Green synthesis of metal nanocarriers: A perspective for targeting glioblastoma

Taskeen F. Docrat [1,*], Ali O.E. Eltahir [2,3], Ahmed A. Hussein [2], Jeanine.L. Marnewick [1]

[1] Applied Microbial and Health Biotechnology Institute, Cape Peninsula University of Technology, Bellville 7535, South Africa
[2] Department of Chemistry, Cape Peninsula University of Technology, Bellville 7535, South Africa
[3] Permanent address: Department of Chemistry, Omdurman Islamic University, Omdurman, P.O. Box 382, Khartoum, Sudan

Glioblastoma, the most aggressive brain cancer, is challenging to treat owing to the difficulty of crossing the blood–brain barrier, high recurrence rates and significant mortality. This review highlights the potential of green synthesis methods in developing metal nanoparticles (MNPs) as a sustainable solution for drug delivery systems targeting glioblastoma. We explore the unique properties and modes of action of MNPs synthesised through eco-friendly processes by focusing on their bioavailability and precision in brain targeting, and discuss the potential of MNPs to target glioblastoma at the molecular level. Integrating green synthesis into cancer therapeutics represents a novel paradigm shift towards treatments with higher efficacy and lower environmental impact, offering hope in the fight against glioblastoma.

Keywords: metal nanoparticles; glioblastoma; green synthesis; oxidative stress

Introduction

Cancer, a devastating disease with increasing prevalence, is often called the 'emperor of all maladies'.[(p1)] Central nervous system (CNS) cancers are known for their severity, with glioblastoma (GBM) making up almost half of all malignant brain tumours (Table 1).[(p2),(p3)] Like most cancers, GBM displays aggressive and invasive behaviour, leading to poor prognosis. Despite advancements in surgical methods, radiation treatment and chemotherapy strategies, GBM frequently reoccurs, resulting in high death rates. Moreover, complete tumour removal is often impossible owing to the location and invasiveness of the glioma cells.[(p4)] Glioma stem cells spread into nearby brain tissue, resisting chemotherapy because the blood–brain barrier (BBB) shields them.[(p5)] Existing chemotherapeutic options for treating GBM have a low success rate and ineffective delivery across the BBB.

Nanotechnology has been gaining attention in cancer-targeted therapy.[(p6)] With varying success rates in overcoming the limitations of targeted GBM therapy, a promising technique is using a nanocarrier system to deliver anticancer agents across the BBB to brain cells. Nanoparticle (NP) carriers range from 10 to 1,000 nm and can transport various substances, such as proteins, peptides, antibodies, chemotherapeutic drugs and nucleic acids.[(p7)] Combining current nanotechnology practices with green chemistry will create a more sustainable and environmentally friendly twenty-first century.[(p8)]

The green synthesis approach allows for developing targets that effectively interact with biological systems[(p9)] to reduce potential passive accumulation and the cytotoxic effects of metal nanocarriers on non-cancerous tissue.[(p10)] Various factors contribute to how NPs interact within a biological system, such as cellular and protein interactions, which could alter their effects.[(p11)] The goal is to improve the therapeutic index of current cancer treatments by using biogenic metal nanoparticles (MNPs) that are highly specific, with increased efficacy and sensitivity.[(p12)] This is a promising avenue because green MNPs can

* *Corresponding author. Docrat, T.F. (docratt@cput.ac.za)*

https://doi.org/10.1016/j.drudis.2024.104219

TABLE 1

Statistics for central nervous system tumours and other brain cancers

Tumour type	Percentage (%)
Malignant	
Glioblastoma	48.6
Other gliomas	17.9
All other malignant	13
Diffuse/anaplastic astrocytoma	11.8
Lymphoma and hemopoietic neoplasms	6.6
Tumours of the meninges	2.1
Non-malignant	
Meningioma	53.9
Pituitary tumour	24
Nerve sheath tumour	12.1
Other non-malignant	7.1
Neuroepithelial tumours	2.9

be easily modified to improve their biocompatibility and surface to promote access to the tumour microenvironment.[p13]

Mitochondria are responsible for cellular respiration and are a common clinical target in cancer therapy.[p14] Various cancers, including GBM, thrive on mitochondrial oxidative phosphorylation (oxPHOS), which produces cellular energy and reactive oxygen species (ROS).[p15] Research indicates that GBM promotes tumour growth by converting approximately 90% of glucose to lactate,[p16] a concept named the Warburg effect in the 1920s.[p17] Reprogramming of the metabolic pathway maintains the rapid proliferation of malignant tumour cells. A recent *in vitro* study has shown that glucose starvation upregulates mitochondrial oxPHOS, facilitating ferroptosis,[p18] suggesting that targeting the metabolic flexibility of GBM cells could potentially hinder their survival mechanisms and induce cell death. Therapies targeting these pathways could provide an effective strategy to combat GBM. In this article, we summarise the significant biochemical challenges in GBM studies and how MNPs can be tailored in an environmentally friendly way to overcome them.

Crossing barriers: transportation and accessibility across the blood–brain barrier

The BBB consists of tightly bound cells that confer the selective passage of molecules to and from the brain. It has a crucial role as the first line of defence against harmful substances, such as toxins and pathogens in the bloodstream. However, some small hydrophobic compounds can cross the BBB via passive diffusion. Other factors, such as molecular weight, size, shape, ionisation state, lipophilicity and protein-binding affinity, can also affect a molecule's ability to pass through the BBB.[p19] Many drugs cannot cross the BBB owing to permeability restraints, and the potential for premature release of drugs from nanocarriers and interactions with biological components can lead to toxicity or other adverse effects.[p20] In addition, non-specific neural receptors exist in other body regions, resulting in potential side effects. The permeability of this complex barrier needs to be explored further to improve drug design and better treat gliomas.[p21]

Endothelial cells form a multicellular structure containing tight junctions, which enable the movement of molecules via diverse routes, including adsorptive-, carrier- and receptor-mediated transport, and endogenous mechanisms. Biomolecule interactions and particle size are important for passive diffusion, receptor-mediated transport, adsorptive-mediated transcytosis and carrier-mediated transcytosis. Passive diffusion is the primary pathway for small lipophilic essential elements to reach the brain, and relies on concentration gradients.[p22] Receptor-mediated transport involves binding ligands to BBB receptors, forming complexes actively transported to the cytoplasm by endocytosis, a process that requires energy. Adsorptive-mediated transcytosis utilises positively charged ligands to interact with negatively charged BBB surfaces via electrostatic interaction, making it suitable for cationic proteins and peptides. Carrier-mediated transcytosis utilises specific carriers to deliver essential molecules to the brain. Modified molecules resembling endogenous molecules can bind to the carrier and be transported to the brain, making this process suitable for drug delivery.

Nanomaterials have become indispensable in brain medicine thanks to their capability to deliver therapeutics by crossing the BBB. Passive diffusion effortlessly facilitates the entrance of lipophilic molecules to endothelial cells and NPs smaller than 4 nm through junctions,[p23] whereas charged cationic NPs depend on endocytosis by adsorption. However, NPs do not have high penetration rates through the BBB, which limits their therapeutic efficacy in the CNS. Functionalised, conjugated and hybrid nanomaterials with BBB receptor ligands have been extensively utilised to overcome this. The use of transferrin to improve the penetration efficiency of NPs by leveraging the strong affinity between transferrin and its receptor is recommended, offering the potential for a more effective and targeted approach to drug delivery.[p24] The arrival of nanomedicine has revolutionised medical diagnosis and treatment by offering a crucial method to circumvent the BBB and deliver drugs to targeted brain areas.

Sustainable synthesis of nanoparticles using green methods

Nanotechnology focuses on using fewer toxic reactants and introducing safe, effective and biocompatible products, especially in the health sector. MNPs such as gold, silver, copper, platinum, iron and metal oxides of zinc, copper and titanium have been extensively studied for future biomedical applications.[p25] MNPs are metals and alloys with particle sizes $\leq$100 nm; they have physical and chemical properties that differ from those of bulk materials.

