Detection of cancer at an early stage is one of the principal factors associated with successful treatment outcome. However, current diagnostic methods are not capable of making sensitive and robust cancer diagnosis. Nanotechnology based products exhibit unique physical, optical and electrical properties that can be useful in diagnosis. These nanotech-enabled diagnostic representatives have proved to be generally more capable and consistent; as they selectively accumulated in the tumor site due to their miniscule size. This article rotates around the conventional imaging techniques, the use of carbon based nanodots viz Carbon Quantum Dots (CQDs), Graphene Quantum Dots (GQDs), Nanodiamonds, Fullerene, and Carbon Nanotubes that have been synthesized in recent years, along with the discovery of a wide range of biomarkers to identify cancer at early stage. Early detection of cancer using nanoconstructs is anticipated to be a distinct reality in the coming years.

**Keywords:** cancer, nanotechnology, cancer diagnosis, quantum dots, carbon nanodots, bioconjugation

**INTRODUCTION**

Cancer remains among the world’s most devastating diseases with about 20 million cases and 10 million deaths reported as of 2020. The disease is perceived by the condition wherein cells divide uncontrollably and attack different tissues. Most prevalent cancers include breast (11.6%), lung (11.4%), colorectal (10.0%), prostate (7.3%), and stomach cancer (5.6%) (Sung et al., 2021). Although significant progress has been made in diagnosing as well as treating cancer, yet it still accounts for a large number of fatalities.

Imaging techniques like computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and ultrasound are widely used in detecting different cancer types. These techniques are used to locate and visualize cancer but are expensive, need trained staff, cannot be taken to field condition, less sensitive and accurate for early cancer detection, and sometimes involve the use of toxic radiolabeled compounds. Albeit an intrusive biopsy after imaging accompanied by histopathological assessment is the preferred method of diagnosis but this invasive technique requires skilled manpower and is not useful in early cancer diagnosis. Non-obtrusive techniques are still in their infancy, however, of much interest, early cancer diagnosis combined with specific cancer therapies can increase patient survival (Chen et al., 2020). Nanomedicine, a novel research area that blends nanomaterials and medicine, can possibly aid the development of innovative diagnostic tools for detection of primary cancers at initial stages, and for effective cancer therapy (Bar-Zeev et al., 2017).

The possibilities of cancer diagnosis and treatment using nanotechnology are colossal. It has led to the creation of nanomaterials with novel surface architecture and properties, thus opening vast
avenues for manipulations at molecular level. Appending antibodies or other targeting agents onto nanocarrier surface for accurately targeting cancer cells is a promising approach for remedial and diagnostic oncology which is bound to take cancer therapy to an altogether different dimension (Farahavar et al., 2019). Nanotechnology is an incredible science not only to modify cancer diagnostics but also to provide detection strategies with higher dependability, sensitivity, and specificity.

Most of the standard chemotherapeutics are non-specific for tumor cells and exhibit toxicity to normal cells in vicinity. In this direction, localizing the drug at the tumor site reduces side effects associated with chemotherapy. Drug delivery systems based on nanotechnology extend the circulation of different chemotherapeutics in blood and improve their solubility (Sharma and Mondal, 2020). The development of biocompatible carbon-based nanomaterials for targeted diagnosis and treatment of diseases is an area of immense interest. This review attempts to give a quick overview of cancer and different imaging techniques used for its detection till date. Further, we aim to highlight emerging applications of nanotechnology, specifically carbon based nanodots for cancer diagnosis along with different bioconjugation techniques employed for this purpose. An extended information is provided in Supplementary file.

