REVIEW ARTICLE

Potential of Ligand Conjugated Metallic Nanoparticles in the Treatment of Carcinoma in the Delivery of Plant-Derived Payload

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Abstract

To attain the required therapeutic concentration of the drug at the target site with minimal exposure to normal cells, a targeted strategy is essential in cancer treatment. Because of its various advantages, a ligand-tagged bioactive medication is the ideal option. The use of natural therapeutic substances payload in the metallic nanoparticles conjugated with ligands is highlighted in the review. The most intriguing delivery system for these naturally occurring oncological medications is a nanoparticle-based drug delivery system because of its selectivity and specificity. Making a nanoparticle with metals enhances these benefits because of the synergistic profile in potential applications.

Key words: Cancer, metallic nanoparticle, ligands, targeted delivery

INTRODUCTION

The unique characteristics of metal nanoparticles are associated with their nanostructures. Metal nanoparticles and metal oxide nanoparticles have different properties because the metallic material is always separated from nanoscale particles.[1] Metal oxide nanoparticles and metal nanoparticles are exercised in various ways, for instance, reactant,[2] medication delivery,[3] augmenting amazing agents,[4] smart food packaging materials,[5] elements indicating nano-biosensor development,[6] transposition system, and nanoelectronic elements.[7] Metal nanoparticles are also used in the identification of microorganisms and pestilence and extended to application in germicides, antibiotics, and disinfectants.[8]

Green synthesis is employed for the making of metal nanoparticles and metal oxide nanoparticles by availing of complete biological structures or cells.[9,10] Distinctive segments or portions of the plant, such as cells, organs, extracts of cells or organs, or entire plant parts like roots, stems, bark, leaves, fruits, and seeds, serve as bio-reductive agents in green synthesis processes. This offers a sustainable and eco-friendly approach to the production of nanoparticles with potential biomedical applications. A significant advancement has been carried out in cancer research, along with the ability of potent drugs to have wide versatility. The obstacles are still there in the path of treatment efficacy which is often fruitless by the insufficiency of pharmaco-selectively to diseased cells, poor patient compliance, and impulsive drug toxicities. The advantages of plant-based green synthesis of a nanoparticle are presented in Figure 1. Therefore, inventive pharmaceutical remedies are required to successfully transport the cytotoxic drug to the tumor site specifically while reducing systemic exposure to persistent and elevated drug doses.[11]

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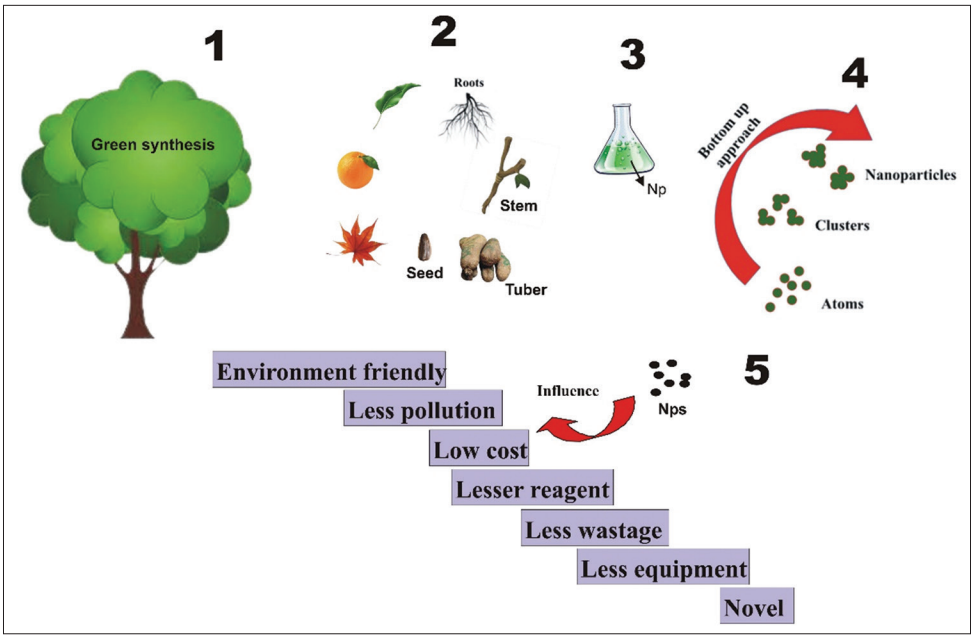