Numerous physical and chemical techniques exist for producing MNPs; nonetheless, these approaches have limitations and challenges that necessitate alignment with the green economy. Some of these problems include sophisticated equipment and the bioaccumulation of toxic chemicals that cause damage to the environment and human health.[p26] Green nanotechnology was developed to overcome this and to produce alternative, sustainable, green economy development methods. An enormous amount of scientific research is produced yearly that focuses on applying biological materials to form, stabilise and activate MNPs, especially for medical applications. As a greener, more sustainable alternative, biological synthesis is being recognised globally. It is gradually replacing physical and chemical methods

because it offers a clean, eco-friendly, cost-effective and biocompatible process for synthesising MNPs. This method's safety margins and biocompatibility have encouraged researchers to exploit different biological sources, such as nano factories. Various natural sources have been reported, such as plants (flowers, fruits, leaves and roots) and microorganisms (bacteria, fungi and algae).[p27]

Roles of natural extracts in the formation of metal nanoparticles

Reduction

The formation of metals from metal slats usually requires a reducing agent to donate electrons to the metal cation in solution. This process can be completed using living organisms or water extracts from dead organisms. The most widely used method involves water extraction from different organs, such as fruits, flowers, leaves, roots (from higher plants), whole organisms and cell lysate (microorganisms). The extracts usually contain a wide variety of primary metabolites (such as proteins, fats and carbohydrates) and secondary metabolites (phenolics, terpenoids and alkaloids). Certain compounds in this plethora of naturally occurring metabolites can donate electrons and reduce the metal salts. The most important donors usually contain hydroxyl, carboxylic or carbonyl active groups (Figure 1). Aliphatic hydroxyls are generally less active than aromatic ones owing to the stability of the intermediate. However, carbohydrates[p28],[p29] such as gum arabic, heparin,[p30] hyaluronic acid,[p31] alginic acid, starch,[p32] cellulose,[p33] dextran[p34],[p35] and glucose,[p36] were reported to reduce and stabilise different MNPs. Phenolic hydroxyl-containing compounds such as tannins, phenolic acids and flavonoids[p37] are the most potent electron-donating compounds owing to the stability of the results of quinonoid structures or phenoxy ions.

Stabilisation

The fate of MNPs in biomedical applications depends on their stability in physiological media, primarily affected by their physical characteristics: their size, shape, solubility and the presence of a capping agent (or agents).[p38] This implies that NPs should be stable in aqueous media with high ionic strength, high protein concentration and a specific range of pH values. In an aqueous solution, capping agents usually play an essential part in keeping the NPs suspended in the solution and preventing aggregation for a specific time, depending on the strength of the interaction between the organic molecules on the surface of the MNPs. The link at the surface of the NPs can be a chemical covalent bond (as in sulphur-containing capping agents) or electrostatic physical attraction (phenolics). The stability of MNPs is determined by zeta potential, and the values above 10 for negative and positive charges indicate the strength of the particles. The molecules on the outer layers of the NP's surface have unbalanced forces and tend to attract molecules from the solution, forming capping layers from different hydrated organic molecules (Figure 2). These organic molecules around the NPs form a shell that prevents the NPs from aggregating. A few examples have been discussed in the literature.[p39]

Activation

Metals such as gold (Au), silver (Ag) and palladium (Pd) are inactive; other metals, such as copper (Cu) and iron (Fe), have some activity owing to the vacant d-orbital on the outer shells of the atoms. They can change their oxidation state depending on the media under consideration. Au, one of the most studied NPs, is inert; however, the attachment of a capping agent with an active functional group (or groups) changes this, and the surface becomes active.[p40] Furthermore, the attachment of organic molecules on the surface of the MNP leads to the formation of proactive forms due to the partial ionisation of the compounds at the surface of the MNP. Thus, when assessing reactivity and functionality in diverse applications, it is essential to note that. In contrast, metals might be inert in their bulk form, their NPs might exhibit reactivity under specific conditions owing to their different properties.

Selective orientation

Smart designs of NPs with specific functionalities that interact with specific targets are shown in Figure 3. The active substance in the synthesis of NPs is derived from the plant extract or biomolecule used for encapsulating the MNPs, providing the NPs with specific functionalities for targeted biomedical applications. The image

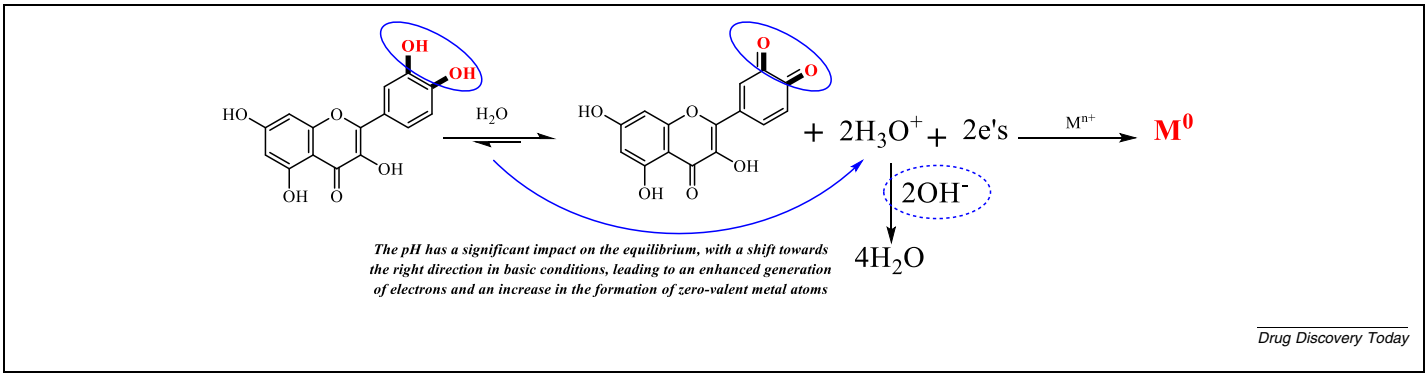

FIGURE 1

An archetype reduction mechanism in NP formation. The reduction process can be influenced by extrinsic factors such as light, heat and pH, which catalyse the process. Compounds such as flavonoids, phenolic acids, glucose, carbonyl compounds and carbohydrates donate electrons during the reduction process. These compounds are crucial in synthesising NPs with distinct properties.[p37]