**CANCER AND ITS PATHOPHYSIOLOGY**

Cancer is a condition involving abnormal division of cells, which invade different tissues. Mutations in genes controlling division of cells gives rise to cancer, which further metastasizes. Typically, human cells grow and divide to create new cells, and therefore the older cells are continually shed and substituted with new cells. But since the lethal disease develops inside the body, this process is hindered. The cells hence become unusual, as damaged cells still survive within the body along with the new cells, while these aren’t actually needed. These additional cells divide ceaselessly, eventually driving tumor spread. The tumor may either be benign or malignant. Benign tumors are not recognized as destructive since they develop gradually and furthermore don’t attack tissues or spread to different parts of the body. On the contrary, malignant tumors spread irrepressibly, resulting in the speedy tumor growth. These tumors in turn attack various parts of the body, through various routes like lymphatic system, blood, and ultimately form new tumors. The human body is composed of trillions of cells, dividing at normal rate and speed. Development of cancer leads to change of normal cells to cancer cells. Cancer cells have different DNA than normal cells, which can trigger extensive damage in the body. The commencement of a cell getting changed into neoplastic cell takes place with change of proto-oncogenes to oncogenes. Proto-oncogenes are significant for typical cell development inside human body. Nevertheless, in contrast, oncogenes cause cell growth to vary and get faster. The second step towards formation of a neoplastic cell is popping off the tumor suppressor genes, which help in preventing cancer from propagating within healthy cells. These genes prevent cell growth, while turning these off ends up in abnormal cell growth and therefore quick division of cells (Figure 1). The last step is turning off of DNA repair genes. These genes are essential for normal functioning of cells and to detect any changes in the DNA. However, turning off these genes makes the cell unable to detect and repair any abnormalities.

**PRESENT DIAGNOSTIC METHODS**

In the battle against cancer, early detection is the key for effective disease treatment. This leads to significant reduction in disease related mortality. Of late, it has become easy to detect and treat cancer because of modern imaging methods and morphological examination of tissues (histopathology) or cells (cytology), which helps in early analysis of malignant growth. Imaging techniques such as X-ray, MRI, CT, endoscopy, and ultrasound can possibly distinguish malignancy when there is a noticeable change in the tissue (Hussain and Nguyen, 2014; García-Figueiras et al., 2019). However, these techniques are unable to differentiate between benign and malignant lesions. These techniques do not permit quantization of the real tumor volume in the specified area. Thus, developing technologies for identification of malignant growth at initial stages is an arduous challenge. Detecting tumors at an early stages is extremely crucial for treatment of cancer. For some cancer types, very few screening tests are available and many of those are not very reliable. Further, non-invasive screening is not available for most of the cancer types and few patients do not adhere to guidelines for screening (Chen et al., 2020).

For accurate cancer detection, nanotechnology based tools with enhanced sensitivity and specificity are being extensively developed (Garrigue et al., 2018). Advances in nanotechnology involve using NPs for non-invasive tumor imaging. Distinctive carbon-based nanomaterials such as CQDs, fullerene, etc. have been in use for cancer diagnosis (Abdolahad et al., 2013; Shi et al., 2014; Kalaiyarasan et al., 2019). A comparative summary of the conventional as well as the relatively new carbon based nanotechnological agents for various cancer diagnoses is provided in Table 1.

**NANOTECHNOLOGY FOR CANCER DIAGNOSIS**

The utilization of nanomaterials for clinical diagnostics and drug delivery is gaining importance. Nanotechnology based agents are used in assortment of medical tests and screens for example, the use of gold nanoparticles (AuNPs) for pregnancy test kits (Hartman et al., 2013; Zhou et al., 2015). NPs are also used to detect malignancy biomarkers (Ye et al., 2018; Amri et al., 2021) such as cancer associated proteins, circulating tumor cells (CTCs) and DNA (Wang et al., 2011; Hu et al., 2018), and exosomes (Martín-Gracia et al., 2020). NPs have enormous surface area to volume ratio in comparison to bulk materials. Due to this, surface of nanoparticles can be coated with different moieties like peptides, antibodies, aptamers etc. These moieties can not only bind but also detect cancer molecules. Tunable shape, size and other surface properties additionally impart proper compatibility.
with different routes of administration, high carrier capacity, and stability, thus rendering them exceptionally alluring for oncological research. These engineered NPs with high contrast bioimaging, fluorescence and carrier functionalities have become admirable tools for molecular diagnostics and delivery of therapeutics. With a reproducible particle size, narrow size distribution and simple synthetic routes; large scale, cost effective products significant for clinical translation can be produced (Bertrand et al., 2014; Chaturvedi et al., 2019).