Figure 1: A prospective of green synthesis of nanoparticle and their benefits

Nanoparticles have been investigated widely for enhanced oncological use. Nanomaterials offer an efficacious therapeutic approach for skin cancer through targeted drug delivery. Through targeted cancer therapy minor differences can be differentiated between normal and cancer cells. As compared to the other conventional treatments, targeted therapies are generally more efficacious and exhibit reduced undesirable adverse effects. Administration of the drug in the highest tolerable dose is required when the drug delivery is non-specific and systemic resulting in rapid elimination of the drug which exhibits potential toxic effects and is also not pocket-friendly.[12] Nanoparticles-based nanosized carrier shows considerable prospects in aiming for cancerous cells that can be admissible, carry out elevated cargo loading, are adjusted to requirements, and are also biocompatible. Active targeting enumerates its worth to selective and site-specific treatment as compared to passive targeting. Paul Ehrlich envisions a nanosized drug dispensing system through active targeting over a century before. Vector molecules are the ordained of carrier's circulation and biological empathy on the specific site of action. Recently, many researchers have shown encouraging outcomes indicating that enhanced cancer therapy targeting nanocarriers constitutes a strategy full of promise.[13]

Targeted therapy has become the central component of cancer research with the implementation of mapping and profiling of specific tumour biomarkers identifying cancer cells and the expertizing of signal cascades implied in the pathogenesis of tumors. A targeted treatment approach is designed to create exceptional new anti-cancer therapeutics intended to precisely target some distinctive features of tumor biology. The targeted therapy approach is a wide and multi-colored platform where the miscellaneous discipline of research time after time is intercrossed. In cancer treatment, specific attention has been addressed to the active targeting of the nanosized delivery system.[13] This originates basically from the shortfall of conventional therapies; yet, the advanced understanding of cancer biology, and the finding of new molecular targets engaged in carcinogenesis, additionally with the emergence and clinical use of monoclonal antibodies (MAbs) and for targeting specific markers used by other macromolecules. A ligand conjugation with a drug moiety or carrier component best fits in active targeting, especially to treat cancerous cells, as it enables selective binding to overexpressed receptors on cancer cells, thereby enhancing therapeutic efficacy and minimizing off-target effects.

Metals can also be incorporated into the nanoparticles as they show high selectivity to cancer cells while having a lower affinity for normal cells thereby leaving their morphological functions unchanged. The incorporation of metal into the Quercetin-loaded nanoparticle can lead to bacteriostatic and antimicrobial effects. Cancerous skin tends to get dry, scaly, and itchy due to continuous wear and tear of the keratinized layer, the addition of metal to the formulation can result in the healing of the wounded skin. It is non-immunogenic and can restore the normal function of cells. Metal nanoparticles consist of distinct physical and chemical characteristics and are frequently contemplated due to their varied shapes and sizes in nanopharmaceuticals and diagnostics. It acquires non-immunogenic behavior, enhances stability, is biocompatible, and deliberates specific characteristics. Nanomedicine is useful in targeted delivery, gene delivery, protein delivery, drug delivery, and elevated cargo delivery by such kind of formulation. Furthermore, by coping with the presystemic metabolism, penetration of drugs can be improved. Above-mentioned facts are the basis for the inventors to explore metal nanoparticles as a drug delivery approach. Frequently used metals are copper (Cu), gold (Au) silver (Ag), silica (SiO_2), etc. in drug delivery.[14] Metal nanoparticles are easily

distributed in blood circulation and engulfed in the infected cell by the endocytosis process followed by the opening of the outer cover by endosomes and lysosomes. Finally, metal nanoparticles are attached to genetic material and stop the process of replication. A mechanism of action of copper nanoparticles in cell death is presented in Figure 2.