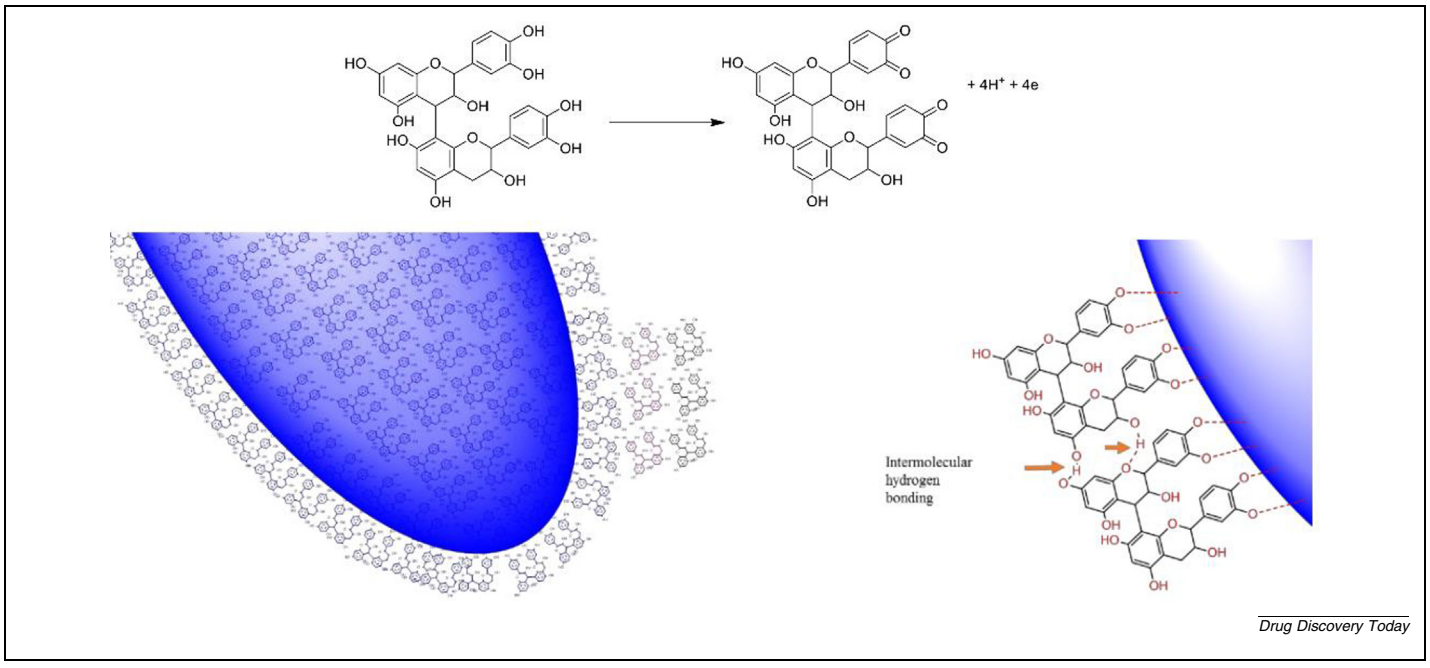

FIGURE 2

The NP synthesis process begins with reducing a metal salt precursor. This step leads to the formation of hybrid MNPs, which are then encapsulated within a phenolic matrix (e.g., procyanidins). The stabilisation of these NPs is achieved through two fundamental mechanisms: first, the oxygen atoms in the procyanidins chelate the surface of the metal, and second, the intermolecular hydrogen bonding between procyanidin molecules forms robust double- and triple-layered capping shells around the NPs. Additionally, the presence of ortho-OH groups in the phenolic structures enhances the reduction potential, promoting the formation of a stable ortho-quinone structure that further contributes to the stability of the capping shell.[p40]

offers an overview of the step-by-step protocol for preparing NPs for biomedical applications. This process involves carefully selecting precursor materials for subsequent synthesis endeavours, cleaning the plant material, and cutting, crushing and boiling to extract aqueous plant biomolecules. Incorporating green synthesis methods, in which natural compounds or plant extracts act as reducing and capping agents, aligns with sustainable practices. The successful synthesis of gold nanoparticles (AuNPs) and silver nanoparticles (AgNPs) using phyto-nanotechnological methods and active substances from various parts of herbal and aquatic plants has been previously outlined.[p41],[p42] Extracts are purified through filtration and centrifugation. The chosen precursors are transformed through reduction reactions into NPs, complemented by their encapsulation within biocompatible matrices, ensuring stability and compatibility for medical use. This is achieved by incubating various ratios of metallic salt solutions with the plant extract at ambient temperatures. The successful formation of MNPs is denoted by a visual colour change. Transparent Ag salt and red Au NaCl solutions turn brown and purple when mixed with organic extracts. Centrifugation at high speeds (12,000–13,000 rp m; 12–30 min) yields the extracted MNP from the solution. Consequent washing steps with water and repeated high centrifugation allow for the removal of unreacted metallic ions. Manipulating reaction conditions and tailoring their attributes to suit diverse biomedical applications is achieved by controlling the size and shape of these NPs. Therefore, the synthesised NPs can be used across the biomedical spectrum, from targeted drug delivery to medical imaging and therapeutic interventions, reshaping modern healthcare practices. Figure 3 summarises the journey from precursor selection to biomedical utility, highlighting the potential of green synthesis techniques to transform NPs' role in advancing medical solutions.

Biocompatibility of metal nanoparticles

When synthesising these biological MNPs, concerns about toxicity must be considered. The biocompatibility of organic synthesised MNPs depends on the encapsulation molecule used, including flavonoids, phenolics, vitamins, tannins, terpenoids, carbohydrates and many others.[p43] The net surface charge controls the mechanism of action, and cell types have varying tolerances to specific green synthesised MNPs. To establish whether this synthesis method eliminates the toxicity associated with the metallic core, various *in vitro* investigations have been conducted and discussed.[p42],[p44],[p45],[p46] A range of assessments in specific disease models covering epigenetic effects, cytotoxicity, neurotoxicity and cell cycle arrest mechanisms can establish the safety profile of the MNPs. Figure 4 outlines the mechanism of green MNPs against cancer, involving ROS upregulation, mediation, DNA damage, endoplasmic reticulum (ER) stress, lactate dehydrogenase (LDH) release, and mitochondrial dysfunction, all of which ultimately lead to caspase-3-induced cell death.[p47],[p48]

GBM hijacks mitochondrial neural networks

GBM requires intricate crosstalk with healthy brain cells that promote cancer cell migration, survival and angiogenesis to maintain invasion and tumour growth.[p49] Investigating the distinct biochemical and cellular environment within the healthy brain that GBM exploits to support plasticity and encourage resistance to chemotherapies is crucial. To better understand these mecha-

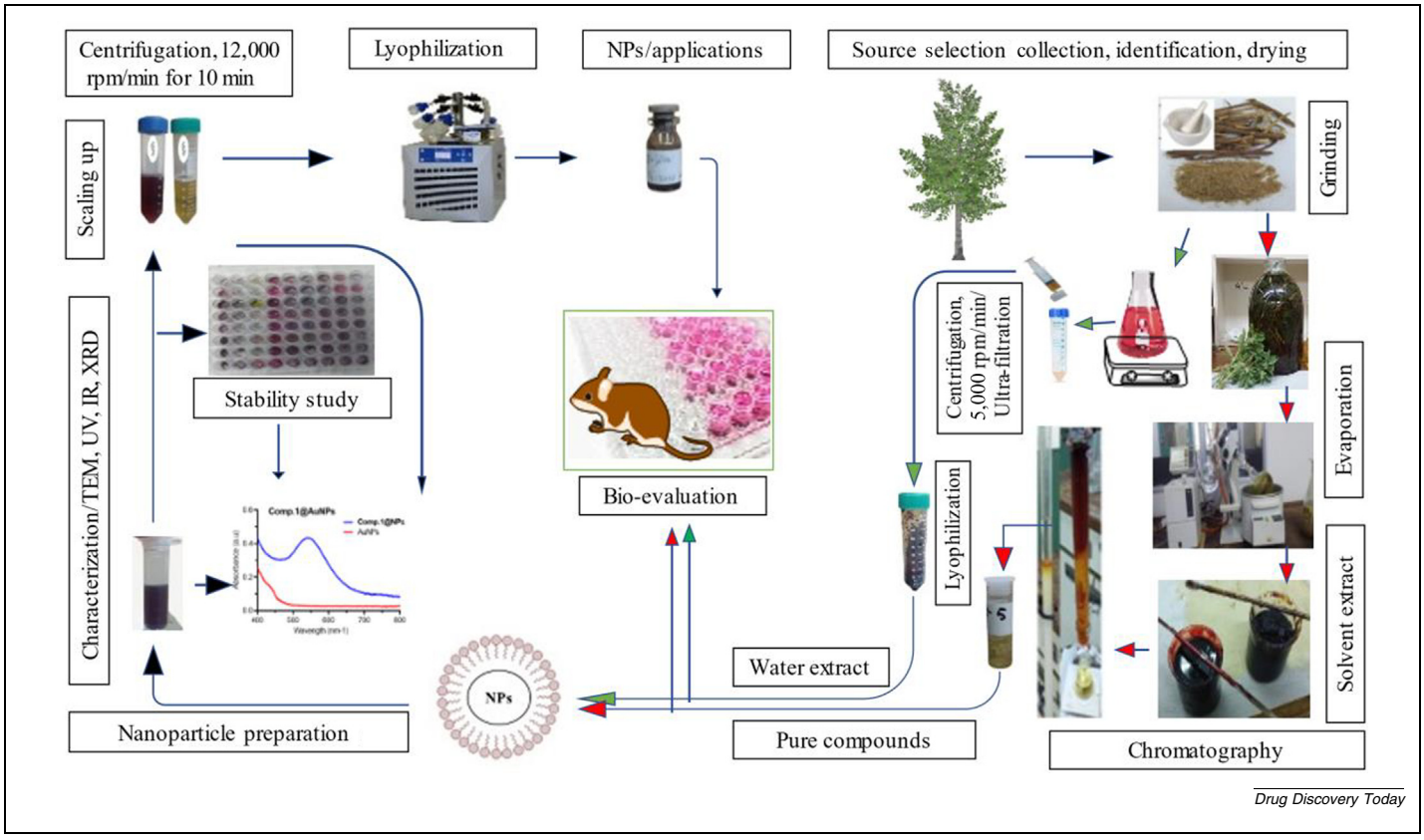

FIGURE 3

A comprehensive protocol for the synthesis and preparation of NPs tailored for various biomedical applications, outlining crucial steps, from selecting materials to final functionalisation for targeted use.

nisms, we discuss the processes that are dysregulated by GBM within mitochondria, which are highly sophisticated organelles.