Further information on role of nanotechnology in developing advanced diagnostic methods is mentioned in the Supplementary file.

The following sub-sections tend to highlight various engineered and functionalized carbon-based nanodots carrying a potential role in diagnosis of cancer.

**Carbon Quantum Dots**

Since the accidental discovery of carbon dots (CDs), also called carbon quantum dots (CQDs) during separation and purification of single walled carbon nanotubes (SWCNTs), their properties like low toxicity, biocompatibility, fluorescence, and chemical inertness have been utilized in theranostic fields (Figure 2) (Ding et al., 2014; Lim et al., 2015).

Fluorescent CQDs are better than organic dyes in aspects like hydrophilicity, biocompatibility, ease of preparation, and lower toxicity. Due to these reasons, CQDs are considered good for cancer detection. Fluorescent CQDs can be used as imaging probes. Metals like Gadolinium have been used in combination with CQDs, which not only reduce their toxicity to organs but also prevent their leakage (Huang et al., 2020; Jiang et al., 2021). Many fluorescent sensors for Fe³⁺ detection are being developed nowadays, most of them are based on CQDs. Abnormal levels of Fe³⁺ are associated with development of cancer and other diseases. A solution comprising CQDs with doped Fe³⁺ was able to distinguish cancer cells from normal cells majorly because of differences in GSH levels (Gao et al., 2018). CQDs also suppress cancer cells in vitro (Pardo et al., 2018; Jia et al., 2020; Su et al., 2020). For visual detection of cancer, green fluorescence CDs and corresponding probe with turn on fluorescence were designed. Cancer cells were imaged by interaction between carbon dots and folic acid. The probe was able to detect folate receptor (FR) positive cells with turn-on fluorescence (Liu et al., 2015). In another study, fluorescent carbon dots conjugated with folic acid that can bind to FR, were prepared. These carbon dots exhibited remarkable biocompatibility and were able to distinguish between normal cells and cancer cells with FR (Song et al., 2012).

**Graphene Quantum Dots**

Derived from graphene, graphene quantum dots (GQDs) have good biocompatibility, luminescence and dispersibility in solvents (Younis et al., 2020; Zhao et al., 2020). Because of their intrinsic fluorescence, GQDs are ideal for anti-cancer therapy, permitting effective tracking of cells in vitro (Dong...
et al., 2018; Zhang et al., 2018; Kortel et al., 2020; Iannazzo et al., 2021). GQDs also increase efficiency of anticancer drugs (Fan et al., 2019; Nasrollahi et al., 2019). GQDs are widely used for bioimaging, due to low cytotoxicity and strong optical absorption (Farwell et al., 2014; Liguori et al., 2015). In addition, fullerenes with anticancer drugs promote ROS production by phagocytes, a promising strategy for treatment of cancer (Skivka et al., 2018).

Fullerenes

Fullerenes (C_{60}) find application as drug carriers; by means of drug conjugation, fullerene enhances therapeutic effects for paclitaxel-embedded C_{60} (Rezaian et al., 2018) and with doxorubicin (DOX) (Liu et al., 2014; Maleki et al., 2020). Conjugation with fullerene makes the drug more hydrophilic and less cytotoxic; fullerenes also facilitate delivery of DNA into cells (Nitta et al., 2015; Illescas et al., 2020). In addition, these are also used as photosensitizers and more efficiently in photodynamic therapy; conjugation of C_{60} with poly ethylene glycol (PEG) enhanced their photosensitive effect. Endohedral fullerenes were used to stop angiogenesis and reduce vessel density in tumor tissues. Fullerenes act as immunomodulators and activate various immune cells by generating reactive oxygen species (ROS), thus killing cancer cells. Fullerenes also overcome tumor resistance to chemotherapeutic drugs and its derivatives are used as antioxidant species (Kepinska et al., 2018; Sergeeva et al., 2019). A study involving anti-cancer drug conjugated to C_{60} fullerene showed C_{60} to trigger phagocyte activity. In addition, fullerenes with anticancer drugs promotes ROS production by phagocytes, a promising strategy for treatment of cancer (Skivka et al., 2018).