The principal motive of this review is to provide a framework for ligands associated with green synthesis resultant nanoparticles coming from fate growth. In various disciplines, appreciable breakthroughs have been accomplished due to plants as the magnificent source for the making of greener biological nanomaterials. In the pharmaceutical industry, fabricated greener biomaterials have a significant implementation for instance manufacture of effective nanomedicine and nanodevices.

SYNTHESIS OF NANOPARTICLES VIA PLANT EXTRACTS

To synthesize nanoparticles plants, establish specific provenance, and an ample number of biochemical features are provided by the plant's variations.[15] Plant leaf extract has many metabolites that function as a reducing agent in nanoparticle synthesis.[16] At room temperature, a solution consisting of metals like silver, gold, and copper is incorporated into the plant leaf extract.[17] The nanoparticle authenticity, amount fabricated, stabilization, and yield estimate are influenced by diverse circumstances like plant leaf phytochemical profile, exposure time, temperature, pH, and concentration of metal salt. Unlike plants, in microorganisms including fungi and bacteria, the metal ion depletion is decelerated as a consequence of the presence of dissolvable phytochemicals compelling extending brooding.[18] For metal nanoparticles and metal oxide nanoparticles, synthesis plant leaf extracts are contemplated as a magnificent vehicle as the phytochemicals can be effortlessly extracted from the plant leaf extract.[19,20] Nanoparticle synthesis with the aid of plant leaf extracts has an added advantage as it alone has both the attributes of stabilizing and reducing agents.[15] A comparison between the conventional and greener approaches for the production of metallic nanoparticles is summarized in Table 1. The nanoparticle synthesis is directly dependent upon the leaf extract composition as distinct leaf extracts have discrete concentrations of biomedical reducing agents.[21] In

Table 1: Comparison between conventional and greener approaches for metallic nanoparticle production

Chemical approach	Greener approach
1. Design nanoparticles that may be toxic.	1. Design nanoparticles that could be safe.
2. Utilize organic solvents and catalysts.	2. Employ safer reagents and solvents.
3. Non-renewable materials are applied.	3. Uses sustainable raw materials.
4. Chemical derivatives used.	4. Utilize no chemically derived products.
5. Stoichiometric reagents used.	5. Using Biocatalysts.
6. Product development without degradability.	6. Creation of biodegradable goods.
7. Accident risk is increased.	7. Less chance of accidents.
8. Waste accumulation is high.	8. Eliminate accumulating waste.
9. Bad Aerospace economy.	9. Elevated atom economy.
10. Possibly dangerous synthesis.	10. Less risky synthesis.

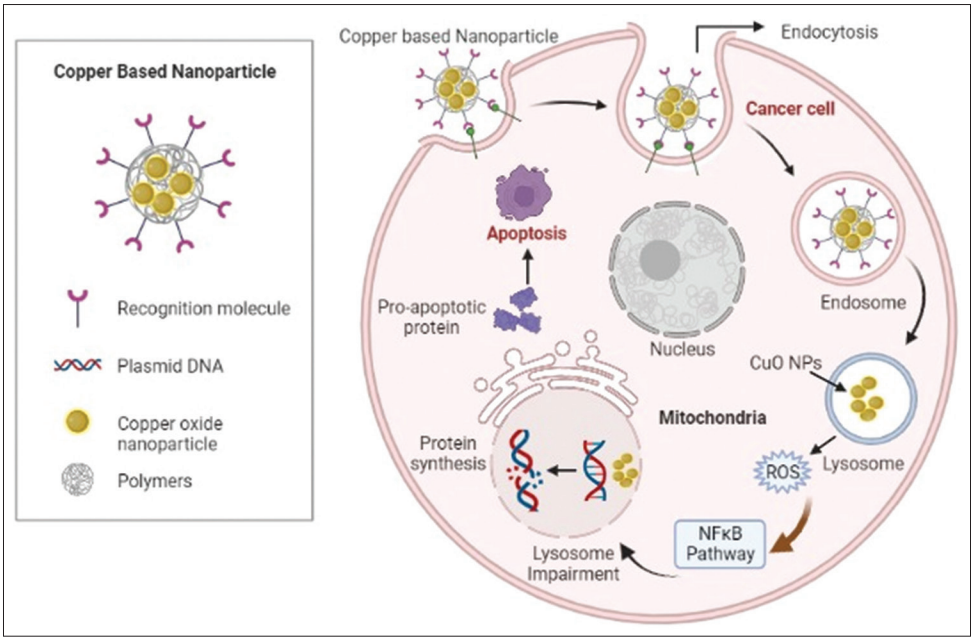

Figure 2: Mechanism of action of copper nanoparticle in cell death

nanoparticle synthesis, various significant phytochemicals such as ketones, aldehydes, flavones, amides, carboxylic acids, and terpenoids are engaged.[16]

