Discovering Novel and Old Drug Targets in Oral Cancer Stem Cells Using bio-inspired methods – A Review

Vijay Kumar Jaiswal [1], Mahendra Kumar Verma [1]

Abstract

Addressing the high mortality rate and limited treatment options for oral cancer is a global public health challenge. To enhance therapeutic approaches, a comprehensive understanding of oral cancer stem cells (OCSCs) is essential. This review employs advanced bio-inspired methods to identify unique pharmacological targets within OCSCs, considering their heterogeneity and resistance to conventional treatments. The Evolutionary Computation Network for Drug Repositioning (ECN-DR) dissects the intricate signaling pathways and molecular networks within OCSCs using bio-inspired techniques. By integrating machine learning, network analysis, and molecular dynamics simulations, this approach identifies potential targets for both new and existing anticancer drugs. Recognizing the key molecular players in OCSCs enables the design of tailored medicines to disrupt these cells, offering more potent and targeted therapy options with fewer side effects. Molecular dynamics simulations, protein-ligand docking studies, and in silico drug screening predict the binding affinity and therapeutic potential of prospective medications against selected OCSC targets. These simulations contribute to a better understanding of targeting specific proteins in oral cancer therapy. Utilizing bio-inspired methods and computational simulations enhances our knowledge of OCSC biology, advancing the prospects of personalized cancer treatment.

Keywords: Oral Cancer, Stem Cells, Bio-Inspired Methods, Evolutionary Computation, Drug Repositioning

Significance | Evolutionary Computation Network for Drug Repositioning reveals oral cancer stem cells, informing targeted therapies for treatment.

*Correspondence: Vijay Kumar Jaiswal, Department of Pharmacy, Kalinga University, Naya Raipur, Chhattisgarh, India.
Email:ku.vijaykumarjaiswal@kalingauniversity.ac.in

Editor Fouad Saleh Al Suede And accepted by the Editorial Board Dec 7, 2023 (received for review Nov 7, 2023)

1. Introduction

Exploring therapeutic targets within oral cancer stem cells is a complex endeavor that can be approached using bio-inspired methods, though not without challenges (Catania, M., 2022). In oral cancer, a subset of tumor cells, known as stem cells, possesses the ability to self-renew and differentiate, contributing to tumor development, progression, and resistance to treatment (Amiri, A., 2022). Bio-inspired approaches, such as computer modeling and artificial intelligence, have demonstrated promise in uncovering potential therapeutic targets by mimicking intricate biological processes (Chen, S., 2022). Despite significant progress, several formidable obstacles remain (Lutz, T. M., 2022). The quest for a universal pharmacological target for oral cancer is complicated by the variability of stem cells among and within patients (Koch, C., 2023).

Moreover, accurate modeling and prediction face challenges due to a lack of complete, high-quality data on oral cancer stem cells (Tripathi, D., 2023). Cancer stem cells' dynamic nature and environment add another layer of difficulty to the target-finding process (Rezaie, J., 2022). Translating computational predictions into clinically applicable medicines is hindered by the expensive and time-consuming validation of potential targets in

Author Affiliation:
[1] Department of Pharmacy, Kalinga University, Naya Raipur, Chhattisgarh, India.

Please cite this article:
Vijay Kumar Jaiswal, Mahendra Kumar Verma. (2023). Discovering Novel and Old Drug Targets in Oral Cancer Stem Cells Using bio-inspired methods – A Review, Journal of Angiotherapy, 7(2), 1-9, 9397

experimental settings (Harun-Ur-Rashid, M., 2023). Despite the promise of bio-inspired approaches in understanding oral cancer stem cells and identifying new therapeutic targets, these obstacles must be overcome before effectively combating this deadly disease (Mukherjee, A., 2020).

Multiple approaches are necessary to comprehensively understand the potential and limitations of bio-inspired methodologies for discovering novel and established therapeutic targets in oral cancer stem cells (De Matteis, V., 2020). The identification of promising therapeutic targets often relies on computational methods like network analysis, machine learning, and molecular docking (Wang, L., 2019). Cancer stem cells serve as the origin of the disease, and a network-based examination of their intricate molecular relationships aids in identifying treatment targets (Gao, P., 2021). Machine learning algorithms leverage large-scale omics data to predict novel targets or biomarkers associated with oral cancer stem cells (Huo, Y., 2023). Molecular docking simulations evaluate prospective drug interactions with molecular targets, facilitating the development of targeted therapeutics (Brogi, S., 2022).

However, certain obstacles persist. The diversity and variability of oral cancer stem cells present a significant challenge, making it challenging to discover pharmacological targets applicable across all cases (Schuh, C. M., 2019). The reliability of computational predictions is influenced by the availability and quality of experimental data, including genomics, proteomics, and metabolomics (Zaszczyńska, A., 2022). Target discovery is already challenging, and the ever-changing nature of cancer stem cells and their environment complicates matters further. While bio-inspired approaches generate numerous potential targets, converting these predictions into safe and effective medications in clinical practice poses a significant challenge (Tong, Q., 2020). Ethical concerns and regulatory barriers in preclinical and clinical studies additionally impede the development of novel therapeutic targets. Bio-inspired approaches offer promising avenues for discovering drug targets in oral cancer stem cells; however, addressing the complexities of cancer stem cell biology, data quality, validation, and translational barriers is imperative to fully harness their potential in advancing therapies for oral cancer patients (Neubi, G. M. N., 2018).