Healthy glial cells produce energy within the cell through mitochondrial aerobic respiration.[p50] However, cellular metabolism in GBM initiates with glycolysis to produce pyruvate, which enters the mitochondria to make acetyl-CoA, an essential component of Krebs' cycle.[p51] The mitochondrial number in GBM is considerably lower, indicating high mitochondrial degradation activity.[p50] As a result, brain cancer cells rely on aerobic glycolysis rather than aerobic respiration as their primary energy source, forcing cells to undergo mitochondrial oxPHOS. This metabolic shift, known as the Warburg effect, is prominent in tumour types such as gliomas.[p52] These cancer cells simultaneously undergo mitochondrial oxPHOS and glycolysis, allowing them to produce higher amounts of ATP than normal cells.[p53]

Mechanisms of infiltration: mitochondrial metabolism and dysfunction

Aside from their crucial functions in oxPHOS and programmed cell death, mitochondria have vital roles in several other cellular processes. These include fatty acid β-oxidation, cell proliferation, haem biosynthesis and proline synthesis.[p54] Consequently, mitochondrial and metabolic dysfunction are responsible for the progression of cancers. Mounting evidence suggests that mitochondrial dysfunction contributes to various stages of cancer development and progression, such as oncogenic transformation, evasion of apoptosis and metastasis.[p15],[p54],[p55] Mitochondria play a vital part in programmed cell death by inducing mitochondrial outer membrane permeabilisation (MOMP), which releases cytochrome *c* into the cytosol. This protein activates caspases, ultimately leading to apoptotic cell death (Figure 4). Mitochondria are the primary source of ROS, which can cause oxidative damage to mitochondrial and genomic DNA, ultimately impairing cellular functions.[p56]

Gliomas exhibit compromised mitochondrial function because of significant modifications in their mitochondrial genome. Such changes lead to atypical bioenergetics, including heightened ROS production and transformations in the morphology of the mitochondria.[p57] The metabolic switch due to the Warburg effect leads to the emergence of abnormal mitochondrial phenotypes, such as swelling and osmophilic granules. It is widely hypothesised that the aberrant mitochondrial phenotypes have a significant role in the pathobiology of gliomas and invasive behaviour.[p58] Dysfunctional mitochondria can initiate apoptosis by activating downstream Bcl-2 family proteins and p53. However, glioma cells can avoid mitochondrial-stress-induced apoptosis through various mechanisms. For instance, oncogenic activation of the phosphoinositide 3-kinase (PI3K)–AKT pathway leads to degradation of the tumour suppressor p53, and mutations in p53 can confer resistance to mitochondrial ROS-induced apoptosis.[p59] Furthermore, ROS generation can activate transcription factors that promote tumorigenesis, such as hypoxia-inducible factor-1α (HIF1α) and nuclear factor

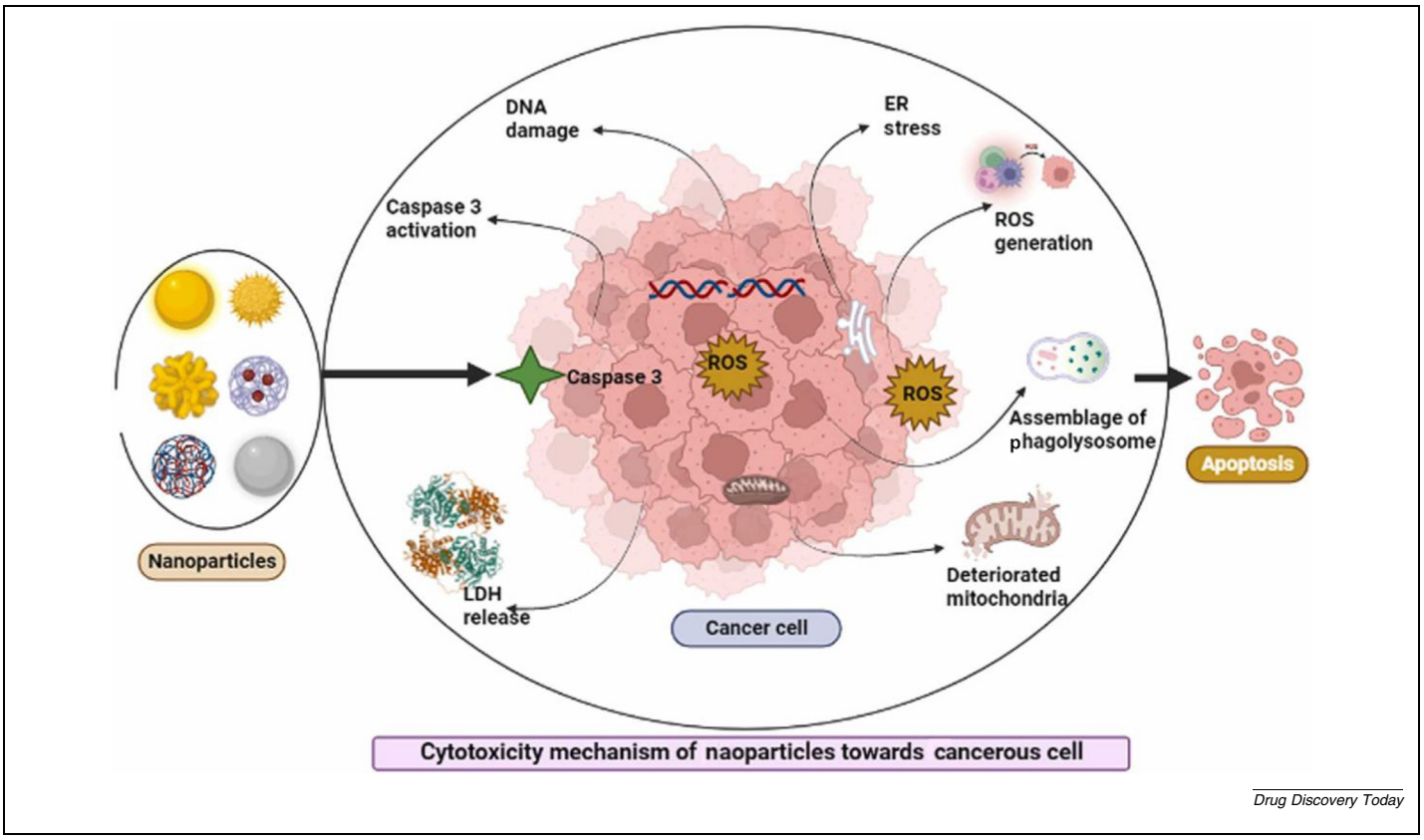

FIGURE 4
The effects of MNPs treated with bio-reducing agents on a cancerous cell, leading to cell death.[p48]

erythroid 2-related factor 2 (NRF2), which increase cell proliferation and survival.[p60]

Nanotechnology in cancers

The enhanced permeability and retention (EPR) effect promotes NP accumulation in tumour tissues and has made nanobiotechnology an attractive approach to improve the prognosis and survival outcomes of patients with GBM through early detection and intervention strategies.[p61] Biological and hybrid NPs are frequently used as diagnostic tools owing to their high specificity for binding sites, enabling them to function as target compounds and facilitate drug transport in neuronal tumours.[p6],[p23]