The metal ion reduction and synthesis of metal nanoparticles proteins and carbohydrates present in plant extracts contribute to its specific part as a reducing agent.[22] In metal ion reduction, proteins and functional amino groups play a prime role in plant extract.[23] The metal nanoparticle formation is assisted by the functional groups of anthracenes, alkaloids, and flavones for example –C-O-C-, -C-O-, -C=C-, and –C=O-.[24] Leaf extract of the plant in particular conjugated cyclic diketones can conduct the metal ion depletion indicating that organic molecules and cyclic composite available in plants can accomplish the formation of extracellular metal nanoparticles, the entire mechanism of plant-aided metal oxide nanoparticles formation is yet to be understood despite its absolute inventiveness, formation of metal oxide nanoparticle example metal nanoparticle are resultant from the plant's phytochemicals. For the metal reduction phytochemicals of the plant, the extract is liable. The reduced metal ions are linked with each other by oxygen generation by photochemical degradation or by the atmosphere. Formation of the nanoparticles is conducted by the linkage of metal oxide ions with each other by electrostatic attraction. Agglomeration of nanoparticles is prevented by phytochemicals which further stabilizes them.[24] A preparation process and steps of plant-based nanoparticles are presented in Figure 3.

DRUG DELIVERY TO TUMOR CELLS VIA LIGAND TARGETING APPROACH

Ligands are classified into five broad classes. In the first heading, selective and non-selective ligands come. Selective ligands tend to bind to extremely restricted sorts of receptors, while on the contrary, non-selective ligands bind to numerous kinds of receptors. In pharmacology, this fact plays a crucial role, where non-selective drugs tend to have adverse effects since they bind to different other receptors along with the one giving the intended effect. The second type of ligand is an hydrophobic ligand. In this non-specific hydrophobic interplay, the propensity of a hydrophobic ligand in amalgamation with a hydrophobic protein i.g lipid-gated ion channels is intricate to establish. Non-specific hydrophobic interactions can be prevailed by increasing the affinity of ligands. The third type is a Bivalent ligand, It comprises a two-drug molecule attached by an inert linker. The Bivalent ligands are classified into several subtypes: - (1) Homo bivalent ligand: - In this two of the same receptor types are targeted. (2) Hetero bivalent ligand: - Two different types of receptors are targeted (3) Bitopic ligand: - Sites for binding of the substrates i.e., orthosteric binding sites and regulatory sites are targeted by a similar receptor.[25,26] Mono-and-polysemic ligands are identified by the number of polypeptide chains. In "monodesmic" ligands a single protein chain is bound with ligands whereas "polydesmic" ligands are protein complexes that are constant and are bound with multiple chains of proteins associated inside and nearby network of proteins.[27,28] The fifth Privileged scaffold is a molecular structure or synthesized component that is analytically recurrent amid familiar drugs or a particular group of biological functional composite.[29] For planning novel active biotic composite, these privileged elements can be utilized.[30]

Conjugation of ligands with nanoparticles is one of the finest ways to resolve the issues related to passive targeting of cancer-specific biomarkers due to defective vasculature, uncontrolled proliferation, and change in pH as demonstrated in Figure 4. Elements for instance aptamers, vitamins, carbohydrates, and peptides can be employed in the targeting.[31] It is obvious that for tumor cells to reach high

