Review Article

International Journal of Bioassays
ISSN: 2278-778X
www.ijbio.com

GREEN NANOMEDICINE: AN ALCHEMY TOUCH TO CANCER TREATMENT

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Received for publication: February 28, 2013; **Revised:** April 09, 2013; **Accepted:** May 21, 2013

Abstract: This paper is an overview of advances and prospects in applications of nanotechnology for cancer detection, prevention and treatment. Here we address preventive measures, disease-time treatment, and diagnosis in the context of some of the most recent advances in nanotechnology. Nanoparticle science is also briefly addressed as the foundation upon which most nanotechnology cancer therapy is based. It is demonstrated how nanotechnology can help solve one of the most challenging and long standing problems in medicine using it's 3 basic methods: Conjagative nanoparticle, Laser ablation of tissues, Hyperthermic method; which is how to prevent cancer in current perspective. This has paved a path for an alchemy touch with our natural friends- "Plants" (Curcumin, Cinnamom, Gum Arabic, Polygala senega) to eliminate cancer without harming normal body tissue.

Keywords: nanomedicine, phytochemical, conjugative nanoparticle, cancer, anticarcenogenic

INTRODUCTION

The economic and societal impact of Green nanotechnology is revolution unfolds to unleash its power on our day-to-day lives. Green nanotechnology is an interdisciplinary rapidly developing knowledge base at the interface of chemistry, physics, medical, engineering. The convergence of nanotechnology and biomedical science opens the possibility for a wide variety of biological research topics and medical uses at the molecular and cellular level. Current and future research achievements in nanobiotech could ultimately lead to the development of revolutionary new modalities of biomolecular manufacturing, early diagonosis, medical treatment and disease prevention beyond the cellular level to that of individual proteins [14]. Biosynthesis is a kind of bottom up approach where the main reaction occuring is reduction/oxidation. The three main steps in the preparation of nanoparticles that should be evaluated from green chemistry perspective are the choice of the solvent medium used, the choice of an environmentally beingn reducing agent and the choice of a non toxic material for the stabilization of the nanoparticle [5]. Toxic chemicals are utilized in several of the processes for production of nanoparticles, either in the form of reducing agents to reduce various metal salts to their corresponding nanoparticles, or as stabilizing agents to prevent agglomeration of nanoparticles. For example, hydrazine and sodium borohydride are powerful reducing agents that are currently used to produce gold and other metallic nanoparticles[4,6]. These reducing agents are highly toxic to living organisms and to the environment, and care must be exercised in their proper handling and disposal of toxic chemicals.

Results indicate that large scale production of nanoparticles using phytochemicals occurring in natural resources such as plant species will minimize or eliminate chemical interventions, thereby resulting in true green and non-polluting eco-friendly industrial processes for the manufacture of nanoparticle-based smart materials [8,14]

Nanotechnology has at last provided a way for us to rearrange and restructure matter on an atomic scale, allowing us to reach down to the very roots of any problem. Provided that we can thoroughly understand the problem on an atomic scale and develop the know-how to turn our innovative ideas for the perfect solution into reality, we now have all the tools that we need to combat the highly scaring disease, cancer. [5,16]

Nanotechnology preventive approach

In fact, nanotechnology-based treatments are no more challenging to devise than the currently used disease-time treatment methods. Nonetheless, it requires time and monetary investments to develop such treatment methods in short time. Preventive treatments are not much good to those who have already developed the disease and since these are the people who require the most immediate medical help, it is no wonder that a majority of innovative treatments are focused here.

Pioneering work was carried out by the researchers to administer the nanoparticle drug formulation directly to the tumour cells. This was done partly to minimise the uptake of the spheres by macrophages and partly to improve the comparison of

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the effectiveness of this new treatment with Cremophor EL (drug for prostate cancer treatment). The results indicated the survival rates of the mice treated with the Cremophor EL suspension were much lower than those treated with conjugated nanoparticles. Furthermore, tumour growth, which was also monitored, was actually reversed with the use of conjugated nanoparticles at 24 mg/kg for the period of observation [34].

