risks. The carbon nanotubes (SWCNTs) used in the above formulation can be hazardous to the people, especially who are producing or handling such nanomaterials. Inhalation of carbon nanotubes has potential to cause inflammation and granuloma formation in the lungs as they can reach the lower respiratory tract and can persist for a year or more. They can also translocate to other organs such as lymph nodes and pleura [87].

Many studies have also shown that nanocomposites composed of gold nanoparticles encapsulated by temperature-sensitive microgel are convenient colloidal systems with trapping capabilities [88, 89]. The biocompatibility of such composites can be used as a system for drug release in low solvent pH, for example in cancer therapy.

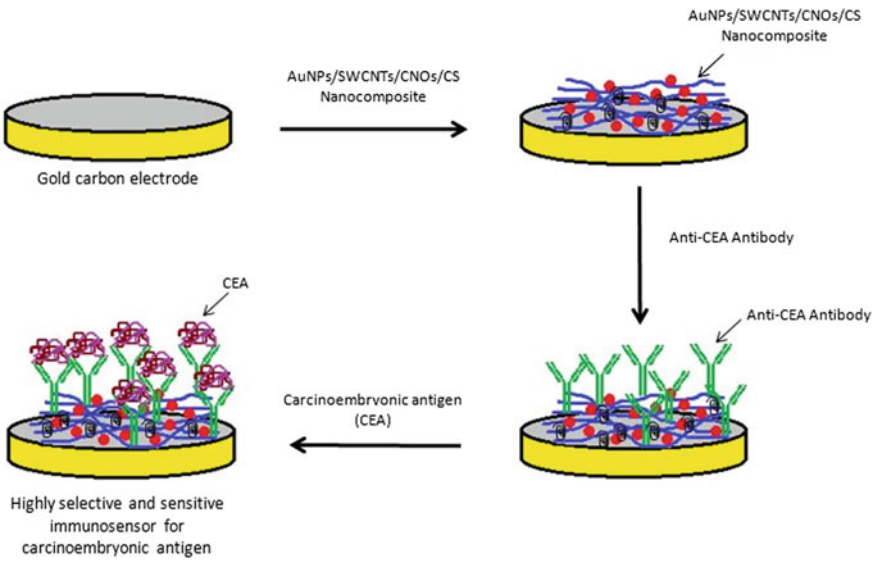


Fig. 7 Fabrication of a highly sensitive and selective immunosensor for carcinoembryonic antigen [86]

2.5 Graphene-Based Gold Nanocomposite

Not only in case of different biomarkers, but many studies have also depicted that these nanocomposites can be very efficient in determining the presence of different components in the environment, especially in the aquatic environment. Researchers have developed gold nanoparticle/Graphene nanocomposite that can be used to determine trace Chromium in water samples [90]. The hexavalent form of chromium acts as a strong oxidizing agent and shows carcinogenic and mutagenic properties, whereas the trivalent form is less toxic and studies have shown that it plays a vital role in many biological processes. So, it is of great importance to determine the level of trace hexavalent chromium in the water bodies to provide control for human and environmental concerns. The gold nanoparticle/Graphene nanocomposite sensors have been used to detect trace hexavalent chromium in the river samples of Indonesia as it shows high stability, high sensitivity, high electrocatalytic activity and low cost of analysis.

Graphene nanocomposites impart toxic effects on human erythrocytes, skin, fibroblasts and on different other cell lines. It is also extensively used in cancer research because of its unique set of characters that provide high mechanical strength and better stability preventing aggregation of the gold nanoparticles [91]. Researchers have constructed biosensors using graphene oxide based AuNP nanocomposite that can detect tumour mutations [92]. Gold nanoparticles were also added as functional agents in N_2- or S- doped graphene sheets (AuNPs-N_2-doped-GN or AuNPs-thiolated GN composite), that shows much enhanced SERS (Surface Enhanced Raman Spectroscopy) attributes on their electro-active surfaces [93, 94]. Along with these efficient diagnostic applications, these graphene oxide/gold nanocomposites have also been proven to be an efficient drug delivery system. Moreover, the whole process of drug delivery and release can be monitored by fluorescent-monitoring [95], making it a more efficient candidate for drug delivery in cancer treatments. Graphene oxide/gold nanocomposite loaded with daunorubicin enhances drug release into cancer cells by inducing morphological changes in cancer cell membrane. This also reduced P-glycoprotein expression and activated apoptosis in cancer cells in both in vitro and in vivo models [96]. Graphene nanocomposites are proposed as potent anti-cancer agents as they produce reactive oxygen species (ROS), induce cell cycle changes and might also initiate apoptosis.

