Introduction

Nanotechnology can be termed as the synthesis, characterization, exploration and application of nanosized (1-100nm) materials for the development of science. The field of nanotechnology is enabling technology that deals with nanometer sized objects and is one of the most active research areas in modern materials science. Nanotechnology is an enormously powerful technology involving chemistry, electronics, biomaterials, biology, and medicine (De Vittorio et al., 2014; Mensah et al., 2015). Nanotechnology holds a great potential for early detection, accurate diagnosis, prevention and treatment of diseases. Now it is being utilized in medicine for diagnosis, therapeutic drug delivery and the development of treatments for many diseases and disorders (Kazuma and Tatsuma, 2014; Nikalje, 2015). There have been inspiring developments in the field of nanotechnology in the recent past years, by the development of numerous methodologies to synthesize nanoparticles of particular shape and size depending on specific requirements. Nanoparticles, because of their small size, exhibit different physicochemical properties in comparison with the bulk form of the same material. These properties of nanomaterials are currently receiving considerable attention, thus offering many new developments in the fields of biosensors, biomedicine, and bio nanotechnology and hence can be used to conquer some of the limitations found in traditional therapeutic and diagnostic agents.
Nanoparticles (NPs) have received extensive attention in plenty of areas, such as catalysis (Safari and Zarnegar, 2014, Cui et al., 2015) and sensing (Nishi et al., 2015), owing to their unique physical and chemical characteristics. Nanoparticles have unique properties and are exciting interest across a broad spectrum of potential applications, including medicine, cosmetics, electronics, innovative food products and environmental remediation.

The Ayurvedic Bhasma: The Ancient Science of Nanomedicine

Ayurveda is an innate science of ancient Indian tradition (Chaudhary, 2011). Ayurvedic medicine is age old tried, tested and trusted practice. Medicinal plants were mainly used for the preparation of curative agents at the time of Charaka and Sushuruta. The Indian alchemist, Nagarjuna for the first initiated the use of metals and minerals like - Swarna (gold), Rajat (silver), Tamra (copper), Abhrak (mica), Makshika (pyrites) etc as remedial agents in 8th century AD. These minerals were used in the form of bhasm (Kumar et al., 2006).

In ancient time metals, minerals like gold, silver, copper, etc. were heated to red hot/burned several times and then mixed with herbs and/or other medicinal agents, considerably changed the efficacy of certain Ayurvedic medicines without producing any harmful side effects (Pal, 2015). However the scientists of ancient times had not enough understanding that continuous burning and cooling of metals and minerals altered the physical and chemical properties of the parent metal. The nano sized particles were totally different from original particles in chemical composition and structure. Nano size not only enhances the surface area but also aid the drugs to reach the target site efficiently. The drugs produced by this method were not only more effective but had rapid action and required in smaller dosage. Thus, the use of metals and minerals became the strength of Ayurvedic therapeutics. Scientific analysis of metallic Bhasma by transmission electron microscopy and atomic force microscopy has demonstrated that the metallic particles are in nanometer dimension (Rai et al., 2008).

The application of nanotechnology to medicine, which is commonly referred to as nanomedicine, involves the use of nanosized materials for the purposes of prevention, treatment and diagnosis of disease (Nikalje, 2015). The aim of nanomedicine is to
revolutions, to health care system by fighting deadly diseases in more efficient ways (Giljohann and Mirkin, 2009; Cadet and Wagner, 2014). Nanomedicine, deals with the use of distinctively engineered nanomaterials to develop novel therapeutic and diagnostic modalities (Prasad et al., 2015). Currently nanomedicine is developing new medical products to revolutionize medical treatments and therapies in areas, such as imaging, faster diagnosis, drug delivery and tissue regeneration. Applications of nanotechnology in diagnosis of disease are developing rapidly and methods in nanoscience are urging the development of more sophisticated tools for delivering drugs to specific sites, early detection of diseases and performing neurosurgery.