A second potential treatment landmarks to gold nanoparticles which readily absorb laser radiation and convert it to heat [5,12]. To achieve the desired results, one may use commercially available gold nanoparticles and conjugate them to certain recognition molecules engineered to target $CD8^+$ lymphocyte cells. To distinguish between $CD8^+$ and regular lymphocytes under a fluorescence microscope, a fluorescent dye (R-phycoerythrin) conjugated to anti-CD8 IgG antibodies was used. Each type of latex microspheres (Iron-oxide doped) was conjugated to recognise the CD8+ protein imbedded within the cell membranes. The cells under study were first labelled with a general fluorescent dye that was non-cell-specific. The cells were then conjugated to both kinds of particles and the population labelled with latex microspheres was analysed by a FITC fluorescence microscope. The cells were briefly irradiated with a 532nm or 565nm laser for 10 ns pulses for the nanoparticle run.These were kept approximately 100 ns after irradiation. The observations showed an interesting phenomenon known as cavitation due to phase transition. Cavitation is caused by the rapid temperature increase, which causes the water in the immediate vicinity of the particle to vapourise and to form a bubble as the vapour pressure overcomes the surface tension of the liquid. As the bubble grows in volume, it cannot sustain itself and collapses inward. The impact can be so violent that for smaller particles, it can cause fragmentation. Particle fragments have been observed which support this phenomena[25]. This phenomena is believed to be the mechanism of cell destruction and responsible for the subsequently observed cell death. Cell death was confirmed by the leaking out of the fluorescent dye due to lacerated cell membranes.

The conclusions to be drawn from this study are that light-responsive nanoparticles are potent tools for nanosurgery and cancer treatment. They are highly effective cell-destruction agents that can be targeted quite effectively at specific cell types by the use of the appropriate recognition molecules. As one of the leading applications of nanoparticles, this technique deserve extra attention from prospective researchers. In fact, some current investigations have successfully applied this technology to biological systems *in vivo* [8,14,17]. A study done on mice has recently shown to be just as effective in leading to complete remission and elimination of malignant tumours, and is scheduled to enter clinical trials in humans in the near future [34] . Finally, the third nanoparticle method for direct cell destruction to be discussed is the magnetic nanoparticle hyperthermia method[43]. This study was done *in vivo* with murine mammary carcinoma cells transplanted in the hind leg of mice. The mice were treated for 30 minutes at a steady intratumoural temperature of 47°C. The study was the first to use nanoionised particles to achieve hyperthermic conditions and has managed to prove the method to be quite effective[44].

In the study, nanoparticles were used to coat the tumour cells, which were then subjected to magnetic fields from 50 kHz to 100 kHz using a prototype AC magnetic field applicator. One benefit of using this method is that it can be applied internally, thus opening up the prospect of treating types of cancer that involve deep-seated tissues and organs. The particles, which consist of aminosilan shell magnetite with a core diameter of about 10 nm, are strongly adhesive to human colon adenocarcinoma cells. However, this effect is either far decreased or not observed at all with other kinds of cells, making prospective conjugation to recognition ligands (artificial antibodies) [42].

Furthermore, basic anatomy and biology tell us that cells within the human body get a vast majority of their nutrients and energy from the bloodstream, and likewise use the bloodstream to eliminate the toxins. Cells that are cut off from circulation quickly undergo necrosis and are effectively eliminated. Therefore, our goal is to separate the tumour from the circulation in order to kill it. Numerous studies have explored the possibility of isolating cancer tumours from the bloodstream. One that is exemplary will be discussed here [44]. The underlying principle of the study is that the cells within the growing tumour produce and send out basic Fibroblast Growth Factor (bFGF) accompanied by Vascular Endothelial Growth Factor (VEGF), the combination of which stimulates the development of new capillaries that grow into the tumour. The study used nanoparticles specifically designed to target cells that make up these freshly created capillaries by delivering to them ATPm-RAF, or pre-synthesised RNA (ribonucleic acid) strands responsible for inducing apoptosis. The nanoparticles consisted of a core of phospholipids, with the hydrophobic tails directed inward, which gave the outer surface of the particle a net negative charge. The charge allowed for facilitated conjugation of any desired DNA or RNA sequence to the particle's surface. Also imbedded in the core were integrin-antagonist lipids, whose tails were identical to the phospholipids tails, and whose heads served as the targeting moieties for the epithelial cells. As a result of intravenous

treatment with these nanoparticles in live mice, the newly formed capillaries were destroyed; cutting off the tumour from circulation and preventing further growth. The tumour cells underwent necrosis and were eliminated shortly thereafter.

Carbon nanotubes [13] possess interesting property of adsorbing materials on their surface and heating up upon absorbing near-infrared light wave. In one study they showed that cancer cells tend to be coated with folate receptors, whereas normal cells are not. This is how carbon nanotubes target to cancer cells. When exposed to near-infrared light, carbon nanotubes quickly release excess energy as heat (~70°C), which can kill cancer cells[42].