In spite of these useful applications of graphene oxide as a composite with gold nanoparticles, it has some cytotoxic effects. Many in vitro studies reported that graphene oxide is cytotoxic to both normal and cancer cells when applied in high concentration and with long exposure time, though cancer cell lines showed more percentage viability may be because of its inbuilt resistance to cellular damage [97–100].

2.6 Dendrimer Stabilized Gold Nanoparticles

Multifunctional nanocomposites constructed by the researchers using gold nanoparticles stabilized by polyamidoamine (PANAM) dendrimers that can be used for combined detection of tumour cells through many processes such as flow cytometry, confocal microscopy, computed tomography, etc. [101]. These dendrimers are highly branched three-dimensional polymeric macromolecules that have highly configurable architecture. The biocompatibility and pharmacokinetics of this nanoconstruct can be adjusted by tuning the chemical synthesis of the dendrimer. Its high biocompatibility, high drug loading capacity and presence of multiple functional groups on its surface makes it a good candidate for photothermal therapy and targeted cancer therapy. Moreover, its good biodegradability and water solubility augment its use as a carrier for anticancer drugs [102–104]. It was also showed by researchers that incorporation of gold to dendrimer can actually lower the toxicity of dendrimer in a selective manner by modulating the physiochemical parameters of dendrimers.

2.7 Iron Oxide Gold Nanocomposite

Another construct with the gold nanoparticles is the Iron oxide/gold nanocomposite, which has immense importance in theranostics that is both in therapeutics and diagnostics. The flower-shaped iron oxide/gold nanocomposites possess a large number of magnetic domains, leading to enhanced magnetic properties that are helpful in magnetic resonance imaging (MRI) [105]. Not only in MRI, but this nanocomposite is also very useful in computed tomography (CT), Fluorescent optical imaging, hyperthermia and many more diagnostic processes. This nanocomposite has also been used as a carrier for drug delivery for chemotherapy such as cisplatin conjugated nanocomposite.

Several iron oxide-based nanocomposites with gold nanoparticles are under clinical trial to understand their toxicity, but only the dextran-coated superparamagnetic iron oxide is approved for human use by FDA. There are very few researches on the complete toxicological profile of the iron oxide nanocomposites and some of the researches are conflicting with each other. Moreover, some reports suggest superparamagnetic iron oxide be toxic on mouse fibroblast cells whereas reports have also shown that high concentration of this composite failed to show any toxicity.

3 Applications and Toxicological Evaluations of Silver Nanocomposites

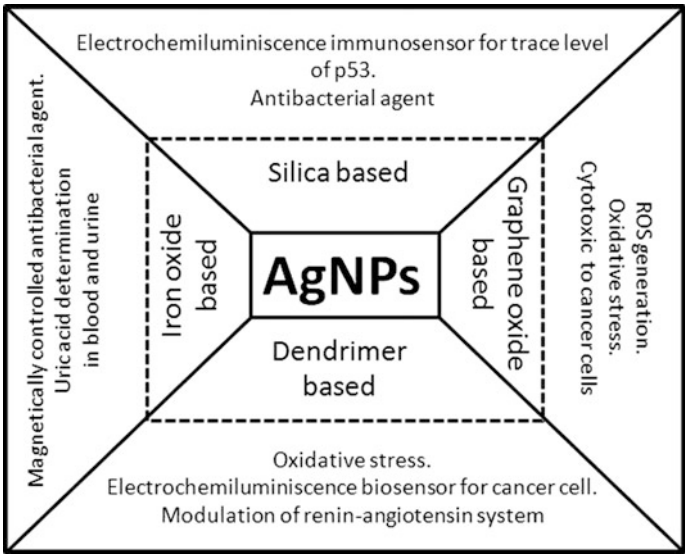
The nanoparticles and nanocomposites are popular for use in various fields for various reasons like high surface area-to-volume ratio, increased solubility of the drug and several others. But silver is definitely a suited choice for several others for