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**TABLE 1** | A comparative summary of different conventional techniques and carbon-based nanomaterials used in early diagnosis of cancer.

| Technique                  | Principle                                                                 | Applications                                                                 | References                                                                 | Carbon based nanomaterial | Size | Applications                                                                 | References |
|----------------------------|---------------------------------------------------------------------------|------------------------------------------------------------------------------|---------------------------------------------------------------------------|---------------------------|------|------------------------------------------------------------------------------|------------|
| Computerized tomography    | X-ray beams are used and results are combined to form an image             | 1. In detecting bone and joint problems                                       | Farwell et al. (2014); Liguori et al. (2015)                              | Carbon quantum dots       | <10 nm | In bioimaging, as biosensors, catalysis, biomedicine delivery system          | Wang and Hu (2014) |
| Positron emission tomography | Radiolabelled tracer molecule administered inside the tissue; depicts image by means of photons/bright spots | 1. Neuroimaging                                                              | Anand et al. (2009)                                                       | Graphene quantum dots     | Few nm to ~100 nm | As photovoltaics, organic light emitting diodes, environment oriented applications, biosensors, cancer bioimaging (i.e., human epithelial cervical cancer) | Bacon et al. (2014) |
| Magnetic resonance imaging | Energy differences between alignment and de-alignment of protons by pre and post magnetic fields are calculated and image is formed | 1. Detecting inflammation, vascular abnormalities, and degenerative diseases | Faghini et al. (2017)                                                     | Fullerene                 | <5 nm  | As antioxidants for inflammatory diseases, anti-viral/anti-bacterial agents, diagnostic MRI contrast agents, theranostic for brain cancer | Delinger et al. (2013) |
| Ultrasound imaging         | Ultrasound waves get reflected by tissue/organ, thus form the image       | 1. Detecting changes in internal organs and tissues                           | Lizzi et al. (2003); Pugash et al. (2008)                                | Carbon nanotubes          | SWCNT: 0.4–3 nm diameter and 20–1,000 nm length MWCNT: 2–100 nm outer diameter 1–3 nm inner diameter and 1– several μm length | As carriers for anti-cancer drugs, for photothermal therapy of cancer, as carrier for immunoactive compounds and genetic material | Elhissi et al. (2012) |
Carbon Nanotubes

CNTs are used as contrast agents in medical imaging. They hold several potential advantages over other nano-sized detection agents, such as an exceptionally high surface area and the possibility for incorporating additional therapeutic and diagnostic moieties either on the surface or their inner cavity. The functionalized CNTs have tremendous potential as ultrasound contrast agent, exhibiting support for their future applications as theranostic tools. (Gao, 2018; Gu et al., 2018; Zhang et al., 2019; Zhang et al., 2020a). Photoacoustic imaging through nanotubes facilitates accurate tumor targeting. After conjugation of an MRI active contrast agent, nanotubes efficiently target tumors in magnetic fields. CNTs also facilitate drug delivery to target site and increase blood circulation after successful uptake by cancerous cells (Sanginario et al., 2017). CNTs are also used extensively in photothermal therapy of cancer cells (Lu et al., 2019).

On the basis of diameter and structure, these are further divided into two categories---single walled carbon nanotubes (SWCNTs), with single sheet of graphene in tube form with 0.4–3 nm diameter and multi walled carbon nanotubes (MWCNTs) which comprise of a few layers of graphite with

**FIGURE 2** | Carbon dots bound to anticancer drug effectively target the tumor cells and deliver the drug molecule at the cell surface, interaction of the drug with tumor cell results in its death.
TABLE 2 | Chart of different biomarkers and carbon based nanomaterials for cancer diagnosis and treatment.