Cancer and other disorders often require repeated administration of medication, making the development of nontoxic pharmaceuticals of major significance in modern treatment protocols. From the above discussions, it is clear that gold nanoparticulate vectors can play a significant role in the advancement of clinically useful diagnostic and therapeutic medical products. A serious drawback in this effort is the rarity of nontoxic gold nanoparticulate constructs and formulations that can be administered as described.

Novel nanotechnologies and delivery systems of curcumin:

Diverse curcumin formulations have been developed with different nanotechnologies consisting of its encapsulation or conjugation with nanoparticles, polymeric micelles or liposomes to improve its stability, bioavailability and specific and sustained delivery into cancer cells and, consequently, its anticarcinogenic effects (Fig.1) [19,21,40]. For instance, it has been shown that the curcumin encapsulation in biodegradable and biocompatible poly (lactic-co-glycolic acid) (PLGA) nanospheres resulted in an enhanced intracellular uptake of curcumin-loaded polymeric nanospheres and improved cytotoxic effects of curcumin on metastatic LNCaP, PC3 and DU145 prostate cancer cell lines *in vitro* relative to free curcumin, *via* the inhibition of NF-κB activity [20,40]. Similarly, a PLGA nanoparticle formulation of curcumin conjugated with a monoclonal antibody specific for ovarian cancer cells also sensibilized the cisplatin-resistant A2780CP ovarian cancer cells to the anti-proliferative and cytotoxic effects induced by cisplatin or radiation *via* the down-regulation of the expression of β-catenin, Bcl-xL and Mcl-1 pro-survival proteins[40]. The complexation of poly-β-cyclodextrin (PCD) and curcumin was also effective at improving the intracellular uptake of curcumin into C4-2, DU145 and PC3 prostate cancer cells and its cytotoxic effects on these cancer cells as compared to free curcumin [37]. Moreover, the cyclodextrin-curcumin complex formulation was more effective than the free curcumin at blocking NF-κB-induced gene expression such as cyclin D1, MMP-9 and VEGF, mediating the anti-inflammatory and anti-proliferative effects on various cancer cell lines and inducing apoptosis in leukemia cells [39]. Moreover, the loading of curcumin into the copolymeric micelles of poly (ethylene oxide)-b-poly (epsilon-caprolactone) (PEO-PCL) has also been shown to be an effective strategy to enhance its solubility, metabolic stability and delivery in diverse cancer cells [36].

In addition, novel curcumin formulations have also been shown to improve the therapeutic effects induced by different chemotherapeutic drugs. For instance, the systemic administration of gemcitabine plus polymeric micelle-encapsulated curcumin formulation displaying higher bioavailability in plasma and tissues as compared to free curcumin, induced greater tumor growth inhibitory and antimetastatic effects than curcumin on pancreatic cancer cells subcutaneously or orthotopically implanted in nude mice *via* an inhibition of NF-kB and its targeted genes [3]. Moreover, the co-administration by oral gavage of liposomal forms of curcumin or resveratrol, prepared by mixing the phytochemical with the liposomal lipid 1, 2 - dimyristoyl - rac-glycero-3-phosphocholine, cooperatively reduced the incidence of prostatic adenocarcinoma development in prostate-specific *PTEN* knockout mice as compared to a single liposomal curcumin or resveratrol formulation [23]. It has also been shown that curcumin or resveratrol, alone or in combination, induced the growth inhibitory and apoptotic effects on PTEN-CaP8 prostate cancer cells derived from PTEN-knockout mice model of PC by the down-regulation of the expression levels of pAkt, cyclin D1, the mammalian target of rapamycin (mTOR) and AR proteins [23]

Hence, the use of these novel chemical analogs and nanotechnology-based formulations of curcumin represents a potential alternative strategy of great clinical interest for overcoming the high metabolic instability and poor bioavailability of curcumin, which are among the principal factors limiting its therapeutic effects when administrated orally.