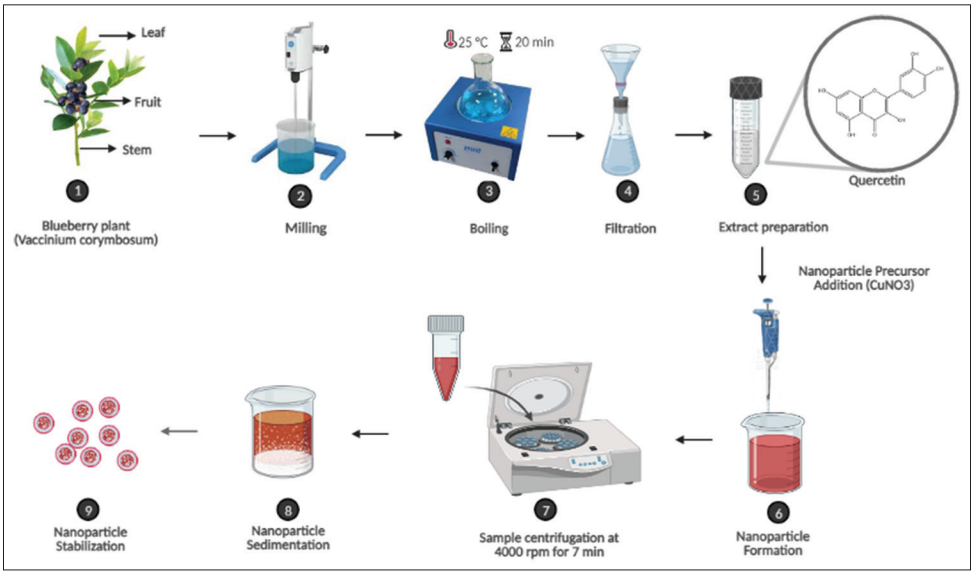

Figure 3: Steps involved in the preparation of plant-based nanoparticles

Table 2: Pros and cons of various ligands in targeting

A) Transferrin conjugated nanoparticles	Pros	• These are thoroughly investigated. • On metastatic and drug-resistant tumors, transferrin receptor is overexpressed. • For targeting cancer, variety of materials can be effortlessly conjugated with transferrin. • Transferrin-conjugated nanoparticles have high intracellular uptake. • Prominent tumor accumulation substantially delayed blood clearance and prolonged tumor residence time.
	Cons	• A nonspecific targeting and circulation. • Through extrinsically delivered transferrin, a rise in the heavy dose of iron transport into the brain can take place.
B) Protein Transduction Domains (PTDs) conjugated nanoparticles	Pros	• Through energy-independent processes, it has the potential to cross the cell membrane. • It has the capability that without negotiating with the biocompatibility of associated biomolecules it can effectively internalize. • Degradation from protease or nuclease can be inhibited by peptides thereby shielding the bioactive conjugates. • Eventually enhancing the cargo's serum half-life. • Higher biological safety & lower cytotoxicity.
	Cons	• Alteration in the biological activity of conjugates in some cases. • The mechanism of Protein transduction domains transmembrane is still not accurate.
C) L D L conjugated nanoparticles	Pros	• LDL nanoparticles are biocompatible as it is a natural carrier. • LDL particles escape recognition by phagocytes as it is non-immunogenic. • The empathetic shell can be filled up by Amphiphilic drugs while on the contrary hydrophobic drugs are pervaded in the hydrophobic core. • LDL has the capability of a large core. • In most tumor cells, LD LR is highly expressed. • By both receptor and non-receptor-mediated pathways uptake of LDL particles occurs.
	Cons	• LDL receptors exist in normal cells. • LDL receptors are expressed by a few of the normal tissues whereas it is not overexpressed by several carcinomas. • The introduction of pathogens is concerning as LDL particles are derived from human blood.
D) Integrin-modified nanoparticles	Pros	• Survival, proliferation, invasion, migration, and diverse functions in tumor cells are managed by integrin signaling. • various cancer cells, some integrants are highly overexpressed. • During angiogenesis on endothelial cells, some integrants such as avB3 and avB5 are induced. • Cell surface receptors are completely approachable.
	Cons	• Normal cells also Integrins exist
E) Carbohydrate-modified nanoparticles	Pros	• To improve the absorption and bioavailability of poorly absorbable drugs • It can be utilized in an effective oral delivery system. • Interactions with carbohydrates based on endogenous lectin are glycotargeting. • Improved bioavailability of the formulation results from the shielding effects of the nanocarrier and cytoadhesive characteristics of the lectin.
	Cons	• In glycotargeting to acquire sufficient binding strength, it frequently needs multiple interacting carbohydrates. Some level of toxicity followed by evoked immune response is carried out by lectin.
F) Folate-modified nanoparticles	Pros	• Although in normal cells and body part, folate receptor's appearance is confined a large part of malignant cells upregulate it. • Folate is pliable for chemical alterations in precise locations since it is compact and durable through an extended degree of temperature and pH scale. • It is modest and insusceptible to immune response. • Despite being linked with analytical or medicinal payload, it attaches with the folate receptor with an elevated proclivity.
	Cons	• By down-regulation of the cell-cell adhesion molecule, promoting cellular metastasis and motility • E-cadherin and folate uptake can aid in cancer cell proliferation • Insufficiency of adherence and relocation.