biocidal properties or microbicidal properties of silver nanoparticles (Table 1) or silver-based nanocomposites [106, 107]. Historically, before penicillin was even discovered, silver was broadly used to combat severe infections, especially for treatment of burns and chronic wounds. Even after the discovery of Penicillin, its use was revitalized in 1968 when silver nitrate was combined with sulfonamide to produce a silver sulfadiazine cream for treating burns [106]. Moreover, antibiotic resistance has imposed a major problem in using the antibiotic drugs available and very recently, silver-based nanocomposites have gained immense importance in instances of infections [108]. Presently, there are a number of medical products available, such as silver-based ointments and bandages that have been proven to be efficiently retarding and preventing bacterial infections [109]. Current researches mainly focus on the improvements in the development of novel silver nanoparticle (Table 1) and composites keeping in mind the wide use and antimicrobial properties of silver. Moreover, researchers are showing more interest towards the exploitation of silver nanoparticle to develop new biologically active materials so that the unique antibacterial properties of silver can be combined with the performance of the biomaterial [110–114]. Silver nanocomposites represent a promising strategy to fight against infections on used medical devices as a problem of proper sterilization as a major cause of hospital deaths in many places around the world. Besides having antibacterial properties, they are also antifungal and antiviral agents. Silver nanoparticles exert cytoprotective effects towards HIV-infected T cells by inhibiting the production of extracellular virions in vitro. They directly interact with the double-stranded DNA of HIV particles. But it is still not known how they affect other viruses. The effects of silver nanoparticles and nanocomposites on fungi are grossly unexplored. Though resistance to existing anti-fungal drugs are less commonly heard and it is not a menace like predominant antibacterial resistance, the long-term concern remains for different types of the antifungal agent as their options are really limited in the present world. Hence, researches are required to develop drugs with novel antifungal mechanisms. Recently, attention has focused on the potential of silver to be used as an antifungal agent, with experimental evidence that silver nanoparticles are capable of exhibiting potent antifungal effects, most likely by destroying the membrane integrity of fungal cells [115–117].

3.1 Graphene Oxide Silver Nanocomposite

The use of silver nanoparticles to develop different nanocomposites is getting very popular among scientists nowadays because of its versatility and high stability. The use of Graphene oxide/silver nanocomposite along with laser exposure (Photodynamic therapy) exhibits a synergistic effect, increasing cytotoxicity to the breast cancer cell lines [118]. This synergistic effect quickly produces reactive oxygen species such as hydroxyl radicals, superoxide ions and singlet oxygen, resulting in oxidative stress and can also include disruption of the cell membrane [119]. These properties of the graphene oxide/silver nanocomposite can be used in

Table 1 Silver nanocomposites and their biological implications



future for biomedical applications, especially in targeted cancer therapy. But it should be mentioned that researchers with two lineages of macrophages—a tumour lineage (J774) and peritoneal macrophage collected from Balb/c mouse showed that graphene oxide silver nanocomposite was toxic and induced significant ROS generation compared to silver nanoparticles, though graphene oxide/silver nanocomposites entered less inside cells. Hence the fate of the nanocomposites used should be carefully monitored and is a major concern in developing biocompatible materials.

3.2 Iron Oxide-Based Silver Nanocomposite

The magnetic iron oxide/silver nanocomposites show high anti-bacterial activity, which was tested against *E. coli*. This nanocomposite can also be used as an antibacterial agent which could be magnetically controlled in different biomedical applications. The reason behind it is the fact of the super magnetic properties of the iron oxide nanoparticles are not affected by the modulation of silver ions [120]. A group of researchers has also studied iron oxide-silver oxide quantum dots (QD) decorated cellulose nanofibres as a drug carrier for skin cancer therapy. They introduced two drugs Etoposide and Methotrexate to the melanoma cells in assistance with Fe_3O_4–Ag_2O QD/cellulose nanofibre carrier and showed that the cell viability decreased [121]. This study also indicated that a high number of unloaded

nanocomposites were not cytotoxic. Iron oxide-based nanocomposites did not induce any possibility of liver or kidney toxicity. On the other hand, silver nanoparticle alone resulted in increased serum alkaline phosphatase, calcium as well as lymphocyte infiltration in liver and kidney, indicating organ toxicity. These results indicate that in vivo kinetics of nanoparticles are required to be studied to understand their hazards and also nanocomposites might be toxicologically less hazardous than the metal nanoparticle itself.

Moreover, polyaniline (PANI) supported iron oxide/silver nanocomposites is presently the composite adopted to develop a sensor for the tracing and assessing uric acid in human blood and urine sample [122]. High sensitivity, selectivity, and low detection limits augment its potential for various applications.

3.3 Dendrimer-Based Silver Nanocomposites

The silver/dendrimer nanocomposites are of great importance in modern day research. Scientists have already demonstrated several uses of this construct. Xin Jin and group have demonstrated that silver/dendrimer (PAMAM) nanocomposite labelled DNA probe shows high sensitivity and selectivity with significantly low detection limit [123].

Researchers have developed electro-chemiluminescence biosensors for HL-60 cancer cell detection from g-C_3N_4 nanosheets and silver-PANAM-luminol nanocomposites, which show great selectivity and low detection limit [124] and has the potential to be used as cell biomarker. 5-fluorouracil loaded silver/PAMAM nanocomposite synergistically induces oxidative stress on cancer cells which were marked by reactive oxygen species and reactive nitrogen intermediate generation, DNA condensation and cytoskeletal compaction, leading to cell blebbing and injury. This also turns on the p53 gene-mediated signalling pathway leading to apoptosis [125].