The review endeavors to uncover novel therapeutic targets within oral cancer stem cells (OCSCs). Given that OCSCs play a pivotal role in cancer initiation, growth, and resistance, they represent a promising focus for therapeutic intervention. Employing state-of-the-art bio-inspired methods, the study aims to identify innovative pharmacological targets within OCSCs, addressing the limited treatment options currently available for oral cancer. Another objective involves delving into the intricate signaling cascades and molecular networks of OCSCs. Utilizing bio-inspired approaches such as the Evolutionary Computation Network for Drug Repositioning (ECN-DR), the research aims to decipher the molecular connections within these cells. This comprehensive understanding facilitates the identification of key molecular players that can be targeted by medications, thereby paving the way for more effective and personalized treatments for oral cancer. Ultimately, the research strives to pinpoint pharmacological targets capable of disrupting OCSCs, with the overarching goal of enhancing oral cancer treatment by developing safer and more efficacious drugs. This approach holds the potential to improve treatment outcomes for patients while minimizing tissue damage.

1. Literature Survey

Significant advancements have been achieved in recent years, particularly in the realms of medication delivery systems and regenerative medicine, owing to the convergence of nanotechnology and bioengineering. Stem cell-derived ECN-DR has emerged as a natural nanocarrier, enhancing cell communication and precise medication administration.

Abudurexiti et al. (2023) introduced extracellular vesicles (EVs) as natural nanoscale particles derived from stem cells, facilitating cell-to-cell communication and drug delivery. The fusion of nanotechnology and bioengineering has led to the development of biomimetic nanocarriers, exemplified by plant-based nanoparticles (P-BN) created by Gulia et al. (2022), which may harbor antioxidants and anti-cancer properties for potential applications in cancer theranostics.

Haring et al. (2019) innovatively crafted dopamine-conjugated (DC) hyaluronic acid, producing bioinks with unique rheological behavior. This approach has implications for biofabrication in regenerative medicine, particularly in creating flexible, free-standing 3D neural tissues.

The necessity for novel solutions that mimic the physiological extracellular environment is underscored by Tampieri et al.'s (2021) Nanotechnological Approach (NA), offering promising outcomes even in challenging scenarios such as cell senescence in the elderly. Sang et al. (2021) proposed modifying polyetheretherketone (PEEK), commonly used in orthopedic implants, resulting in a 3D porous structure that, when combined with a gentamicin-silk protein coating, ensures a stable release of gentamicin.

In the realm of medication repositioning and cutting-edge drug delivery systems, the Evolutionary Computation Network for medication Repositioning (ECN-DR) is a groundbreaking development (Gulia, K., 2022). While other research explores nanotechnology, bioengineering, and biomimetics, ECN-DR stands out for its integrative, computationally driven approach to drug repositioning (Catania, M., 2022).

2. Revolutionizing oral cancer treatment by combining bio-inspired techniques and molecular profiling

The study highlights the potential of bio-inspired techniques and nanotechnology-based drug delivery systems in transforming oral cancer diagnosis and treatment. While promising, further research is needed to optimize these approaches for clinical applications and address safety concerns, paving the way for personalized and effective oral cancer therapies (Abbasi et al,2012). Researchers combine bio-inspired techniques and molecular profiling to target therapy for oral cancer stem cells. Using nature's principles, they create innovative drug delivery systems like FeAu@MOF nanostructures, IRMOF3-DSF-FA, and MN-based sensors (Alberti et al,2015). These systems demonstrate enhanced imaging, tumor reduction, and selective drug delivery, promising improved oral cancer treatments. Nanotechnology, drug-loaded MOFs, and AuNPs show potential for effective drug delivery and diagnostics in oral cancer therapy (Conti et al,2016). Further research is needed to optimize these approaches for clinical applications and address biosafety concerns.

Integrating bio-inspired methodologies with cutting-edge molecular profiling emerges as a groundbreaking tool for identifying therapeutic targets in oral cancer stem cells (Crich et al,2015). This innovative approach leverages nature's design principles to explore potential therapeutic targets within elusive cells, offering promising prospects for advancing oral cancer treatments (DeFrates et al,2018).

In recent decades, various inorganic and organic vehicles have been employed to deliver anticancer agents and drugs to oral cancer cells. These include carbon structures, mesoporous silica nanoparticles, nitric oxide and oxide structures, as well as dendrimers and polymers such as micelles. (Hasan et al,2015) However, a deeper investigation into the metabolic processes, biological transportation, and immunogenicity of inorganic systems is essential. Organic compounds often suffer from insufficient transferability and premature drug release when utilized as carriers (Hong et al,2020). In this context, metal-organic frameworks (MOFs) stand out as promising candidates due to their potential to address a wide range of issues related to medication delivery, accommodating hydrophilic, hydrophobic, and amphiphilic drugs for encapsulation.

Equation (1) symbolizes the encapsulation of the hydrophobic pharmaceutical Dox within nanocarriers (FeAu@MIL-100), showcasing the potential of MOFs. Researchers demonstrated superparamagnetism induced by hyperthermia and a fluctuating magnetic field, illustrating the viability of MOFs for cancer theranostics (Jithan et al,2011). In vivo experiments with FeAu@MOF nanostructures showed enhanced imaging contrast, reduced tumor volume, and decreased tumor weight, promising improved symptom management for oral cavity cancer.

Equation (2) introduces a formula (CA) representing cell apoptosis, highlighting the significance of metal-organic framework-FeAu NPs nanoparticles for curative and imaging purposes in hyperthermia-induced cancer (Khalid et al,2016). These nanostructures effectively reduced tumor development and increased survival in a mouse model.