| Cancer type | Biomarkers | References | Carbon-based nanomaterial for detection and/or treatment |
|-------------|------------|------------|--------------------------------------------------------|
| Bladder     | Nuclear matrix protein 22 (NMP-22), BTA Stat and BTA-TRAK, UroVysion, ImmunoCyt/Ucyt+, Uromonitor and Uromonitor-V2, UroSEEK, EpCheck, TERRap mutations and methylhydation | Batista et al. (2020) | • Graphene quantum dots Deng et al. (2020) |
| Breast      | Conventional and non-conventional markers: Estrogen receptor (ER), progesterone receptor (PR), nuclear antigen Ki-67, human epidermal growth factor receptor (HER) 2 MammaPrint®; Oncotype DX®, Prosigna®, EndoPredict® | Colorner et al. (2018) | • Carbon dots from N-hydroxyphthalimide (CD-NHP) Tiron et al. (2020) |
| Cervical    | Human papillomavirus DNA (HPV DNA), squamous cell carcinoma antigen (SCC-Ag), squamous papilloma, viral oncogene homolog (KRA), microsatellite instability (MSI-H+) | Kori and Yalcin Arga (2018) | • Carbon dots embedded molecularly imprinted polymers (C-MIP) Zhang et al. (2020b) |
| Colorectal  | Tissue-based biomarkers: serine/threonine protein kinase (encoded by RAF gene), Kirsten rat sarcoma viral oncogene homolog (KRAS), microsatellite instability (MSI-H+) | Vacante et al. (2018) | • Graphene oxide, carbon nano-ions Ibáñez-Redín et al. (2019) |
|             | Epigenetic markers: CpG island methylator phenotype (CIMP), adenomatous polyposis coli (APC) | Parikh et al. (2020) | • Hyaluronate functionalized graphene (HG) Jing et al. (2018) |
| Liver       | Alpha-fetoprotein (AFP) L3, des-γ-carboxyprothrombin, glypican-3, cytokeratin 19, golgi protein-73, midline, osteopontin, SCC Ag, annexin A2, circulating microRNAs, cell-free DNA | Parkh et al. (2020) | • Multi-wall carbon nanotube loaded with sorafenib Elsayied et al. (2019) |
| Lung        | Genomic biomarkers: Epidermal growth factor receptor (EGFR), Anaplastic lymphoma kinase (ALK), (KRA), ROS proto-oncogene 1, receptor tyrosine kinase (ROS1), HER2, RET proto-oncogene, MET proto-oncogene, BRAF proto-oncogene, BRAF, Phosphatidylinositol 3-kinase (PI3K), Neurotrophic receptor tyrosine kinase 1 (NTRK1), Fibroblast growth factor receptor (FGFR), Discoidin domain receptor tyrosine kinase 2 (DDR2) | Vilalobos and Wistuba (2017) | • Single-wall carbon nanotubes Aasi et al. (2020) |
|             | Immunotherapy markers in lung cancer: Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), Programmed death-ligand 1 receptor (PD-1) | | • Multi-wall carbon nanotubes with gold nanoparticles Quintana-Jaime et al. (2019) |
| Oesophagus  | p75 neurotrophin receptor (NTR) (CD271), CD44, aldehyde dehydrogenase (ALDH), CD90, intercellular adhesion molecule 1 (ICAM1), Cripto-1, ALDH1A1, CD133, CXCR4, ABCG2 | Liu et al. (2019) | • Hollow columbia spheres Zhang et al. (2017) |
| Prostate    | Aberrant serum PSA glycosylation (S2, 3PSA), prostates PCA3 assay, transmembrane prostatease serine 2 (TMPRSS2)- erythroblastosis virus E26 oncogene homolog (ERG) fusion gene, Mi-prostate score (MPS), oncofetal DX test, prolactin test, decipher genomic classifier (decipher GC), ProMark, Core 2 β-1,6-N-acetylglucosaminyltransferase-1 (GCDT1), circulating tumor cells (CTCs), urokinase plasminogen activator (uPA) | Hatakeyama et al. (2017) | • Simple wall carbon nanotubes Williams et al. (2018) |
| Stomach     | Carcinembryonic antigen (CEA), cancer antigen 19-9 (CA 19-9), CA12-4, AFP, CA125, HER2 | Matsuoka and Yashiro (2018) | • Multi-wall carbon nanotubes with gold nanoparticles Quintana-Jaime et al. (2019) |
| Thyroid     | Thyroid peroxidase, calcitonin, cytokeratin-19, hector battifora mesothelial antigen, galectin-3, Oep/p300-interacting transactivator with Gli/Asp-rich carboxy-terminal domain 1 (CITED-1), hepatocyte growth factor, epidermal growth factor | Arcola et al. (2017); Xiao et al. (2020) | • Nanodiamonds loaded with doxorubicin Qin et al. (2019) |