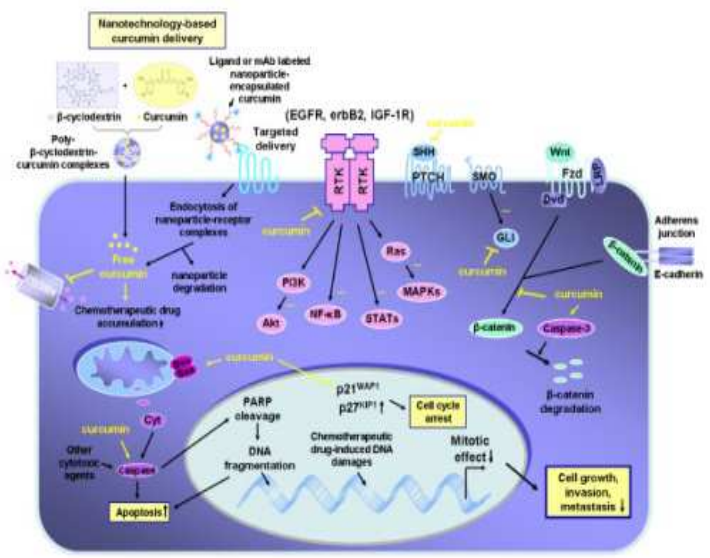

Fig.1: Tumorigenic cascades initiated by different growth factors in cancer cells and the anticarcinogenic effects induced by dietary curcumin on the transduction signaling elements.
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The inhibitory effect of curcumin on the expression and/or activity of EGFR, erbB2, IGF-1R, and their downstream signaling elements, sonic hedgehog (SHH/SMO/GLIs), Wnt/β-catenin and ATP-binding cassette multidrug transporters such as ABCG2 in cancer cells are indicated. Moreover, the enhanced expression of $p21^{WAP1}$ and $p27^{KIP1}$ cyclin-dependent kinase inhibitors and inhibition of mitotic effects induced by curcumin resulting in a cell cycle arrest and reduced expression levels of different gene products involved in the growth, invasion and metastasis of cancer cells as well as the activation by curcumin of mitochondrial factors and caspase pathway-induced apoptosis are also indicated. In addition, the scheme also shows novel nanotechnology-based curcumin delivery systems consisting of using either a poly(β-cyclodextrin)-curcumin complex formulation, or a polymeric micelle-encapsulated curcumin labeled with a ligand or monoclonal antibody (mAb) that specifically interacts with a receptor expressing by cancer cells for the selective targeting of curcumin are also illustrated.

Cinnamon mediated synthesis:

The application of phytochemicals available within soy, tea and cumin as dual reducing and stabilizing agents for the synthesis of gold nanoparticles have been reported [6,10,12] The utility of phytochemicals concluded within cinnamon as reducing and stabilizing agents to synthesize biocompatible gold nanoparticles from the precursor gold salts are dealt here. Phytochemical constituents of cinnamon include up to 1-4% of an essential oil, 5-10% polyphenols, 80-90% carbohydrates, and other ingredients that include gum, mucilage, resin and calcium monoterpenes oxalate.[16,18,20,22]

Detailed investigations encompassing (i) cinnamon phytochemicals mediated synthesis of gold nanoparticles (Cin-AuNPs) [28]; detailed characterization including size and shape analysis; (ii) cellular toxicity (cytotoxicity) on normal human fibroblast cells; (iii) cellular internalization efficacy of Cin-AuNPs under in vitro conditions with cancerous (PC-3 and MCF-7) cells; (iv) efficacy of Cin-AuNPs toward in vitro detection of cancerous cells (PC-3) using photoacoustic technique; (v) *in vivo* biodistribution of Cin-AuNPs in normal mice; and (iv) ability of Cin-AuNPs to serve as contrast enhancers for use in CT molecular imaging [31].

Attempted synthesis of gold nanoparticles from NaAuCl has been done with each of the major components present in cinnamon as phytochemicals (linalool, epicatechin, catechin and trans-cinnamaldehyde) depicting a narrow size distribution. The hydrodynamic size (155 nm) of cinnamon coated gold nanopaprticles is greater than the core size measured by TEM and DCS (32±2 nm) techniques. The negative zeta potential value (-31.0 mV) for the Cin-AuNPs provide the necessary repulsive forces for the particles to remain stable in solution [30]

Results of their experiments have unambiguously confirmed that cinnamaldehyde and linalool are the primary reducing agents to reduce Au(III) to gold nanoparticles. The carbohydrates present in cinnamon act as stabilizers for the gold nanoparticles. AuNPs demonstrated excellent *in vitro* stability under pH 4 to 9 range implying that these nanoparticles can be used in a wide pH range for various biomedical applications. number of live cells. The experiment performed using a wide range of concentrations of Cin-AuNPs (0, 0.25, 0.5, 0.75 and 1 mg/mL) showed cell viability to ~ 90% for 24 h post treatment. The primary aromatic aldehydes (e.g. benzaldehyde) showed reduction potential in the vicinity of -1.5 V, a value that is far below the reduction potential of [AuCl4]/Au (+0.99 V) [24]. Considering these values, a redox couple of NaAuCl -cinnamaldehyde is thermodynamically feasible and therefore cinnamaldehyde is able to reduce NaAuCl to gold nanoparticles.