NPs can be targeted to biological barriers through active and passive methods. Passive targeting relies on the EPR effect, which facilitates NP accumulation in the brain as a result of tumours' abnormal and deficient endothelial cells and poor tumour vasculature (Figure 5). This allows particles smaller than 400 nm to extravasate and accumulate in the perivascular spaces.[p62] Conversely, active targeting involves functionalising NPs to recognise specific surface receptors of GBM, promoting their accumulation in tumours.[p63]

MNPs, specifically AgNPs and AuNPs, offer distinct advantages, such as surface plasmon resonance,[p64] that cannot be found in dendrimers, micelles and liposomes. AuNPs have versatile surface functionalisation features and are biocompatible, making them useful for drug delivery. Physical absorption, covalent and ionic methods can be used to conjugate AuNPs to drugs to increase their efficacy in delivery. In addition, AgNPs have been used for drug delivery, with studies showing their potential to release ornidazole. *In vitro,* release rates of up to 98.5% have been reported.[p65] Furthermore, titanium dioxide NPs, AuNPs and AgNPs can be engineered to create extremely small homogeneous NPs ranging from 3 to 30 nm.[p66] Owing to their advantageous physicochemical properties, surface charges and drug, antibody and protein-binding abilities, MNPs are currently being investigated for their use in infectious diseases. By being shielded from the host's immune system, MNPs can circulate longer in the bloodstream, making them a promising option for medical treatments.[p67] AuNPs are commonly used as core components in NP preparation owing to their bioinert property, characterisation and ease of synthesis.[p68]

Gold nanoparticles for cancer therapy

Plant-synthesized AuNPs offer a promising avenue for advancing cancer treatment. Extracted from *Hibiscus sabdariffa* leaves, these AuNPs, spanning sizes from 10.0 to 60.0 nm and adopting a spherical morphology, hold the potential for inducing cytotoxicity in U87 GBM cells through the degradation of the glyceraldehyde 3-phosphate dehydrogenase (GAPDH) enzyme.[p69] Likewise, *Jasminum auriculatum* leaf-derived AuNPs, ranging in size from 8.0 to 37.0 nm and characterised by a spherical shape, exhibit antimicrobial effects against pathogens and demonstrate anticancer activity in human cervical cancer cells (HeLa cell line), suggesting a dual therapeutic role.[p70] This suggests a broader

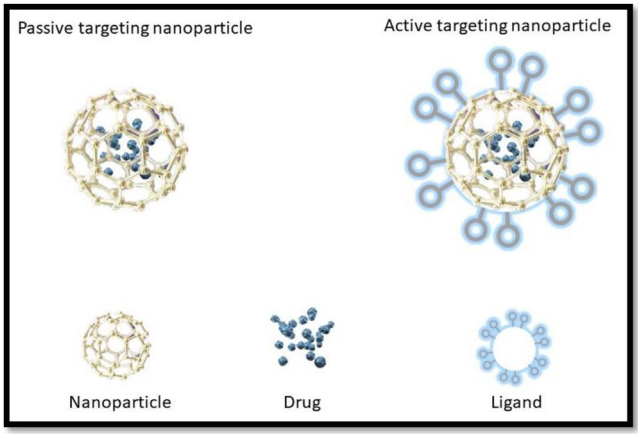

FIGURE 5

NPs can utilise either active or passive targeting strategies. Active targeting is characterised by the deliberate interaction with and recognition of specific cellular targets, enhancing the precision of NP delivery. Conversely, passive targeting capitalises on the intrinsic properties of tissues, allowing for the accumulation of NPs on the basis of the physiological and pathological state of the tissue. Both methods are utilised, but there is a marked preference for active targeting in clinical studies. This preference is attributed to its ability to mitigate the unintended accumulation of NPs in non-target regions, thereby enhancing the specificity and efficacy of therapeutic interventions.

spectrum of therapeutic applications that could address the complexities of cancer and the risks of infections in immunocompromised patients. *Butea monosperma* leaf-sourced AuNPs (30.0 nm), which present varied shapes including spherical, rod-shaped, triangular and hexagonal, display selective cytotoxicity against GBM cells while sparing regular fibroblast cell lines, hinting at their potential for targeted cancer therapy.[p71] This specificity reduces healthy cell damage and might provide a significant step towards precision medicine in oncology.

Silver nanoparticles in cancer therapy

Exploring plant-derived AgNPs holds promise for innovative cancer treatments. Notably, *B. monosperma* leaf-extracted AgNPs (50.0 nm) have emerged as a prospective drug delivery system for cancer therapy, showcasing superior therapeutic efficacy compared with free drug administration.[p71] *Plumeria alba* leaf-derived AgNPs (26.43 nm) have shown substantial cytotoxic potential on GBM U118 MG cancer cells by inducing apoptosis, suggesting a promising source for novel antimicrobial and anticancer agents,[p72] and offering a dual-functional approach to cancer treatment strategies. Alginate and chitosan-based AgNPs (~633.2 nm) exhibit robust anticancer effects on U-87 MG cells due to their size and surface characteristics, involving DNA damage, oxidative stress, mitochondrial dysfunction and apoptosis mechanisms.[p73]

Zinc oxide nanoparticles in cancer therapy

The integration of plant-synthesised zinc oxide nanoparticles (ZnO NPs) holds potential in cancer therapy. Derived from *Glycyrrhiza glabra* seeds, ZnO NPs (35.0 nm) in spherical form effectively minimise cell death in GBM cell lines while preserving neural integrity, thereby minimising potential side effects.[p74] *Salvadora persica* aerial parts-derived Zn ONPs and Ag-doped ZnO NPs (ranging from 15.0 to 40.0 nm and 11.7 to 20.8 nm) exhibit intricate interactions between NP composition, concentration and cellular responses.[p75] Moreover, coating materials such as polyethylene glycol, antibodies and folic acid have been investigated for increased specificity of ZnO NPs to cancer cells. There might be room for synergistic therapy with existing treatment regimens. A combination of ZnO NPs with chemotherapy and radiation could enhance therapeutic effects by reducing the dosage and associated adverse effects. Leveraging the ability of ZnO NPs to sensitise GBM to other treatments by capitalising on its intrinsic anticancer abilities can yield better therapies.

Potential of iron(III) oxide nanoparticles

Iron(III) oxide nanoparticles (Fe_2O_3 NPs) obtained from *Prosopis farcta* aerial parts, ranging in sizes from 20.0 to 45.0 nm and exhibiting a spherical morphology, exhibit no cytotoxic activity against U87 cells at concentrations up to 500 μg/mL. This positions them as potential candidates for drug delivery in cancer treatment.[p76] These NPs have an advantage due to their biocompatibility, allowing for use *in vivo* with no side effects on healthy cells. Furthermore, cellular uptake and targeted delivery can be achieved by surface modification, thus enhancing the efficiency of encapsulated drugs.

Carbon dots from spices

Although carbon dots are not metallic NPs, their unique properties make them an intriguing alternative to MNPs and worthy of mention. Derived from various spices, including cinnamon, red chilli, turmeric and black pepper, carbon dots (3.4 to 4.3 nm) exhibit impressive imaging capabilities and display selective cytotoxicity against GBM cells while maintaining a favourable response in non-cancerous cells, highlighting their potential as promising theranostic agents with minimal side effects.[p77]

Table 2 outlines the diverse applications of plant-synthesised NPs created through environmentally friendly methods, underscoring their substantial potential within cancer therapy. The distinctive attributes of AuNPs, AgNPs, ZnO NPs, Fe_2O_3 NPs, and carbon dots contribute to their unique therapeutic roles, illustrating the path for transforming cancer treatment approaches.