Oxidative stress plays an important role in the pathogenesis of many diseases. Humans are exposed to various kinds of xenobiotics, which are constantly generating free radicals. Drugs and antibiotics are normally specified as xenobiotics in humans and the body removes the xenobiotics with the help of liver (Lu et al., 2015). Natural resources such cosmic radiation and cellular metabolisms also create free radicals. The most commonly reported cellular free radicals are hydroxyl (OH·), superoxide (O2·−) and nitric monoxide (NO·). Molecules such as hydrogen peroxide (H2O2) and peroxynitrite (ONOO−) are not considered as free radicals, however in many cases they are reported to generate free radicals through various chemical reactions (Weidinger and Kozlov, 2015). Overproduction of free radicals can cause oxidative damage to biomolecules such as lipids, proteins and DNA, which eventually leading to many serious health problems such as atherosclerosis, cancer, diabetes, rheumatoid arthritis, myocardial infarction, cardiovascular diseases, chronic inflammation, liver injury, aging and other degenerative diseases in humans (Schwab et al., 2014).

**Hepatotoxicity: The most serious health problem**

The liver, one of the largest and most complex organs in the body, is a miracle worker; it purifies, detoxifies and also has a power of regeneration. Liver plays an astonishing array of vital functions in the maintenance of body homeostasis by performing multiple functions, including the growth, synthesis and production of enzymes, carbohydrate, protein and fat metabolism, fight against diseases, metabolic functions, detoxification of toxic metabolites, regulation of cholesterol and blood clotting, nutrient supply and energy provision (Valdivia-Correa et al., 2016). Liver is
located between the absorptive surfaces of the gastrointestinal tract and is the chief site for intense metabolism and excretion (Visentin et al., 2014).

Due to central role of liver in metabolism of virtually every foreign substance, it is susceptible to xenobiotic induced liver injury (Bjornsson, 2016). Certain medicinal agents, when taken in overdoses or sometimes within therapeutic ranges, may damage the liver (Woolbright et al., 2012). Chemicals that cause liver damage are called hepatotoxins. Hepatotoxicity is the most serious health problem in modern world and is a major cause of morbidity and mortality (Xie et al., 2016). About 20,000 deaths occur every year due to liver disorders (Xu et al., 2016). Unfortunately, conventional or synthetic drugs used in the treatment of liver diseases are inadequate and sometimes can have serious side effects. More than 900 toxins, drugs, and herbs have been reported to cause hepatocellular damage. Over consumption of anti-tubercular, anticancer, anticonvulsant drugs and alcohol are main causes of drug-induced liver injury (DILI) (Bjornsson et al., 2015). CCl₄, Paracetamol, Ethanol, Lead, Arsenic, Ephedra, Microcystsins, Aflatoxin also induced hepatic damage (Schulz et al., 2014). It has been noted that hepatitis, hepatic necrosis, hepatic steatosis, jaundice, cirrhosis, fibrosis, liver cancer are main cause of hepatotoxicity which ultimately leads to liver dysfunction (Pinter et al., 2016). Chronic liver disease is responsible for about 800,000 deaths a year due to cirrhosis and its complications (Crosas-Molist et al., 2014). Viral hepatitis, chronic alcohol consumption, and nonalcoholic fatty liver diseases are the most common cause of liver disease worldwide. All these conditions generate liver injury and inflammation, thereby activating liver fibrogenesis, which can progress to cirrhosis and the life-threatening complications of liver failure, portal hypertension and incident hepatocellular carcinoma as well (Blachier et al., 2013; Bridgewater et al., 2014).

**Facts about liver disorders**

- Approximately 7Lakh people die each year from hepatitis C related liver diseases (WHO, 2016)
- Approximately 75% of the idiosyncratic drug reactions result in liver transplantation or death (Kosanan and Boyina, 2015; Singh et al., 2015)
According to recent estimates, the yearly incidence of DILI is estimated to be between 14-19% cases per Lakh (Bjornsson et al., 2013; Chughlay et al., 2015)

Alcohol related liver disease accounts for 84% of liver deaths (British society of gastroenterology, 2015)

Hepatitis E can masquerade as drug induced liver injury in 3-13% of cases (Leise et al., 2014)

Chronic hepatitis B is the most common cause of viral liver diseases worldwide with over 350 million infected individuals (5% of world wide population) (Ganbarin-Gelwan, 2013)

Liver cancer is the 5th most commonly diagnosed cancer worldwide with over half a million cases diagnosed annually (Ganbarin-Gelwan, 2013)

Excess alcohol consumption is the main cause of liver related deaths. In France 69% of cases of liver cancer were attributed to heavy drinking (Carter et al., 2013)

1.3 million deaths worldwide are due to Chronic viral hepatitis (Tucker, 2013)

**Cancer: Challenge to scientific world**

Cancer is a deadly disease next to cardiovascular diseases due to unavailability of specific drugs. Cancer is the third leading cause of death in developed countries and the second leading cause of death in the United States (Torre et al., 2015). Cancer is a diverse class of diseases which differ widely in their causes and biology. The common thread in all known cancers is the acquisition of abnormalities in the genetic material of the cancer cell and its progeny (Blachier et al., 2013).