Equation (3) elucidates the formation of Dox gel (D_o) for cancer treatment, emphasizing the potential of Zn2+-based compounds to inhibit ALDH1+ cancerous stem cells (Lohcharoenkal et al,2014). The drug delivery system IRMOF3-DSF-FA demonstrated effective tumor inhibition without negatively impacting key organs.

Equations (4) and (5) delve into the treatment of oral cancer, showcasing the role of molecular organic frameworks (MOFs) in encapsulating molecules and offering slow, regulated drug release patterns (Lu et al,2019). The utilization of MNs (microneedles) is explored in Equation (6), presenting various applications such as painless oral fluid collection for cancer detection, targeted drug delivery, and adjunctive periodontal medical care (Martinez et al,2017). Equation (7) delves into oral anesthesia, demonstrating the potential of mucosa-coated MNs for localized relief in basic dental operations.

The algorithm presented outlines a systematic analysis of cancer cells to determine the tumor factor, enabling personalized recommendations for medical care (Mottaghitalab et al,2017). The use of nanotechnology-based drug delivery systems in cancer treatment is emphasized, offering improved bioavailability, reduced drug resistance, and better patient compliance.

While AuNPs (gold nanoparticles) show promise in oral cancer detection and therapy, concerns about their health risks necessitate further research and resolution. The multifaceted applications of AuNPs, from early diagnosis to combination therapies, are highlighted, emphasizing the need for comprehensive studies to address biosafety concerns (Onafuye et al,2019).

$$\Delta Dox = |nc(\text{FeAu} - NP - 1) + \log e(dt)| \quad (1)$$

Equation (1) implies the hydrophobic pharmaceutical Dox, ΔDox has been enclosed in a nanocarrier represented by nc that is (FeAu@MIL-100) in a work by researchers.

Researchers developed FeAu@MOF nanostructures by combining FeAu nanoparticles with MIL-100 (Fe) MOFs, achieving high drug encapsulation efficiency (69.95%) and production (97.19%) for the anticancer drug Dox. The nanostructures exhibited superparamagnetism under hyperthermia, killing 90% of oral cancer cells (HSC-3) in vitro with an alternating magnetic field (Peñalva et al,2015). In vivo, these nanostructures enhanced

imaging contrast, reduced tumor volume by 30%, and decreased tumor weight by a factor of 10, promising improved oral cancer theranostics and prolonged survival (Rong et al,2015). This resulted in longer cumulative survival and showed the method's promise in managing the symptoms of oral cavity cancer shown in Figure 1.

$$CA = \frac{\emptyset - \partial + MI - DE}{\sqrt{2\log L}} + MF \quad (2)$$

CA be the cell apoptosis , $\emptyset$ be the cancer cell ingestion, ∂ be the metal organic framework, MI be the magnetic field, DE be the doxorubicin encapsulation and MF be the metal organic framework in equation (2).

$$D_o = T - \frac{Zn_{nm} + NH_{nm}}{m} (m = 1,2,3 \dots \dots n) \quad (3)$$

Equation (3) denotes D_o be the Dox gel , T be the treatment, Zn_{nm} be the zn o cluster, NH be the component, m be the mouse model.

A novel approach to inhibit ALDH1+ cancerous stem cells involves using Zn2+ and the hydrophilic drug disulfiram (DSF). Researchers developed the first metal-organic scaffold (IRMOF3)-Zn2+, incorporating DSF. Further, they created the drug delivery system IRMOF3-DSF-FA by loading the surface with folic acid (FA) (Seib et al,2013). This system demonstrated high metal ion packing capacity, excellent biocompatibility, and efficient cell uptake. In in vivo experiments, IRMOF3 effectively suppressed tumor and ALDH1+ CSC growth in treating oral cancer without adverse effects on vital organs (Shenget al,2014).

$$O_i(t) = \frac{\sum_{j=1}^{N} T_{ij}(1+[D-C_j]^{2/(S+1)})}{N} + (1 - [D - C_j]^{2/(S+1)}) \quad (4)$$

$$i = 1, 2, \dots \dots C \text{ and } j = 1, 2 \dots \dots \dots N$$

$$O(y) = \min\left(T_{ij}(y) \right) \quad i = 1, 2, \dots \dots, C \quad (5)$$

In equation (4) and (5) , $O_i(t)$ be the organs in the treatment of oral cancer, T_{ij} be the tumour, D be the drug delivery system, C_j be the capacity, N be the number of tumour cells. Molecular organic frameworks (MOFs) can be used of encapsulating molecules because of the non-covalent bonds formed among the molecules and the MOFs, which also allow the MOF's pores to swallow up molecules whose sizes are less than the MOF's pore size (Alberti et al,2015).

Dedicated researchers and clinicians are fervently exploring innovative equipment and strategies for oral health prevention and therapy, particularly in the field of Health and Fitness Monitoring (HFM). Recent laboratory and clinical studies, as depicted in Figure 3, focus on incorporating HFM principles to detect, treat, and prevent dental problems and diseases, showcasing a proactive approach to oral healthcare (Asadi et al,2021).

$$D_P = \frac{(O_h - OP)}{(O_h - O_T)} \log \frac{[O_T - O_{DP}]}{O_D} \quad (6)$$

In equation (6), D_P be the dental problem, O_h be the oral health , OP be the oral health prevention, O_T be the oral therapy, O_{DP} be the oral dental problem, O_D be the detection of oral therapy,

Micro-needles (MNs) offer a versatile approach in oral healthcare. They enable painless collection of oral fluids for diagnostic purposes, aiding in the early detection of oral cancer by examining tissues for malignant cells. MNs can also deliver targeted chemotherapy in micro-doses for oral cancer treatment (Goswami et al,2018). Additionally, they play a role in mucosal immunization, vaccine delivery, drug administration for enhanced efficacy, periodontal care by delivering medications to the gum, antibacterial treatment, and oral anesthesia for pain relief during dental procedures (Tarhini et al,2018). MNs demonstrate potential in improving various aspects of oral healthcare.

$$OT_A = M_k^{-} * MC_k = M_k^{-}(L_k x + L_k y + L_k), \text{ k= 1, 2…N} \quad (7)$$

Equation (7) denotes the OT_A be the Oral anesthesia, M_k be the mucosa prior, MC_k be the mucosa prior to local anesthetic injection, $L_k x$ be the basic dental operations for localized releief.