Challenges

Integrating plant-derived NPs synthesised through environmentally friendly methods opens a promising pathway for driving cancer therapy. However, integrating metals in these synthesis processes raises concerns about the potential toxicity of metallic NPs. Despite the tremendous potential of this field, addressing and effectively mitigating any accompanying risks is imperative. Green synthesis methodologies, which aim to minimise ecological impact and enhance biocompatibility, encounter a challenge in the form of the intrinsic properties of metals, which might cause adverse effects within living systems. Although metals can improve NPs' structural properties and therapeutic potential,

TABLE 2

Plant-derived NPs for GBM therapy: a comprehensive review of natural compounds and their therapeutic potential

Reducing/capping agent (extract/compound)	Part used	Metal	Size	Shape	Mode of action	Refs
Hibiscus sabdariffa	Leaves	AuNPs	10.0–60.0	Spherical	Induces cytotoxicity in U87 GBM cells by degrading the GAPDH enzyme	(p65)
Jasminum auriculatum	Leaves	AuNPs	8.0–37.0	Spherical	Exerts antimicrobial effects against human pathogens and exhibits anticancer activity in human cervical cancer cells (HeLa cell line), suggesting potential for dual therapeutic applications	(p74)
Gellan gum	Gum	AuNPs	13.0 ± 1.0	Spherical	Enhanced cytotoxicity of doxorubicin hydrochloride (DOX), specifically in human glioma cell lines (LN-229 and LN-18), indicating a potential strategy to improve the effectiveness of DOX in targeting glioma cells	(p75)
Cudrania tricuspidata	Root	AuNPs	23.3 ± 3.7	Spherical	Exhibits anticancer effects by downregulating the activity and expression of matrix metalloproteinase 2 (MMP2), MMP9 and phospholipase D1 (PLD1), indicating a potential role in inhibiting cancer cell invasion and metastasis	(p74)
Spatoglossum asperum	Total algae	AuNPs	20.0	Spherical and cubic	Exhibited cytotoxicity against LN-18 GBM cells, with no damage to normal human fibroblast cell lines	(p75)
Butea monosperma	Leaves	AuNPs	30.0	Spherical, triangular, hexagonal and rod-shaped	Selective cytotoxicity against LN-18 GBM cells while sparing normal human fibroblast cell lines, indicating the potential of the treatment to specifically target cancer cells without causing harm to healthy cells	(p78)
Butea monosperma	Leaves	AgNPs	50.0	Spherical and triangular	Can potentially be an effective drug delivery system for cancer therapy and other diseases, as evidenced by its superior therapeutic efficacy compared with free drug administration	(p78)
Plumeria alba	Leaves	AgNPs	26.43	Spherical	P-AgNPs induced cell death in GBM U118 MG cancer cells by elevating early and late apoptosis populations, suggesting that P-AgNPs could be a promising source for novel antimicrobial and anticancer agents	(p72)
Alginate and chitosan	–	AgNPs	~633.2	Spherical	Potent anticancer effect on U87 MG cells, inducing DNA damage, oxidative stress, mitochondrial dysfunction and apoptosis, thereby highlighting potential as a promising tool for cancer therapy	(p79)
Glycyrrhiza glabra	Roots	ZnO NPs	35.0	Spherical	Reduces cell death of GBM cell lines while preserving the integrity of other neural parts of the body, thus minimising potential side effects	(p69)
Salvadora persica	Aerial parts	ZnO NPs and Ag-doped ZnO	15.0–40.0, 11.7–20.8	Spherical	Undoped ZnO NPs exhibited more potent inhibition than Ag-doped ones, akin to DOX at 100 μg/mL. Doped NPs displayed reduced toxicity at low silver doping but heightened effects with increased silver content. This highlights a complex interplay among NP composition, concentration and cellular response	(p75)
Prosopis farcta	Aerial parts	Fe_2O_3 NPs	20.0–45.0	Spherical	Fe_2O_3 NPs exhibited no cytotoxic activity against U87 cells up to a concentration of 500 μg/mL, making them a potential candidate for cancer treatment drug delivery	(p71)
Different spices (cinnamon, red chilli, turmeric and black pepper)	Spices	Carbon dots	3.4–4.3	–	Fluorescent carbon dots derived from spices showed excellent imaging abilities and selective cytotoxicity against GBM cells while maintaining good tolerance in non-cancerous cells, highlighting their potential as theranostic agents with minimal side effects	(p72)

their potential for bioaccumulation and interactions with biological molecules require careful evaluation.

Given this scenario, assuring the safe and responsible application of metal-based plant-derived NPs requires thoroughly exploring their toxicological profiles. Researchers must conduct a comprehensive investigation, including biodistribution studies, analysis of cellular responses and assessment of potential long-term effects. Understanding how these NPs are distributed throughout the body, how they interact with various cell types and whether they lead to unintended consequences will be crucial for their clinical translation.

Biodistribution studies track the journey of NPs after administration, shedding light on their accumulation sites within the body in non-target tissues and organs, and indicating potential toxicity concerns. Cellular interactions involve studying how these NPs engage with cellular components, including proteins

and genetic material, to determine whether they lead to disturbances in normal cellular functions or provoke unwanted immune responses. Long-term effects must also be investigated, assessing whether the NPs induce any delayed toxicity or accumulate over time, possibly affecting the patient's health in the long run.

The delicate balance between therapeutic efficacy and safety remains paramount when pursuing revolutionary cancer treatment paradigms. The promising potential of metal-incorporating plant-derived NPs must be realised while considering the potential risks. A robust understanding of the mechanisms underlying their potential toxicity will guide researchers in refining NP design, administration strategies and patient monitoring protocols. By addressing these challenges head-on, the scientific community can harness the full potential of these innovative therapies, making substantial contributions to the field of cancer treatment while ensuring patient well-being.

Conclusions and prospects

We have reviewed potential strategies to enhance outcomes for patients with GBM by repurposing existing drugs and highlighting the promising potential of green synthesis methods. GBM presents a great challenge for cancer treatment due to its elaborate nature, including its location within the brain, the intricacies of drug penetration across the BBB, and GBM's distinct molecular and cellular attributes. The unique hurdles GBM poses underscore the importance of exploring unconventional approaches beyond traditional drug development paradigms.

Green synthesis methods have emerged as a beacon of innovation within pharmaceutical research. These eco-friendly approaches harness the inherent capabilities of natural compounds and plant-derived materials to create NPs with distinct properties. Notably, the versatility of green synthesis methods has the potential to revolutionise GBM treatment by effectively targeting its molecular vulnerabilities. The biocompatible nature of green-synthesised NPs further adds to their appeal as potential therapeutic agents for GBM.

Within this context, one particularly promising avenue is the exploration of mitochondria as a target for GBM treatment. The vulnerabilities exhibited by GBM cells to drug interventions present an exciting opportunity to leverage mitochondria-focused interventions. Green-synthesised NPs, with unique characteristics and precise targeting abilities, can be tailored to interact with mitochondria, disrupting their function and inducing selective cytotoxic effects within GBM cells.

Future developments must consider the specificity and efficiency of MNPs alongside reducing their toxicity. The primary focus should be research innovations that adjust the surface properties to achieve targeted delivery to cancer cells without affecting healthy tissue. Specifically, NP functionalising or coating with biocompatible ligands and materials could enhance their ability to recognise specific cell markers and reduce their side effects. In addition, using green synthesis techniques and environmentally safe materials could reduce the toxicity of MNPs, rendering them safe for clinical use. Collectively, these strategies aim to determine safer treatments by utilising the complete therapeutic potential of MNPs.

The insights provided in this review are expected to catalyse further investigations in this area, inspiring researchers to explore the synergy between green synthesis methods and innovative GBM treatment strategies. As the pharmaceutical industry seeks unconventional solutions to address the challenges posed by GBM, the collaboration between basic researchers and pharmaceutical innovators will be pivotal in advancing the field. Ultimately, we hope this review will catalyse future inquiry and innovation, guiding the development of novel therapeutic avenues to address the complex landscape of GBM treatment.