an inner diameter around 1–3 nm and outer diameter between 2 and 100 nm. Like other NPs, CNTs are difficult to dissolve in aqueous medium; hence, these are modified or functionalized, for improved biocompatibility (Chen et al., 2017b).

SWCNTs have applications in delivery of drugs (Kamel et al., 2018), proteins (Antonucci et al., 2017) and siRNA inside target cells (Ravi Kiran et al., 2020). Conjugation of SWCNT with DOX demonstrated better clinical efficacy in comparison to when DOX was used alone. Nanotubes are effective for administering cancer therapy in vivo (Mahajan et al., 2018). Another anti-cancer drug, Paclitaxel (PTX) in conjugation with SWCNT effectively suppressed tumors without causing toxicity to other organs, providing evidence that nanotube based drug delivery is favorable for cancer therapy due to high treatment efficiency and low toxicity (Yu et al., 2016; Hashemzadeh and Raissi, 2017). MWCNTs were used for developing magnetic nanocarrier using iron oxide NPs. MWCNTs thus developed showed dual targeted delivery (Boncel et al., 2017; Fan et al., 2018; Hossen et al., 2019). A new method for
delivering DNA and siRNA into microglia for brain cancer therapy via MWCNTs has been devised (Xiang et al., 2020).

**Nanodiamonds**

Nanodiamonds refer to a colloidal suspension of diamond particles. The use of these fluorescent nanodiamonds has started extensively, especially for bioimaging due to their low toxicity in comparison to quantum dots (Wei et al., 2019; Lai et al., 2020; Reineck et al., 2021). Nanodiamonds coupled to fluorophores are capable of targeting tumor cells without affecting cell viability and getting degraded due to changing pH (Yu et al., 2019; Liu et al., 2020; Perevedentseva et al., 2020).

Even the poorly soluble drugs can be adsorbed on the surface of nanodiamonds, which then mediate their slow and sustained release (Chipaux et al., 2018). The nanodiamonds based drug delivery systems are associated with reduced resistance to chemotherapeutics in different cancer types. DOX, considered effective for many types of cancer has been successfully adsorbed on nanodiamonds (called NDX). The resulting NDX particles were found to be taken up by living cells rapidly, facilitating drug delivery inside the cells. Another drug, epirubicin when adsorbed on nanodiamonds, leads to improved retention of tumor cells thereby killing cancer as well as non-cancer stem cells both in vivo and in vitro conditions. This prevents the formation of secondary tumors (Lai et al., 2020). Nanodiamonds have been used as vector for delivery of siRNA on sarcoma cells (Claveau et al., 2020). Detonation Nanodiamonds (DNDs) have been reported to be useful in radiotherapy. Irradiation of cancer cells resistant to radiotherapy is more effective when DNMs are incorporated inside the cells (Matshitse et al., 2020). For tumor therapy, delivery of sodium ions inside the cell has been easily carried out with the help of nanodiamonds (Chen et al., 2017a; Gupta et al., 2017). Nanodiamonds have been successfully used to target autophagy in tumor cells and promote their programmed cell death (PCD) in hypoxic conditions in vivo (Chen et al., 2018).