Detecting oral malignancies, particularly squamous cell carcinoma, in their early stages is challenging due to the absence of warning signs. Biomarkers such as lactic acid, valine, stromal polypeptide molecule, lysine, proline, citrulline, and ornithine have been linked to oral cancer, making the utilization of MN-based sensors for early detection in the interstitial fluid (ISF) of potential oral lesions a promising advancement (Wang et al,2014). The use of microneedles (MNs) as a drug delivery mechanism has evolved significantly since the initial MN patents were filed in the 1970s. MNs have been employed in recent years for delivering medications through oral mucosal barriers. Traditional treatments combining surgery with chemotherapy and/or radiotherapy may fall short in achieving optimal outcomes for recurrent oral cancer due to substantial maxillofacial anatomy scarring and inadequate perfusions from previous therapies at the initial detection of malignancy (Wu et al,2018). An alternative therapeutic approach involves injecting anti-cancer medications directly into tumors, but this method faces challenges such as inefficient drug distribution within the tumor, causing discomfort and potential harm to patients. Researchers addressed these issues by developing a poly(lactic-co-glycolic) acid (PLGA) coating of dioxane (DOX)

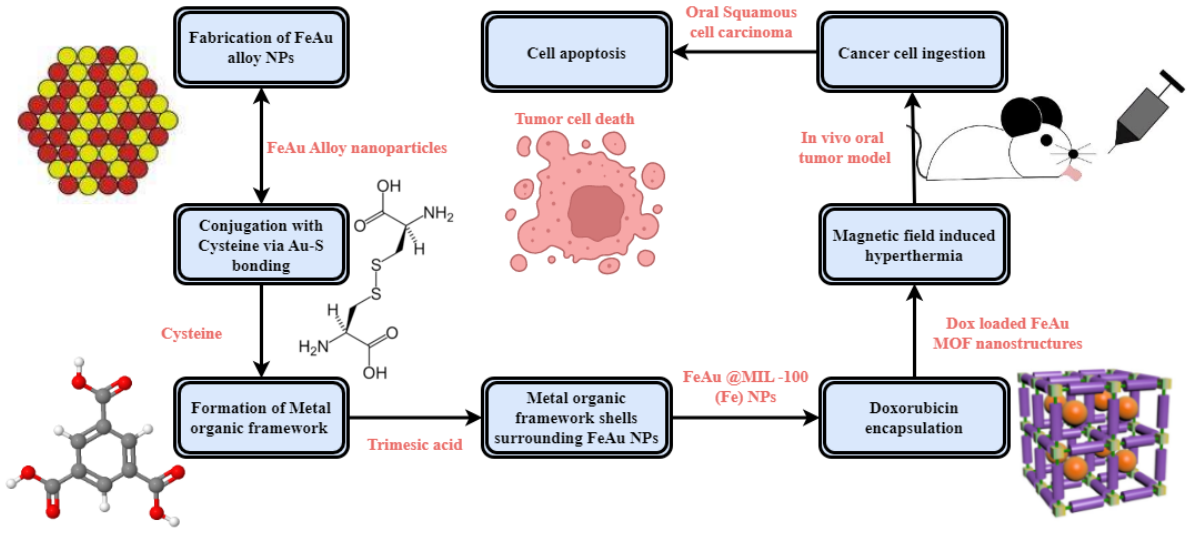

Figure 1. Nanostructures made of metal-organic frameworks and ferrocenyl aluminide (FeAu) were developed for the treatment and diagnosis of hyperthermia-induced cancer

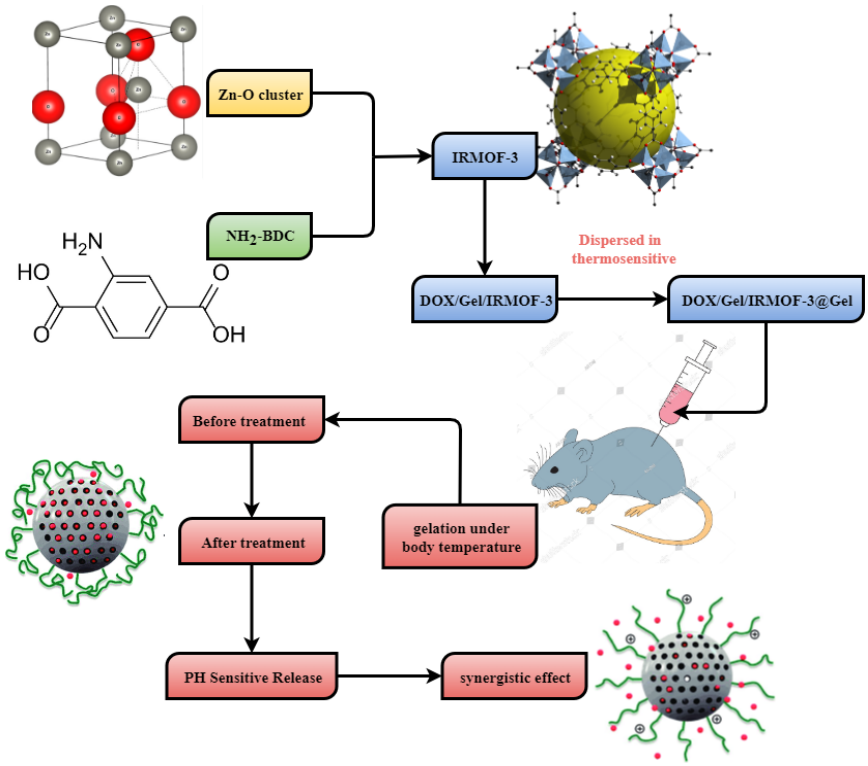

Figure 2. Cancer treatment using an injectable metal-organic scaffold Cancer Therapy

Box 1. Predictive algorithmm model.