Author contributions

T.F.D: conceptualisation, investigation, methodology, resources, visualisation and writing (original draft preparation). A.O.E.E: conceptualisation, investigation, methodology, resources and writing. A.A.H and J.L.M.: conceptualisation and design, visualisation, writing (review). All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

CRediT authorship contribution statement

Taskeen F. Docrat: . **Ali O.E. Eltahir:** Writing – review & editing, Writing – original draft. **Ahmed A. Hussein:** Writing – review & editing, Writing – original draft. **Jeanine.L. Marnewick:** Writing – review & editing, Writing – original draft, Conceptualization.

Data availability

No data was used for the research described in the article.

References

1. Mukherjee S. *The emperor of all maladies: a biography of cancer*. Fourth Estate Ltd.; 2011.
2. Lin S et al. Prognosis analysis and validation of m6A signature and tumor immune microenvironment in glioma. *Front Oncol*. 2020;10, 541401.
3. Miller KD et al. Brain and other central nervous system tumor statistics, 2021. *CA Cancer J Clin*. 2021;71:381–406.
4. Davis ME. Glioblastoma: overview of disease and treatment. *Clin J Oncol Nurs*. 2016;20:S2.
5. Van Tellingen O, Yetkin-Arik B, De Gooijer M, Wesseling P, Wurdinger T, De Vries H. Overcoming the blood–brain tumor barrier for effective glioblastoma treatment. *Drug Resist Updat*. 2015;19:1–12.
6. Zottel A, Videtič Paska A, Jovčevska I. Nanotechnology meets oncology: nanomaterials in brain cancer research, diagnosis and therapy. *Materials*. 2019;12:1588.
7. Caraway CA, Gaitsch H, Wicks EE, Kalluri A, Kunadi N, Tyler BM. Polymeric nanoparticles in brain cancer therapy: a review of current approaches. *Polymers*. 2022;14:2963.
8. Schmidt KF. *NanoFrontiers: visions for the future of nanotechnology*. Woodrow Wilson International Center for Scholars; 2007.
9. Stephen BJ, Suchanti S, Mishra R, Singh A. Cancer nanotechnology in medicine: a promising approach for cancer detection and diagnosis. *Crit Rev Ther Drug Carrier Syst*. 2020;37:375–405.

10. Kashkooli FM, Soltani M, Momeni MM, Rahmim A. Enhanced drug delivery to solid tumors via drug-loaded nanocarriers: an image-based computational framework. *Front Oncol*. 2021;11, 655781.
11. Lane LA. Physics in nanomedicine: phenomena governing the *in vivo* performance of nanoparticles. *Appl Phys Rev*. 2020;7, 011316.
12. Nethi S, Mukherjee A, Mukherjee S. Biosynthesized gold and silver nanoparticles in cancer theranostics. In: Kharissova OV, ed. *Handbook of Nanomaterials and Nanocomposites for Energy and Environmental Applications*. Springer; 2020.
13. Peng J, Liang X. Progress in research on gold nanoparticles in cancer management. *Medicine*. 2019;98, e15311.
14. Dong L, Neuzil J. Targeting mitochondria as an anticancer strategy. *Cancer Commun*. 2019;39:63.
15. Wu Z, Ho WS, Lu R. Targeting mitochondrial oxidative phosphorylation in glioblastoma therapy. *Neuromolecular Med*. 2022;24:18–22.
16. DeBerardinis RJ et al. Beyond aerobic glycolysis: transformed cells can engage in glutamine metabolism that exceeds the requirement for protein and nucleotide synthesis. *Proc Natl Acad Sci USA*. 2007;104:19345–19350.
17. Warburg O, Wind F, Negelein E. Killing-off of tumor cells *in vitro*. *J Gen Physiol*. 1927;8:519–530.
18. Miki K, Yagi M, Yoshimoto K, Kang D, Uchiumi T. Mitochondrial dysfunction and impaired growth of glioblastoma cell lines caused by antimicrobial agents inducing ferroptosis under glucose starvation. *Oncogenesis*. 2022;11:59.
19. Banerjee D, Shamshad H, Mishra N. Nanotechnology for brain targeting. In: Keservani RK, ed. *Nanocarriers for Brain Targeting*. Apple Academic Press; 2019:69–90.
20. Harilal S et al. Revisiting the blood–brain barrier: a hard nut to crack in the transportation of drug molecules. *Brain Res Bull*. 2020;160:121–140.
21. Pawlowski KD, Duffy JT, Babak MV, Balyasnikova IV. Modeling glioblastoma complexity with organoids for personalized treatments. *Trends Mol Med*. 2023;29:282–296.
22. Kadry H, Noorani B, Cucullo L. A blood–brain barrier overview on structure, function, impairment, and biomarkers of integrity. *Fluids Barriers CNS*. 2020;17:69.
23. Cilingir EK et al. Metformin derived carbon dots: highly biocompatible fluorescent nanomaterials as mitochondrial targeting and blood–brain barrier penetrating biomarkers. *J Colloid Interface Sci*. 2021;592:485–497.
24. Zhou Y, Peng Z, Seven ES, Leblanc RM. Crossing the blood–brain barrier with nanoparticles. *J Control Release*. 2018;270:290–303.
25. Madkour LH. Biogenic–biosynthesis metallic nanoparticles (MNPs) for pharmacological, biomedical and environmental nanobiotechnological applications. *Chron Pharm Sci J*. 2018;2:384–444.
26. Ying S et al. Green synthesis of nanoparticles: current developments and limitations. *Environ Technol Innov*. 2022;26, 102336.
27. Aslam M, Rani A, Pant BN, Singh P, Pandey G. Recent development in the production and utilization of plant biomass-based nanomaterials. In: Tiwari SK, ed. *Biomass-Based Functional Carbon Nanostructures for Supercapacitors*. Springer; 2023:331–368.
28. Chawla P et al. Gum arabic capped copper nanoparticles: synthesis, characterization, and applications. *Int J Biol Macromol*. 2020;146:232–242.
29. Mzwd E et al. Green synthesis of gold nanoparticles in Gum Arabic using pulsed laser ablation for CT imaging. *Sci Rep*. 2022;12:10549.
30. Yuan W, Fu J, Su K, Ji J. Self-assembled chitosan/heparin multilayer film as a novel template for *in situ* synthesis of silver nanoparticles. *Colloids Surf B Biointerfaces*. 2010;76:549–555.
31. Uthappa UT, Suneetha M, Ajeya KV, Ji SM. Hyaluronic acid modified metal nanoparticles and their derived substituents for cancer therapy: a review. *Pharmaceutics*. 2023;15:1713.
32. Aktürk A, Taygun ME, Güler FK, Goller G, Küçükbayrak S. Fabrication of antibacterial polyvinylalcohol nanocomposite mats with soluble starch coated silver nanoparticles. *Colloids Surf Physicochem Eng Asp*. 2019;562:255–262.
33. Biliuta G, Coseri S. Cellulose: a ubiquitous platform for ecofriendly metal nanoparticles preparation. *Coord Chem Rev*. 2019;383:155–173.
34. Meguerdichian AG et al. Facile preparation of porous manganese oxide foams, sponges, and merged spherical networks, using Polydopamine/Dextran for catalytic oxidation of cyclohexane. *Microporous Mesoporous Mater*. 2020;295, 109740.
35. Walsh D, Arcelli L, Ikoma T, Tanaka J, Mann S. Dextran templating for the synthesis of metallic and metal oxide sponges. *Nat Mater*. 2003;2:386–390.
36. Panigrahi S, Kundu S, Ghosh S, Nath S, Pal T. General method of synthesis for metal nanoparticles. *J Nanoparticle Res*. 2004;6:411–414.
37. Rapachi D, Peixoto CR de M, Pavan FA, Gelesky MA. Metallic nanoparticles biosynthesized by phenolic-rich extracts: interaction, characterization and application. *J Clust Sci*. 2023;34:2743–2757.
38. Soliman MG, Pelaz B, Parak WJ, del Pino P. Phase transfer and polymer coating methods toward improving the stability of metallic nanoparticles for biological applications. *Chem Mater*. 2015;27:990–997.
39. Bhutto AA, Kalay Ş, Sherazi STH, Culha M. Quantitative structure–activity relationship between antioxidant capacity of phenolic compounds and the plasmonic properties of silver nanoparticles. *Talanta*. 2018;189:174–181.
40. Badeggi UM et al. Green synthesis of gold nanoparticles capped with procyanidins from Leucosidea sericea as potential antidiabetic and antioxidant agents. *Biomolecules*. 2020;10:452.
41. Ahmad F, Ashraf N, Ashraf T, Zhou RB, Yin DC. Biological synthesis of metallic nanoparticles (MNPs) by plants and microbes: their cellular uptake, biocompatibility, and biomedical applications. *Appl Microbiol Biotechnol*. 2019;103:2913–2935.
42. Vijayaram S et al. Applications of green synthesized metal nanoparticles—a review. *Biol Trace Elem Res*. 2024;202:360–386.
43. Aditya N, Espinosa YG, Norton IT. Encapsulation systems for the delivery of hydrophilic nutraceuticals: food application. *Biotechnol Adv*. 2017;35:450–457.
44. Chandra H, Kumari P, Bontempi E, Yadav S. Medicinal plants: treasure trove for green synthesis of metallic nanoparticles and their biomedical applications. *Biocatal Agric Biotechnol*. 2020;24, 101518.
45. Jeyarani S et al. Biomimetic gold nanoparticles for its cytotoxicity and biocompatibility evidenced by fluorescence-based assays in cancer (MDA-MB-231) and non-cancerous (HEK-293) cells. *J Photochem Photobiol B*. 2020;202, 111715.
46. Shafey AME. Green synthesis of metal and metal oxide nanoparticles from plant leaf extracts and their applications: a review. *Green Process Synth*. 2020;9:304–339.
47. Mujahid MH et al. Metallic and metal oxide-derived nanohybrid as a tool for biomedical applications. *Biomed Pharmacother*. 2022;155, 113791.
48. Trivedi R et al. Recent advancements in plant-derived nanomaterials research for biomedical applications. *Processes*. 2022;10:338.
49. Dai X et al. Crosstalk between microglia and neural stem cells influences the relapse of glioblastoma in GBM immunological microenvironment. *Clin Immunol*. 2023;251, 109333.
50. Iranmanesh Y et al. Mitochondria's role in the maintenance of cancer stem cells in glioblastoma. *Front Oncol*. 2021;11, 582694.
51. Arthurs AL, Keating DJ, Stringer BW, Conn SJ. The suitability of glioblastoma cell lines as models for primary glioblastoma cell metabolism. *Cancers*. 2020;12:3722.
52. Pavlova NN, Zhu J, Thompson CB. The hallmarks of cancer metabolism: still emerging. *Cell Metab*. 2022;34:355–377.
53. Galarraga J et al. Glucose metabolism in human gliomas: correspondence of *in situ* and *in vitro* metabolic rates and altered energy metabolism. *Metab Brain Dis*. 1986;1:279–291.
54. Luo Y, Ma J, Lu W. The significance of mitochondrial dysfunction in cancer. *Int J Mol Sci*. 2020;21:5598.
55. Lu RO, Ho WS. Mitochondrial dysfunction, macrophage, and microglia in brain cancer. *Front Cell Dev Biol*. 2021;8, 620788.
56. Ostrowski RP, Pucko EB. Harnessing oxidative stress for anti-glioma therapy. *Neurochem Int*. 2022;154, 105281.
57. Beylerli O et al. Therapeutic effect of natural polyphenols against glioblastoma. *Front Cell Dev Biol*. 2022;10, 1036809.
58. Garcia JH, Jain S, Aghi MK. Metabolic drivers of invasion in glioblastoma. *Front Cell Dev Biol*. 2021;9, 683276.
59. Wang Z, Chen G. Insights about circadian clock in glioma: from molecular pathways to therapeutic drugs. *CNS Neurosci Ther*. 2022;28:1930–1941.
60. Huang R et al. Dual role of reactive oxygen species and their application in cancer therapy. *J Cancer*. 2021;12:5543.
61. Yekula A et al. Large and small extracellular vesicles released by glioma cells *in vitro* and *in vivo*. *J Extracell Vesicles*. 2020;9, 1689784.
62. Su YL, Hu SH. Functional nanoparticles for tumor penetration of therapeutics. *Pharmaceutics*. 2018;10:193.
63. Wadajkar AS et al. Tumor-targeted nanotherapeutics: overcoming treatment barriers for glioblastoma. *Wiley Interdiscip Rev Nanomed Nanobiotechnol*. 2017;9, e1439.
64. Mkandawire M et al. Induction of apoptosis in human cancer cells by targeting mitochondria with gold nanoparticles. *Nanoscale*. 2015;7:10634–10640.
65. Patra JK et al. Nano based drug delivery systems: recent developments and future prospects. *J Nanobiotechnol*. 2018;16:71.
66. Bhanvase BA, Pawade VB, Dhoble SJ, Sonawane SH, Ashokkumar M, eds. *Nanomaterials for Green Energy*. Elsevier; 2018.
67. Amini SM, Akbari A. Metal nanoparticles synthesis through natural phenolic acids. *IET Nanobiotechnol*. 2019;13:771–777.