In addition to these versatile applications of dendrimer-based silver and gold nanocomposites, researchers have also demonstrated the adverse effect of different dendrimers on biological organisms. Researches indicate that the stability of some dendrimers in different physiological conditions varies considerably. In vitro studies in a fish cell line (PLHC-1) have depicted that the PAMAM dendrimer induces toxicity by the generation of reactive oxygen species, which is followed by DNA damage and cell death [126]. In vivo studies have also demonstrated that PAMAM dendrimers induce aggregation of different blood proteins and results in clots in blood vessels [127]. Administration of PAMAM dendrimer in the mouse model induce acute lung failure by modulating the renin-angiotensin system [128]. A considerable number of dendrimers have also been found to be accumulated in some other important organs of the body such as the liver, kidney, heart and in the brain of neonatal rabbit with cerebral palsy. Akhtar and group showed that PAMAM inhibits ERK1/2 and p38 MAPK phosphorylation in both the cortex and medulla region of rat kidney, modulating the MAPK signalling pathway [129].

Even the sub-lethal dose of this dendrimer effects growth and development of zebrafish adversely [130]. So, it is important to do more research on the surface modifications and drug release of such dendrimers for designing a more biocompatible dendrimer construct and make it more suitable for various biological and biomedical applications [131].

3.4 Silica-Based Silver Nanocomposite

Silica-based silver nanocomposites have been extensively used in biomedical fields, especially for developing immunosensors. Researchers have developed an electrochemiluminescence immunosensor for p53 with $Ru(bpy)_3^{2+}$/silver nanoparticles doped silica core-shell nanocomposite (RuAg/SiO2) that shows excellent electrochemiluminescence behaviour with wide linear range, high selectivity, stability and low detection limit [132]. It efficiently detects trace level p53, so can be a very useful tool to be used as a tumour biomarker. Moreover, Yiyan Song and the group have prepared nanocomposite of polydopamine/silver nanoparticle on mesoporous silica (SBA15) that has potential as an antimicrobial agent along with the industrial role as a catalyst [133]. This composite successfully inhibited the growth of *E.coli*, *S. aureus*, and *A. fumigatus*. Mesoporous silica/silver nanocomposite (Ag-SBA-15) also shows high Hg^0 capture capacity with high ability of regeneration and high recyclability, therefore can be used as a catalyst to capture Hg^0 from coal-fired power plant flue gases [134]. These depict the importance of silver/silica nanocomposites in both environmental as well as biomedical applications.

4 Conclusions

In this chapter, different synthetic methods to prepare metal nanocomposites based on recent studies are well described. There is a large scope of future research developing facile, green synthetic route to synthesize metal nanocomposites minimizing the use of hazardous chemical reagents. Synthesis of nanocomposites on a metal base can be done by two different methods: in situ method and ex situ method as described before. Mesoporous metal oxide nanocomposites, silver/gold-supported graphene nanocomposite, silver/gold supported polymer nanocomposites and silver/gold-supported dendrimer nanocomposites are a few varieties of nanocomposites whose synthesis have been discussed in this chapter keeping in mind their wide research usage in causing cell cytotoxicity, in experimental cancer therapy, in antibacterial activity and antifungal activity and in developing immunosensors to name a few. Their roles in the biological system have made it exigent to study and understand the toxicological evaluations of the same in the system as well as to the person exposed to it.

Silver, gold, graphene nanocomposites have shown promising evidence indicating their importance in cancer research and various other fields. They have promising cytotoxic effects on various cancer cells and have potent antibacterial and antifungal activities. But, in spite of their goodness in terms of human healthcare, very few of the researches are actually translating into effective market available drugs and have reached the stage of clinical trial. The reason behind the lag between innovative research to identify new nanocomposites with immense biological potency and the effective market available drug is the dearth of research studies to evaluate the toxicity generated by the composites in the cell system, in animal models and in users who are actually working with the nanocomposites.

It is important to understand the control of the concentrations in using the nanocomposites to have the beneficial effects. Though there are a large number of researches are going on in this field, a systematic in vitro–in vivo extrapolation studies after the application of the nanocomposites is necessary. There are very little information available till to date about the toxic effects of the biomarkers, such as their immunomodulatory effect or ability to alter the genetic expression. In this chapter, the synthesis of nanocomposites relevant to biological research, their wide applications and toxicological evaluations have been discussed with special reference to cancer. But more studies are required on the toxicological implications of the nanocomposites to use them as our friends and not as foes. Intensive toxicological evaluation along with the ongoing research of finding new nanocomposites are required to effectively use nanocomposites in biological systems and as a tool for cancer therapy which will lead to the innovation of modern day target-specific drugs and new arenas in chemotherapy.

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