Start: Resulting Events in a Dataset
Result: Warning signal
Step 1: Calculate the tumor factor (TF) of the patient.
Step 2: If TF = Contagious, then
Step 3: Access to close medical personnel or caregivers
Step 4: Inform adjacent hospitals of a patient's location
Step 5: else if TF = Possibility of low risk then
Step 6: Personal caregivers required
Step 7: Recommend medications for home speedy recovery
End if

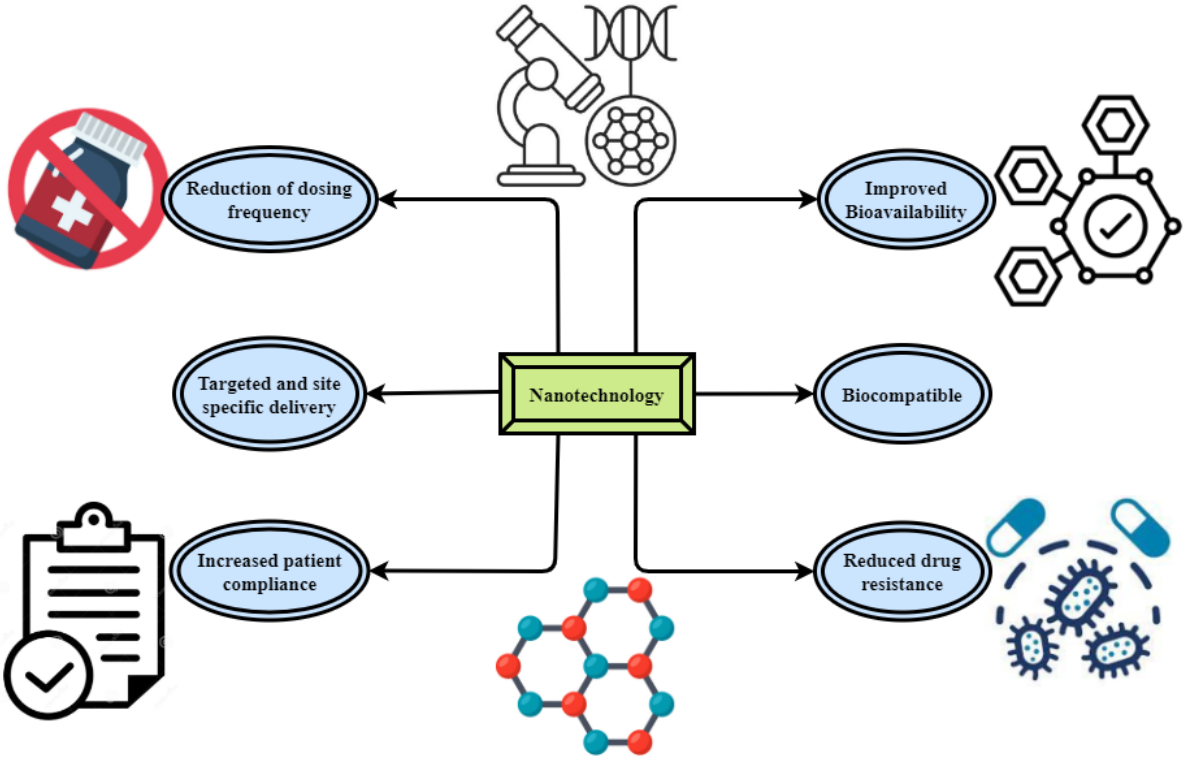

Figure 4. Nano systems of naturally occurring chemicals have several potential benefits for treating mouth cancer