Researchers have recently demonstrated internalizations[30]. To internalize negatively charged DNA molecules inside the cells, they utilized cationic ammonium ions as vectors which interact effectively with a negatively charged cell membrane, facilitating the charge-mediated endocytosis [31]. It is important to recognize that Cin-AuNPs also have a negative potential of -31.0 mV. This means that Cin-AuNPs are expected to show minimal or no interaction with a

negatively charged cell surface. The phytochemicals present in cinnamon when coated onto AuNPs provide optimal charge, hydrophobic pockets, and hydrodyanamic sizeall of which singularly or synergistically result in excellent internalization of Cin-AuNPs in PC-3 and MCF-7 cancerous cells. This unique synergistic cocktail effect of Cin-AuNPs may provide new opportunities for generating biocompatible AuNPs for applications *in vitro* [31] and *in vivo* nanoparticulate-mediated imaging and therapy[42].

Gum Arabic mediated phytonanomedicine:

The ability of plants to absorb and assimilate metals provides the potential to utilize plant extracts as nontoxic vehicles to stabilize and deliver nanoparticles for *in vivo* nanomedicinal applications. In this context, Gum Arabic (*Acasia* Gum) as a plant-derived construct for stabilizing gold nanoparticles [4]. Emulsification, acid stability, low viscosity at high temperatures, adhesive and binding properties and good mouth feel are among the reasons for its wide acceptance as an additive in confectionaries, beverages, bakery products, brewing, and in pharmaceutical formulations. In addition, Gum Arabic has unique structural features that made it turn to nano stabilizer. It has a highly branched polysaccharide structure consisting of a complex mixture of potassium, calcium and magnesium salts derived from arabic acid with galactose, rhamose, glucuronic acid, 4-O-methyl glucuronic acid and arabinos residues. Its molecular structure is comprised of three main components: the dominant being arabinogalactan (90%) which has a low protein content (5%), a high protein content (10%) segment with 10% arabinogalactan and the third component (<1%) contains glycoproteins with over 50% protein content. Recent studies [10] have produced a new class of injectable, *in vivo* stable hybrid nanoparticles derived from the tagging of Gum Arabic glycoprotein matrix with gold nanoparticles. Preliminary results of *in vivo* pharmacokinetics studies of GA-AuNP in pigs have demonstrated that these nanoparticulate phyto-constructs are nontoxic and thus may be utilized for human imaging and therapy applications. Results [14] demonstrated the ability of Gum Arabic to provide *in vitro* and *in vivo* stability to maintain the nanoparticulate properties of gold nanoparticles intact for several months in aqueous/saline/phosphate buffered solutions, as well as in the solid state, represent a significant advance.

Table.1: *in vitro* cytotoxicity assay of some crude protein extracts/purified protein using prostate cancer cell line (PC-3)

Plant Extract	IC50-SD (µg/ml)
White cumin- *Cuminum cymium*	>100
Black cumin-*Carum carvi*	83.51+-1.08
Methi –*Trigonella foenumgraecum*	46.89+-0.65
Kalonji- *Nigella sativa*	20.13+-0.41
Mako- *Solanum nigrum*	1.82+-0.16
Doxorubicin- standard	0.28

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Advancement in phyto nano medicne using PLGA coat

Only *Polygala senega* has been encapsulated using PLGA technique while most of the nanoformulations are based on metals especially gold and silver [20]. Gelsemium sempervirens; a homeopathic mother tincture is in the course of this direction by researchers. In 2010, first reportfor the ethanolic extract of Polygala senega (EEPS) was reported to have little or no cytotoxic effects on normal lung cells,but caused cell death and apoptosis to lung cancer cell line A549 [8]. The principal active constituent of *P. senega* are saponin glycosides polygallic acid and senegin, which make up 5% and 4% of the dried root. Their studies used ethanolic root extract of *P. senega* (EEPS) was nanoencapsulated (size:147.7nm) by deploying a biodegradable poly(lactic-co-glycolic)acid(PLGA) using a stabilizer (Pluronic F-68). The small size of the NEEPS resulted in an enhanced cellular entry and greater bioavailability. The growth of cancer cells was inhibited better by NEEPS than EEPS [40]. Both EEPS and NEEPS induced apoptosis of A549cells, which was associated with decreased expression of survivin, PCNA, mRNA, and increased expression of caspase 3 , p53mRNAs of A549cells. The results show that the anticancer potential of the formulation of EEPS loaded PLGA nanoparticles was more effective than EEPS per se. Therefore, nanoencapsulated ethanolic root extract of *P. senega* may serve as a potential chemopreventive agent against lungcancer.