There were 10 million new cases, 6 million deaths, and 22 million people living with cancer worldwide in the year 2000 (Britton and Bogdanovica, 2014). These numbers represent an increase of about 22% in incidence and mortality from that of the year 1990. According to National Cancer Registry Programme estimates, 7-9 lakh new cancer cases occur in India every year (HSCIC, 2014; Chalasani et al., 2015). According to WHO each year about 15 million new cancer cases will be diagnosed by
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2020 worldwide (Bridgewater et al., 2014). Many challenges remain in treating cancer patients, including treatment-related adverse events, poor outcomes, the lack of a therapeutic target and balancing treatment toxicity with quality of life in patients with metastatic cancer who have already received extensive therapy. Therefore, there is still an urgent need for new therapeutic options for cancer.

Increasing global burden of cancer

With the continuing growth of the world’s population, the global burden of new cancer cases is estimated to rise:

- Worldwide there were an estimated 14.9 million cases of cancer diagnosed and 8.2 million cancer deaths were reported in 2013. Growing burden is in its alarming pace; in 2030 alone, about 21.7 million new cancer cases and 13.0 million cancer deaths are expected to occur (Siegel et al., 2015)

- About 8 million new cases each year and 24 million prevalent cases of cancer are reported in India (Nair et al., 2015)

- According to the cancer mortality profile, 357,500 {Mouth and oropharynx (18.3%), Trachea, bronchus, lung (13.6%), Stomach (11.4%), Colorectum(7.8%), Oesophagus (7.0%) other (41.8%)} deaths in male and 326,300 {Breast (21.5%), Cervix uteri (20.7%), Mouth and oropharynx (6.8%), Colorectum(6.4%), Ovary (6.0%) and other 38.7% } deaths in female have been reported (WHO, 2014)

Looking in to a variety of biomedical applications of Nanomedicine, we made a thorough literature survey and scientific experimentation and thus an attempt has been made for the evaluation of therapeutic potential of AuNPs and AgNPs in ameliorating cancer and xenobiotic induced hepatorenal injury prompted through model toxicant acetaminophen (APAP).
Therefore in the present study the aim and objectives are as follows:

**Aim**

Nanoparticle therapeutics: To investigate the therapeutic effects of silver and gold nanoparticles as an emerging treatment modality for cancer and hepatorenal disorders

**Objectives**

Evaluation of test drugs, AuNPs and AgNPs on:

- Cancer cell lines and primary hepatocytes
- APAP induced toxicity using battery of liver and kidney function tests
- Oxidative stress induced by model toxicant
- Drug metabolizing enzymes
- Regulation of cytokines; TNF-α and Interluekins-6
- Recovery pattern in histological and ultrastructural alterations
- APAP induced DNA damage by comet assay

**Test drugs:**

Gold and silver nanoparticles (AuNPs and AgNPs) (3-5nm) used in this study were procured from the manufacturer, Gold NanoTech, Inc., Taipei, Taiwan. Nanoparticles were prepared by physical vapor deposition (PVD), suspended in sterilized water, which maintains 99.99% purity of gold and silver nanoparticles, and the unique technology was applied to allow our AuNPs and AgNPs to be evenly dispersed in sterilized water. Therefore, unlike nanogold and nanosilver made with chemical reduction which requires the addition of dispersing agent to avoid the aggregation of nanoparticles, the gold nanoparticles used in this study are evenly suspended in water without addition of dispersing agent. This further increases the purity of nanogold. In addition, the 3-5 nm size of AuNPs and AgNPs used in this study can be efficiently excreted, and the nanoparticles do not accumulate inside the body.
Expected outcome of the proposed work

An attempt has been made for the evaluation of nanotherapeutic strategies of AuNPs and AgNPs in ameliorating most cancers and xenobiotic induced liver and kidney damage. Consequently, the present investigation will strengthen our understanding on the induction of apoptosis in cancer cells, non toxic effects on primary hepatocytes and protection of hepatorenal damage. The results will throw light on the mechanism of action related to the potential of drugs for the treatment of cancer and hepatorenal diseases at clinical and preclinical level, thus may help in the development of effective drug for the welfare of human kind.