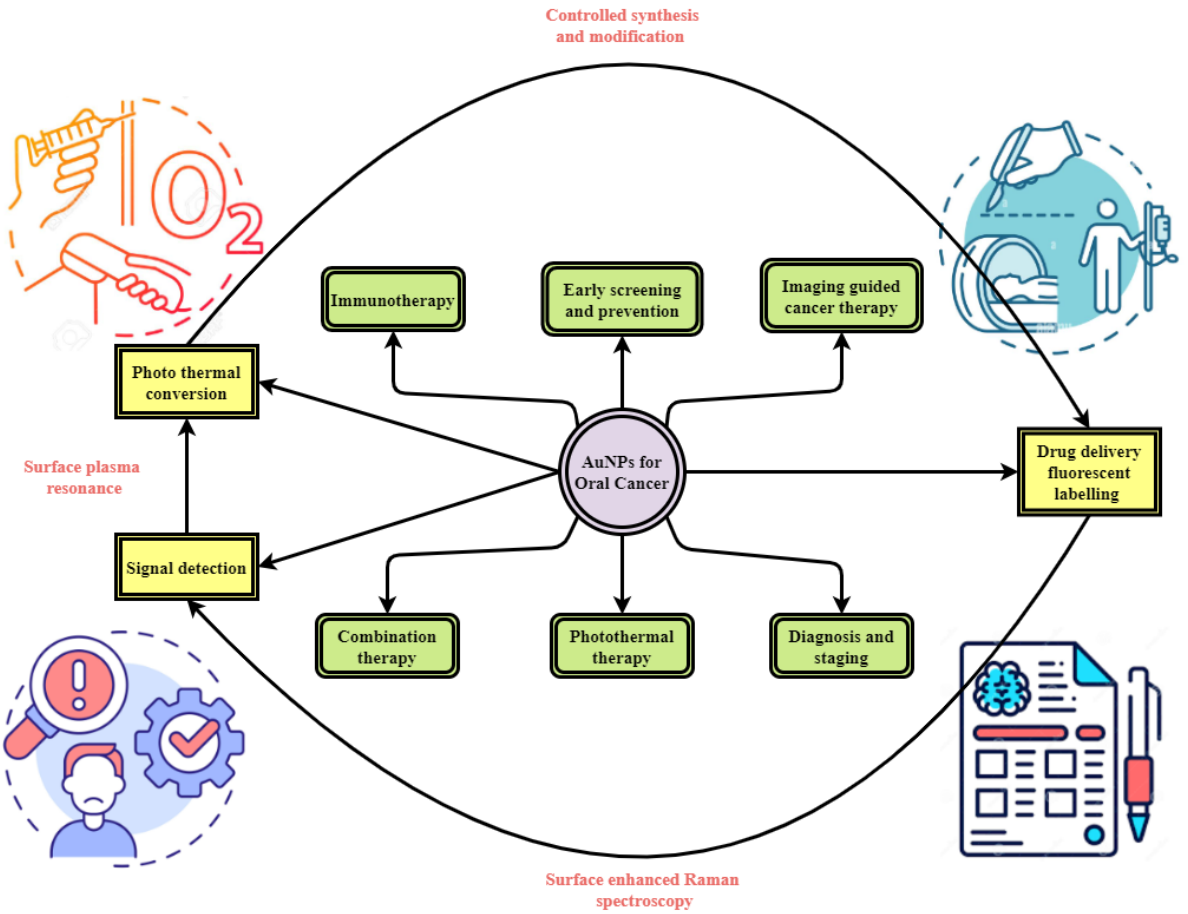

Figure 5. Diagram depicting the potential use of gold nanoparticles (AuNPs) in the treatment of oral cancer.

with a particle size of 137 nm (Xu et al,2019).. This approach demonstrated effective tissue destruction in a 3D malignant tumor model, reaching cancer cells within a 1 cm radius of the MN array. Another research group created cellulose MN patches to locally deliver the chemotherapeutic drug 5-fluorouracil to the buccal mucosa, providing a potential solution for addressing oral carcinoma locally. Additionally, a microneedle patch equipped with a photosensitizer showed promise in enhancing treatment quality with light for oral cancer cases, leading to a significant decrease in tumor volume in a xenograft model after local patch application and subsequent near-infrared laser irradiation (Yahya et al,2021).

Oral cancer (OC) has become a prevalent and deadly global cancer, with higher death rates observed in populations with heavy alcohol and cigarette use. Standard treatment options like chemotherapy, radiation, and surgery are often ineffective against tumors and may induce cell death in inappropriate areas. Adopting alternative treatment methods may address issues associated with traditional therapies, including their damaging effects (Zhang et al,2016). While the toxicity of radiation therapy remains a concern, natural ingredients offer potential mitigation. Various natural compounds discussed in this summary show promise as effective anticancer drugs by inhibiting the development of oral tumor cells through blocking specific signaling pathways. Overcoming common challenges associated with natural products, such as poor absorption and targeting, can be achieved through innovative drug delivery vehicles (Zhu et al,2017).

The algorithm presented above analyzes drug responses in cancer cells, assessing the patient's tumor factor. If the factor is contagious, medical personnel are alerted for immediate care; otherwise, if the tumor factor suggests low risk, personalized caregivers are recommended, and medications for home recovery may be advised (Watt et al,2011).

Nanotechnology-based medication delivery systems offer promising advancements in treating various cancers, including oral cancer (OC). This study reviews recent breakthroughs in OC treatment, focusing on innovative drug delivery strategies utilizing microscopic and location-based targeted systems. The research demonstrates that these groundbreaking techniques enhance the absorption of natural chemicals through mechanisms such as enhanced permeability and retention (EPR), small particle reduction, molecular bonding, and drug encapsulation (Song et al,2019). The benefits include increased bioavailability, reduced drug resistance, improved patient compliance, and fewer missed doses. However, challenges such as the lack of in vivo bioavailability data for new formulations and limited research on drug metabolism and linkage studies need to be addressed. Further research, particularly clinical investigations, is recommended for a better understanding of optimal therapeutic dosages and strategies for efficient drug release in the medical management of malignancies (Onafuye et al,2019).

While there is limited FDA-approved research on gold nanoparticles (AuNPs) for cancer therapy, initial clinical studies, such as CYT-6091, showed promise in tumor targeting and damage. In the context of oral cancer, AuNPs have demonstrated potential applications in early diagnosis, tumor staging, drug administration, photothermal therapy (PTT), and combination therapies (Pericleous et al,2012). Multimodal combination therapy and immunological treatments based on AuNPs have shown efficacy, but clinical studies on AuNPs for oral cancer theranostics are yet to begin. Despite the potential, the health risks of AuNPs, particularly variations in their synthesis processes, size, and structure, pose concerns, and resolving biosafety issues is crucial before clinical trials can proceed (Von er al,2012).