CONCLUSION

An important aspect of cancer treatment is its early detection. There have been significant improvements largely due to breakthroughs, both, in the bottom-up and in the top-down nanotechnology. Developments in such areas as in nanoarrays, nanosensors, liposomes, monoclonal antibodies, improved nanoparticles (dendrimers, diamondoids, gold-based nanoparticles, magnetic nanoparticles, and quantum dots) and nanoelectronics are making early detection, prevention and treatment with a high degree of accuracy and ease possible. Also other recent discoveries and inventions in nanotechnology are suggesting that a safe and effective cure for cancer is just around the corner.

Despite the encouraging preamble and the abundant literature describing the molecular mechanisms triggered by phytochemicals to inhibit cell growth and induce apoptosis in cancer cells, only few of them entered clinical trials. Hence,there is a need to pay attention on a selection of representative molecules, namely isothiocyanate, curcumin, genistein, epigallocatechin gallate, lycopene and resveratrol, which largely are present in the literatures and reports conducted previously[18]. For each of them, their putative mechanism(s) of action from in vitro and animal studies, and the current status of their clinical application has to amalgmated with the upcoming technologies for the preparation of novel anti-cancer drugs.

REFERENCES

1. Shan B, Cai YZ, Brooks JD and Corke H. (2007). Antibacterial properties and major bioactive components of cinnamon stick (Cinnamomum burmannii): activity against foodborne pathogenic bacteria. *J Agric Food Chem*. 55: 5484-5490.

2. Shan B, Cai YZ, Sun M, and Corke H. (2005). Antioxidant capacity of 26 spice extracts and characterization of their phenolic constituents. *J Agric Food Chem.* 53: 7749-7759.

3. Bisht S, Mizuma M, Feldmann G, Ottenhof NA, Hong SM, Pramanik D, Chenna V, Karikari C, Sharma R, Goggins MG, Rudek MA, Ravi R, Maitra A, (2010). A: Systemic administration of polymeric nanoparticle-encapsulated curcumin (NanoCurc) blocks tumor growth and metastases in preclinical models of pancreatic cancer. *Mol Cancer Ther*, 9:2255-2264.

4. Fent GM, Casteel SW, Kim DY, Kannan R, Katti R and Chanda N. (2009). Biodistribution of maltose and gum arabic hybrid gold nanoparticles after intravenous injection in juvenile swine. *Nanomedicine:NBM* 5: 128-135.

5. Ferrari M. (2005). 'Cancer nanotechnology: opportunities and challenges', *Nat. Rev. Cancer*, Vol. 5, No. 3, March, pp.161–171.

6. Gupta V, Aseh A, Rios CN, Aggarwal BB, Mathur AB. (2009). Fabrication and characterization of silk fibroin-derived curcumin nanoparticles for cancer therapy. *Int J Nanomedicine*, 4:115-122

7. Haley B, Frenkel E. (2008). Nanoparticles for drug delivery in cancer treatment. *Urol Oncol*, 26:57-64.

8. Hindawi Publishing Corporation. (2011). Evidence-Based Complementary and Alternative Medicine; Polygala senega and It's Anticancer Potential of Root Extract of PLGA Nanoparticles-Encapsulated Form;,Article ID 517204,pp.13.

9. Usta J, Kreydiyyeh, P, Barnabe Y, Bou-Moughlabay and Nakkash-Chmaisse (2003). Comparative study on the effect of cinnamon and clove extracts and their main components on different types of ATPases. *Hum Exp Toxicol.* 22: 355-362.

10. Katti KK, Kattamuri V, Bhaskaran S, Kannan R and Katti KV. (2009). Facile and General Method for Synthesis of Sugar-Coated Gold Nanoparticles *International Journal of Nanotechnology: Biomedicine.* 1: B53-B59.