**Nanocantilevers**

Nanocantilevers can be coated with substrates that can selectively bind the target and detect even minute molecules in biological fluids. Binding of nanocantilevers to biomolecules changes the baseline probe frequency. These differences in frequency are measured by light diffraction pattern or by electrical means (Jabbari Behrouz et al., 2019). As the target sequence binds, the signal is transduced mechanically to surface of cantilever, resulting in its bending. Detection of cancer molecules can be done on the basis of deflection, which depends on the amount of DNA bound to cantilever surface and can be observed (Wang et al., 2016; Haring et al., 2017). This technology has been successfully used for differentiating between BRAF and its wild type gene in melanoma patients (Huber et al., 2013). The elevated levels of prostate specific antigen (PSA) are associated with increased risk of prostate cancer among men. Using antibodies bound to the surface of cantilevers, PSA assay was performed (Damborska et al., 2017; Basu et al., 2020).

**BIOCONJUGATION STRATEGIES FOR NANOTECHNOLOGY-BASED AGENTS**

The surface of nanodots must be modified for compatibility with biological systems in order to facilitate their in vitro and in vivo applications. Surface functionalization improves stability and water-solubility of nanodots, which can be further conjugated with biomolecules of interest for biomedical applications (Valcourt et al., 2018; Xu et al., 2020). Different techniques involving coupling are in use for a long time. There are two main strategies for conjugation of biomolecules: covalent and non-covalent binding. Non-covalent binding further involves coupling through direct absorption and electrostatic interactions (Foubert et al., 2016). As the name implies, direct absorption approach involves direct interaction of biomolecules with various NPs. Cell structures can be nonspecifically stained using hydrophilic NPs. Usually, the interaction is nonspecific and weak. Biomolecules with particular functional groups can be directly attached to NPs, e.g., thiol groups from cystine can bind proteins to noble metal NPs. Another methodology is to absorb biomolecules on surface of NPs through electrostatic interaction, e.g., positively charged NPs can be attached to negatively charged nucleic acid (Sapsford et al., 2013; Boehnke et al., 2020).

Covalent coupling involves precise and stable conjugation of biomolecules with NPs. Generally, coupling reactions to crosslink biomolecules are carried out on the surface of NPs using functional groups like carboxylic, amine, and thiol group. Carboxyl group coupling includes reaction of primary amines with carboxylic group. The coupling agent used is 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC). Additionally, stabilizing agents like N-hydroxysuccinimide (NHS) or sulfo-NHS enhance coupling efficiency by arrangement of a succinimide ester intermediate (Blanco-Canosa et al., 2014; Karakoti et al., 2015; Saallah and Lenggorn, 2018). Amine group coupling involves reaction of carboxylic group with amine group for forming an amide bond. The coupling reagent used is glutaraldehyde, which activates NH2-functionalized NPs. The aldehyde group produced throughout actuation will conjugate with amino groups of biomolecules (Barbosa et al., 2014; Zhang et al., 2015). Thiol group coupling involves conjugation of thiol group with primary amine groups. The reaction begins quickly using reagents like maleimides and iodoacetamides.

**CANCER BIOMARKERS**

Cancer markers assist detection of specific types of cancer in the body and in noticing the progression of cancer treatment. Cancer biomarkers register their presence in body fluids, blood or tissues that aid in detection of cancer cells and assist
in setting up specific diagnosis. This is particularly the circumstance when there is a need to decide if the tumors are primary or metastatic in origin. Many biomarkers specific to different cancer types have been discovered till date. These have crucial roles for early diagnosis of cancer. A description of some such biomarkers for different cancers is given in Table 2 along with an assortment of carbon nanomaterials used for the detection and/or treatment of cancer types. Detailed information on cancer biomarkers that aid the diagnosis of different cancer types is provided in Supplementary file.

CONCLUSION

Cancer nanotechnology holds promise in providing novel techniques for cancer detection at initial stages, resulting in improved diagnosis, and treatment. Conventional imaging techniques are exceptionally intrusive, non-specific, and are frequently associated with toxicity to both tumor and solid cells. The advancement of novel nanomaterials has enabled the identification of cancer biomarkers with more sensitivity and accuracy that was not feasible previously. Steady and coordinated exploration endeavors should be embraced to utilize tremendous capability of nanotechnology in distinguishing cancer growth in early stages, and monitoring the disease with treatment precision.

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All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fchem.2021.669169/full?supplementary-material

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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