The study explores a bio-inspired approach to discovering therapeutic targets in oral stem cells for cancer. Utilizing multi-omics data and network analysis, the research unveils molecular connections and weaknesses specific to malignant oral cells. This novel technique holds substantial potential in advancing tailored medicines and improving outcomes in the medical management of gastrointestinal cancer by bridging the gap between traditional manufacturing and computational methods.

This comprehensive review underscores the potential of innovative approaches, from bio-inspired techniques to nanotechnology-based drug delivery systems, in advancing the diagnosis and treatment of oral cancer. The integration of computational methods with traditional medicinal product manufacturing holds great promise for identifying novel therapeutic targets and improving patient outcomes in the management of oral cancer.

3. Discussion

The Evolutionary Computation Network for Drug Repositioning (ECN-DR) plays a pivotal role in advancing oral cancer treatment and personalized medicine through a comprehensive array of analytical methods. This in-depth exploration of Oral Cancer Stem Cells (OCSCs) includes expression profile analysis, network analysis, mutation analysis, functional experiments, and dose-response curve analysis.

Within the realm of ECN-DR, expression profile analysis is a critical element in the drug discovery process. This involves scrutinizing the gene or protein expression profiles of OCSCs to unearth potential therapeutic targets or repurpose existing drugs. By identifying overexpressed or under-expressed genes or proteins, researchers gain insights into their roles in cancer development and stem cell biology (Luo et al,2023). Leveraging computational tools and bio-inspired approaches, ECN-DR

enhances drug repositioning by identifying potential therapeutic targets and facilitates the discovery of chemicals for modifying target expression. This nuanced understanding of OCSC biology expedites the discovery of novel drug targets and repositioning opportunities, holding significant implications for advancing oral cancer treatment and personalized medicine (Chen et al,2020).

In the context of OCSCs, network analysis becomes integral within ECN-DR, transforming the drug discovery landscape. Analyzing molecular connections, signaling cascades, and protein-protein networks at the OCSC level enables the identification of prospective therapeutic targets amidst the intricate web of biological interactions. By constructing network models, ECN-DR sheds light on important molecular players in OCSC biology, offering promising targets for suppressing tumor growth by interfering with OCSC activities. The comprehensive approach facilitated by network analysis not only expedites the identification of therapeutic targets but also contributes to the development of more targeted and effective therapies for oral cancer (Hao et al,2022).

ECN-DR's focus on mutation analysis is paramount for identifying potential therapeutic targets and repositioning existing medications in the context of OCSCs. This analysis delves into the genomic changes, mutations, and variations within OCSCs to uncover the underlying genetic alterations responsible for their malignant properties and resistance to standard therapy (Xiong et al,2021). By identifying OCSC genetic abnormalities amenable to precision medicine, ECN-DR exposes potential weaknesses, paving the way for promising therapeutic targets. Additionally, mutation analysis aids in the repurposing of existing pharmaceuticals by revealing drugs that may selectively target OCSC-specific genetic alterations or their downstream signaling pathways, offering individualized care for each patient.

Functional tests within ECN-DR are crucial for characterizing potential therapeutic targets in OCSCs. These experiments involve manipulating the expression of certain genes or proteins to understand their impact on OCSCs' abilities related to tumorigenicity, self-renewal, differentiation, and therapy resistance. Functional tests provide valuable insights into how targeted molecular interventions affect OCSC behavior, aiding in the prioritization of pharmacological candidates that can disrupt OCSC functions. This integration of data from functional assays, computational analysis, and network modeling enhances the effectiveness of drug repositioning efforts and contributes to the development of personalized treatments for oral cancer (Huang et al,2014).

Dose-response curve analysis in ECN-DR quantitatively and methodically evaluates the efficacy of drug candidates for OCSCs. By exposing OCSCs to varying concentrations of drug candidates, researchers can determine the optimal medication concentration for growth suppression or apoptosis induction. This analysis calculates essential metrics such as the half-maximal inhibitory concentration (IC50) to gauge a drug's potency in targeting OCSCs. Dose-response curve analysis not only helps identify effective drug candidates but also ensures their safety by assessing dose-dependent toxicity. This method aids in the objective evaluation of drug candidates' effects on OCSCs, facilitating the prioritization of oral cancer treatments based on comprehensive data-driven insights (Miao et al,2014).

The Evolutionary Computation Network for Drug Repositioning (ECN-DR) represents a cutting-edge approach at the forefront of oral cancer research. Through its multifaceted analytical methods, ECN-DR accelerates drug discovery, repositions existing medications, and holds promise for achieving better outcomes in the challenging battle against oral cancer.

4. Conclusion

The bio-inspired exploration of therapeutic targets within Oral Cancer Stem Cells (OCSCs) represents a crucial step in addressing the global health challenge posed by oral cancer. Given the high mortality rates and limited therapeutic options, a fresh perspective on the disease's biology is essential. The current research employs advanced techniques, including the Evolutionary Computation Network for Drug Repositioning (ECN-DR), to unravel the intricate chemical interactions and signaling pathways inherent in OCSCs.

Utilizing a fusion of machine learning, network analysis, and molecular dynamics simulations, the study aims to identify key molecular entities within OCSCs that could serve as strategic targets for future cancer therapies. This groundbreaking approach opens avenues for the development of drugs specifically designed to selectively disrupt OCSCs, expanding therapeutic possibilities while minimizing the risk of undesired side effects.

Accurate prediction of binding affinity and therapeutic potential of prospective medications against these identified targets is crucial for developing effective oral cancer therapies. Molecular dynamics simulations, protein-ligand docking studies, and in silico drug screening play integral roles in this process.