11. Katti K, Chanda N, Shukla R, Zambre A, Suibramanian T, Kulkarni RR, Kannan R and Katti KV. (2009). Green Nanotechnology from Cumin Phytochemicals: Generation of Biocompatible Gold Nanoparticles. *International Journal of Nanotechnology: Biomedicine* 1: B39-B52.

12. Kim NW, Piatyszek MA, Prowse KR, Harley CB, West MD, Coviello GM, Wright WE, Weinrich SLand Shay JW. Specific association of human telomerase activity with immortal cells and cancer, *Science*, Vol. 266, No. 5193, December 23, pp.2011–2015.

13. Au L, Lu X, and Xia Y. (2008) A Comparative Study of Galvanic Replacement Reactions Involving Ag Nanocubes and AuCl (2) or AuCl (4). *Adv Mater Deerfield* 20; 2517-2522.

14. Singh M, Manikandan S and Kumaraguru AK (2010) Nanoparticles: A new technology with wide applications; *Research Journal of Nanoscience and Nanotechnology*, ISSN 1996-5044.

15. Maher DM, Bell MC, Donnell EA, Gupta BK, Jaggi M, Chauhan SC. (2011). Curcumin suppresses human papillomavirus oncoproteins, restores p53, Rb, and PTPN13 proteins and inhibits benzo[a]pyrene-induced upregulation of HPV E7. *Mol Carcinog*, 50:47-57.

16. Mansoori, GA. (2005) Principles of Nanotechnology: Molecular Based Study of Condensed Matter in Small Systems, World Scientific Pub. Co., New York.

17. Mansoori, GA and Soelaiman, TAF. (2005) Nanotechnology – an introduction for the standards community, J. ASTM Int'l, Vol. 2, No. 6, Paper ID: JAI13110, p.21.

18. Russo M, Spagnuolo C, Tedesco I and Russo GL (2010) Phytochemicals in Cancer Prevention and Therapy: Truth or Dare?

19. Mohanty C, Acharya S, Mohanty AK, Dilnawaz F, Sahoo SK (2010) Curcumin-encapsulated MePEG/PCL diblock copolymeric micelles: a novel controlled delivery vehicle for cancer therapy. *Nanomedicine (Lond)*, 5:433-449.

20. Mukerjee A, Vishwanatha JK (2009) Formulation, characterization and evaluation of curcumin-loaded PLGA nanospheres for cancer therapy. *Anticancer Res*, 29:3867-3875.

21. Murielle Mimeault and Surinder K Batra (2011) Potential applications of curcumin and its novel synthetic analogs and nanotechnology-based formulations in cancer prevention and therapy. *Chinese Medicine* 2011, 6:31 doi:10.1186/1749-8546-6-31.

22. Armstrong NR, Quinn RK, and Vanderborgh NE. (1974).Voltammetry in sulfolane. Electrochemical behavior of benzaldehyde and substituted benzaldehydes. Analytical Chemistry 46: 1759-1764.

23. Narayanan NK, Nargi D, Randolph C, Narayanan BA (2009) Liposome encapsulation of curcumin and resveratrol in combination reduces prostate cancer incidence in PTEN knockout mice. *Int J Cancer*, 125:1-8.

24. Lopez P, Sanchez C, Batlle R and Nerin C. (2007).Vapor-phase activities of cinnamon, thyme, and oregano essential oils and key constituents against foodborne microorganisms. *J Agric Food Chem.* 55: 4348-4356.

25. Pitsillides CM, Joe EK., Wei X., Anderson RR and Lin CP. (2003) Selective cell targeting with light-absorbing microparticles and nanoparticles, *Biophysical J*., Vol. 84, June, pp.4023–4032.

26. Mimeault M and Batra SK. (2011) Potential applications of curcumin and its novel synthetic analogs and nanotechnology-based formulations in cancer prevention and therapy. *Chinese Medicine* 2011, 6:31 doi:10.1186/1749-8546-6-31.

27. Van Q, Nayak BK, Reimer M, Jones PJH and Rempel CB (2009). Anti-imflammatory effect of *Inonotus obliquus, Polygala senega and Viburnum trilobum* in screening assay", *Journal of Ethnopharmacology*, vol.125, no 3, pp. 487-493.

28. Gow RT, Li D, Sypert GW, and Alberte RS. (2007) Extracts and Methods Comprising Cinnamon Species. US Patent Application Publication US 2007/0292540 Al.