(Contd...)

Table 2: *(Continued)*

G) Epidermal Growth Receptor Factor conjugated nanoparticle	Pros	• These are pivotal factors for numerous biological actions involving cell-cell communications, cell survival, migration, differentiation, and apoptosis. • For targeting drug molecules for nanoparticles, compact size of the epidermal growth receptor factor makes it an appealing alternative. • In contrast to the unchanged form of nanoparticles EGFR conjugated with gelatin, nanoparticles showed elevated nanoparticles concentration in the cancerous site. • Overexpressed in different kinds of tumor cell lines. • Related to low prognosis and lessened existence. • In tumor cells, it can withstand radiation therapy and chemotherapy.
	Cons	• EGFR is present in normal cells as well. • They could perhaps cease to identify and bind to a modified version of the receptors' extracellular realm.

Table 3: Instrumental tools for protein-ligand interaction study

Hydrodynamic and calorimetric techniques	Spectroscopic and structural methods
Differential scanning calorimetry (DSC)	Atomic force microscope
X-ray diffraction (XRD)	Nuclear magnetic resonance
Differential light scattering (DLS)	Fluorescence spectroscopy,
Transmission electron microscopy (TEM)	Raman spectroscopy,
Scanning electron microscopy (SEM)	Mass spectrometry,
Thermal gravimetric analysis (TGA)	Paramagnetic probes,
Electrophoretic light scattering (ELS)	Multi-parametric surface plasmon resonance
Dual polarization interferometry (DPI)	Circular dichroism,
Fourier transform spectroscopy (FTS)	Ligand binding assay,
Inductively coupled plasma-optical emission spectrometer (ICP-OES)	Radioligand binding assay
	UV-visible spectroscopy

specificity cancer-specific biomarkers should be what is expressed. The cargo can be liberated with the increase in the acidic pH or enzyme as the internalization of ligands with receptors takes place through receptor-mediated endocytosis followed by the association of ligands with receptors by tumor cells. Active targeting is highly desirable for malignant cells in contradiction to the passive approach relevant to the exceeding probability of phagocytosis and pinocytosis is collectively known as endocytosis.[32] Among numerous targeting ligands for active targeting epidermal growth factor receptors (EGFRs), folate, glycoproteins, and transferrin are the most explored molecules. One of the main targets of various researchers is to reduce the administration dose of therapeutic agents specifically for high cytotoxic drug-like anti-cancer drugs. Therefore, to deliver the specific drug into cancer cells various ligands are conjugated with nanoparticles or with several tumor-specific or associated markers.