68. Bai X et al. The basic properties of gold nanoparticles and their applications in tumor diagnosis and treatment. *Int J Mol Sci*. 2020;21:2480.
69. Mishra P et al. Facile bio-synthesis of gold nanoparticles by using extract of Hibiscus sabdariffa and evaluation of its cytotoxicity against U87 glioblastoma cells under hyperglycemic condition. *Biochem Eng J*. 2016;105:264–272.
70. Balasubramanian S, Kala SMJ, Pushparaj TL. Biogenic synthesis of gold nanoparticles using Jasminum auriculatum leaf extract and their catalytic, antimicrobial and anticancer activities. *J Drug Deliv Sci Technol*. 2020;57, 101620.
71. Patra S, Mukherjee S, Barui AK, Ganguly A, Sreedhar B, Patra CR. Green synthesis, characterization of gold and silver nanoparticles and their potential application for cancer therapeutics. *Mater Sci Eng C*. 2015;53:298–309.
72. Rudrappa M, Rudayni HA, Assiri RA, et al. Plumeria alba-Mediated Green Synthesis of Silver Nanoparticles Exhibits Antimicrobial Effect and Anti-Oncogenic Activity against Glioblastoma U118 MG Cancer Cell Line. *Nanomaterials*. 2022;12(3):493.
73. Sharma S, S C, Sanpui P, Chattopadhyay A, Ghosh SS. Silver nanoparticles impregnated alginate–chitosan-blended nanocarrier induces apoptosis in human glioblastoma cells. *Adv Healthc Mater*. 2014;3:106–114.
74. Zheng M, Wang S, Liu Z, Xie L, Deng Y. Development of temozolomide coated nano zinc oxide for reversing the resistance of malignant glioma stem cells. *Mater Sci Eng C*. 2018;83:44–50.
75. Hamidian K, Sarani M, Sheikhi E, Khatami M. Cytotoxicity evaluation of green synthesized ZnO and Ag-doped ZnO nanoparticles on brain glioblastoma cells. *J Mol Struct*. 2022;1251, 131962.
76. Akbarizadeh MR, Naderifar M, Mousazadeh F, Zafarnia N, Sarani M. Cytotoxic activity and magnetic behavior of green synthesized iron oxide nanoparticles on brain glioblastoma cells. *Nanomed Res J*. 2022;7:99–106.
77. Vasimalai N et al. Green synthesis of fluorescent carbon dots from spices for *in vitro* imaging and tumour cell growth inhibition. *Beilstein J Nanotechnol*. 2018;9:530–544.
78. Mukherjee A, Waters AK, Kalyan P, Achrol AS, Kesari S, Yenugonda VM. Lipid–polymer hybrid nanoparticles as a next-generation drug delivery platform: state of the art, emerging technologies, and perspectives. *Int J Nanomed*. 2019;14:1937.
79. Rivas-García L et al. Ultra-small iron nanoparticles target mitochondria inducing autophagy, acting on mitochondrial dna and reducing respiration. *Pharmaceutics*. 2021;13:90.