29. Shukla R, Nune SK, Chanda N, Katti K, Mekapothula S, Kulkarni RR, Welshons WV, Kannan R, and Katti KV. (2008). Soybeans as a phytochemical reservoir for the production and stabilization of biocompatible gold nanoparticles. Small 4: 1425-1436.

30. Gratton SE, Ropp PA, Pohlhaus PD, Luft JC, Madden VJ, Napier ME, and DeSimone JM. (2008).The effect of particle design on cellular internalization pathways.*Proc Natl Acad Sci* USA 105: 11613-11618.

31. Mathew S, and Abraham TE (2006). Studies on the antioxidant activities of cinnamon (Cinnamomum verum) bark extracts, through various in vitro models. *Food Chemistry* 94: 520-528.

32. Nune S, Chanda N, Shukla R, Katti K, Kulkarni RR, Thilakavathy S, Mekapothula S, Kannan R, and Katti KV. (2009). Green nanotechnology from tea:phytochemicals in tea as building blocks for production of biocompatible gold nanoparticles. *J. Mater. Chem.* 19: 2912-2920.

33. Bhatacharya SS, Paul S and Khuda-buksh AR. (2010) Encapsulated plant extract (*Gelsemium sempervirens*) PLGA nanoparticle enhance cellular uptake and increase bioactivity *in vitro*, Experimental *Biology and Medicine*, Vol.235, no.6, pp. 678-688.

34. Sahoo SK., Ma W and Labhasetwar V. (2004) 'Efficacy of transferrin-conjugated paclitaxel-loaded nanoparticles in a murine model of prostate cancer', Int'l. *J. Cancer*, Vol. 112, No. 2, pp.335–340.

35. Paul S, Bhattacharyya SS, Boujedaini N, and Anisur Rahman Khuda-Bukhsh doi:10.1155/2011/517204.

36. Shay JW and Bacchetti, S. (1997) 'A survey of telomerase activity in human cancer', *Eur. J. Cancer*, Vol. 33, No. 5, April, pp.787–791.

37. Tang H, Murphy CJ, Zhang B, Shen Y, Van Kirk EA, Murdoch WJ, Radosz M. (2010) Curcumin polymers as anticancer conjugates. *Biomaterials*, 31:7139-7149.

38. Kattumuri V, Katti K, Bhaskaran S, Boote EJ, Casteel SW, Fent GM, Robertson DJ, Chandrasekhar M, Kannan R and Katti KV. (2009). Gum arabic as a phytochemical construct for the stabilization of gold nanoparticles: *in vivo* pharmacokinetics and X-ray-contrast-imaging studies. Small 3: 333-341.

39. Yadav VR, Prasad S, Kannappan R, Ravindran J, Chaturvedi MM, Vaahtera L, Parkkinen J, Aggarwal BB. (2010) Cyclodextrin-complexed curcumin exhibits anti-inflammatory and antiproliferative activities superior to those of curcumin through higher cellular uptake. *Biochem Pharmacol*, 80:1021-1032.

40. Yallapu MM, Gupta BK, Jaggi M, Chauhan SC. (2010) Fabrication of curcumin encapsulated PLGA nanoparticles for improved therapeutic effects in metastatic cancer cells. *J Colloid Interface Sci*, 351:19-29.

41. Krista A, Frankenberry D, Chaipan C, Bagni R, Wyvill K, Yarchoan R, and PathakVK. (2011) Lack of Detection of Xenotropic Murine Leukemia Virus-Related Virus in HIV-1 Lymphoma Patients, Advances in Virology, Volume 2011 Article ID 797820, 4 pages, doi:10.1155/2011/797820.

42. Alexandre Albanese, Peter S. Tang, and Warren C.W. Chan. (2012) The Effect of Nanoparticle Size, Shape, and Surface Chemistry on Biological Systems, Annual Review of Biomedical Engineering, DOI: 10.1146/annurev-bioeng-071811-150124, Vol. 14: 1-16.

43. Jordan A, Scholz R, Wust P, Fakhling H, Felix R. (1999) Magnetic fluid hyperthermia (MFH): Cancer treatment with AC magnetic field induced excitation of biocompatible super paramagnetic nanoparticles Journal of Magnetism and Magnetic Materials 201 413:419.

44. Lowery AR, Gobin AM, Day ES, Halas NS, Jennifer L. (2006) West Immunonanoshells for targeted photothermal ablation of tumor cells, International Journal of Nanomedicine 2006:1(2) 149–154.

Source of support: Nil
Conflict of interest: None Declared