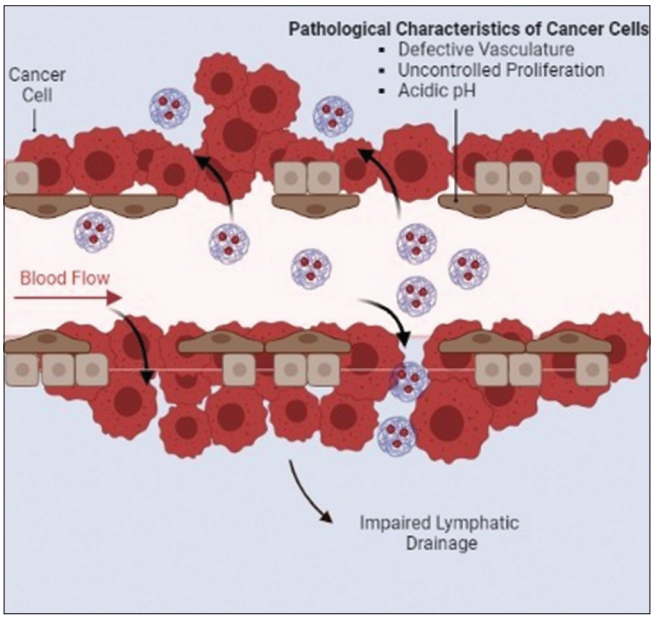

Figure 4: Pathological characteristics of cancer cells

The binding of the ligand to its receptor results in higher affinity when conjugated with a tumor-specific biomarker.[33] Several ligands-based targeting approaches for nano-drug delivery into cancerous tissues have been tested against various tumor biomarkers. The main investigation is based on transferrin receptor (TfRs), cell-penetrating peptides (CPPs), LDL-LDL (Low-density lipid) receptors, Integrins and integrin ligands, Carbohydrates (lectin ligands), Folate receptors, EGFRs-based nanoparticles.[34] The pros and cons of the individual are summarized in Table 2.

THE RECEPTOR AND LIGAND BINDING AFFINITY

By the binding affinity facts, solely the general strength of a drug cannot be dogged. The consequence of efficacy is the complex interplay of binding affinity and ligand effectiveness. Ligand efficacy is defined as the potentiality of the ligand after binding with the specific receptor, the biological reaction followed by the quantitative magnitude

thus produced is known as ligand efficacy. Depending on the binding affinity ligands and their specific receptors can be identified. Greater attractive forces are higher in the binding affinity of a ligand and its specific receptor and vice-versa. Higher occupancy of the receptor by its ligand is a result of the high-affinity binding then is the case for low-affinity binding and vice versa. Biologically, as a configuration switch in the receptor, elevated-affinity binding of ligands to the receptor is generally imperative which can be persuaded by the usage of binding energy that can be developed in modification of conduct, as in the case of a frequently connected ion channel or enzyme. Ligands that bind but fall short of stimulating the biological reaction of a receptor are known as receptor antagonists on the contrary a ligand that can bind to a receptor and prompt the biological reaction by transforming the role of the receptor is called the agonist.[35-38] Various analytical tools are used in the study of the protein-ligand interaction which is classified into two segments summarized in Table 3.

CONCLUSIONS

Probable overuse and misuse of nanoparticles can be severe health issues that need to be handled promptly followed by unchecked production and application specifically in global advancement. Appropriate surveillance technique is the need of the hour as the resulting occurrence of most of the nano-inventions emerged from the experimental batches. The severe effects of the use of nanomaterials are mostly demoralizing when in the user goods Noble nanomaterials are being produced and incorporated at an unnerving rate. Thus, the experimental work should be built on specifications and directions or commandments from regulatory authorities, the outlay of which should not be augmented in the final product. For the ill effects related to nanotechnology health and security ruling bodies will have to thoroughly work out the monitoring of trial price charges which can turn out to be a key part of the process. Thus, green synthesis of nanomaterial and medicine leads to the lowering of damaging effects associated with nanotechnology. It is high time that the unfortunate consequences should be controlled so that they may not cause deleterious effects on mankind and the environment as a whole. Green chemistry is a technology that is in its preliminary or advanced growth stage and is anticipated to be extensively availed globally due to its utilization of Noble matter and its reinforcement. A conjugated metal nanoparticle loaded with can turn out to be a potential and promising tool in combating skin cancer, thereby providing favorable targeting of skin cancer formulation to converge unfulfilled requisite of the medicament delivery in carcinoma of the skin with nominal adverse effects and enhanced delivery. This review summarizes the ligands conjugated metal nanocarrier that can be utilized for better fruitful delivery of skin cancer. Green chemistry grants us the opportunity to avert the adverse impact. With the aid of green chemistry, the persisting ecological concerns can be settled by diminishing pollution by reducing waste material and with no use of hazardous chemicals.

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