The review advances our understanding of OCSC biology and sets the stage for more tailored approaches to cancer treatment. This offers optimism in the ongoing battle against oral cancer, promising improved clinical outcomes and an enhanced quality of life for individuals grappling with this challenging disease.

Author Contributions

V.K.J. and M.K.V. conceptualized, wrote, and reviewed the article.

Acknowledgment

None declared.

Competing financial interests

The authors have no conflict of interest.

References

Abbasi, S., Paul, A., Shao, W., & Prakash, S. (2012). Cationic albumin nanoparticles for enhanced drug delivery to treat breast cancer: preparation and in vitro assessment. Journal of drug delivery, 2012.

Abudurexiti, M., Zhao, Y., Wang, X., Han, L., Liu, T., Wang, C., & Yuan, Z. (2023). Bio-Inspired Nanocarriers Derived from Stem Cells and Their Extracellular Vesicles for Targeted Drug Delivery. Pharmaceutics, 15(7), 2011.

Alberti, D., Protti, N., Toppino, A., Deagostino, A., Lanzardo, S., Bortolussi, S., … & Aime, S. (2015). A theranostic approach based on the use of a dual boron/Gd agent to improve the efficacy of Boron Neutron Capture Therapy in the lung cancer treatment. Nanomedicine: Nanotechnology, Biology and Medicine, 11(3), 741-750.

Amiri, A., Bagherifar, R., Ansari Dezfouli, E., Kiaie, S. H., Jafari, R., & Ramezani, R. (2022). Exosomes as bio-inspired nanocarriers for RNA delivery: Preparation and applications. Journal of Translational Medicine, 20(1), 1-16.

Asadi, M., Salami, M., Hajikhani, M., Emam-Djomeh, Z., Aghakhani, A., & Ghasemi, A. (2021). Electrospray production of curcumin-walnut protein nanoparticles. Food Biophysics, 16, 15-26.

Brogi, S., Tabanelli, R., & Calderone, V. (2022). Combinatorial approaches for novel cardiovascular drug discovery: a review of the literature. Expert Opinion on Drug Discovery, 17(10), 1111-1129.

Catania, M., Colombo, L., Sorrentino, S., Cagnotto, A., Lucchetti, J., Barbagallo, M. C., ... & Di Fede, G. (2022). A novel bio-inspired strategy to prevent amyloidogenesis and synaptic damage in Alzheimer's disease. Molecular Psychiatry, 27(12), 5227-5234.

Catania, M., Colombo, L., Sorrentino, S., Cagnotto, A., Lucchetti, J., Barbagallo, M. C., ... & Di Fede, G. (2022). A novel bio-inspired strategy to prevent amyloidogenesis and synaptic damage in Alzheimer's disease. Molecular Psychiatry, 27(12), 5227-5234.

Chen, J., Fan, T., Xie, Z., Zeng, Q., Xue, P., Zheng, T., … & Zhang, H. (2020). Advances in nanomaterials for photodynamic therapy applications: Status and challenges. Biomaterials, 237, 119827.

Chen, S., Guo, Q., & Yu, J. (2022). Bio-inspired functional coacervates: Special Issue: Emerging Investigators. Aggregate, 3(6), e293.

Conti, L., Lanzardo, S., Ruiu, R., Cadenazzi, M., Cavallo, F., Aime, S., & Crich, S. G. (2016). L-Ferritin targets breast cancer stem cells and delivers therapeutic and imaging agents. Oncotarget, 7(41), 66713.

Corbin, I. R., Li, H., Chen, J., Lund-Katz, S., Zhou, R., Glickson, J. D., & Zheng, G. (2006). Low-density lipoprotein nanoparticles as magnetic resonance imaging contrast agents. Neoplasia, 8(6), 488-498.

De Matteis, V., & Rizzello, L. (2020). Noble metals and soft bio-inspired nanoparticles in retinal diseases treatment: A perspective. Cells, 9(3), 679.

Ding, D., Tang, X., Cao, X., Wu, J., Yuan, A., Qiao, Q., … & Hu, Y. (2014). Novel self-assembly endows human serum albumin nanoparticles with an enhanced antitumor efficacy. Aaps Pharmscitech, 15, 213-222.

Gao, P., Chang, X., Zhang, D., Cai, Y., Chen, G., Wang, H., & Wang, T. (2021). Synergistic integration of metal nanoclusters and biomolecules as hybrid systems for therapeutic applications. Acta Pharmaceutica Sinica B, 11(5), 1175-1199.

Goswami, U., Dutta, A., Raza, A., Kandimalla, R., Kalita, S., Ghosh, S. S., & Chattopadhyay, A. (2018). Transferrin–copper nanocluster–doxorubicin nanoparticles as targeted theranostic cancer Nanodrug. ACS applied materials & interfaces, 10(4), 3282-3294.

Gulia, K., James, A., Pandey, S., Dev, K., Kumar, D., & Sourirajan, A. (2022). Bio-inspired smart nanoparticles in enhanced cancer theranostics and targeted drug delivery. Journal of Functional Biomaterials, 13(4), 207.

Gulia, K., James, A., Pandey, S., Dev, K., Kumar, D., & Sourirajan, A. (2022). Bio-inspired smart nanoparticles in enhanced cancer theranostics and targeted drug delivery. Journal of Functional Biomaterials, 13(4), 207.

Hao, Y., Chung, C. K., Gu, Z., Schomann, T., Dong, X., Veld, R. V. H. I. T., … & Cruz, L. J. (2022). Combinatorial therapeutic approaches of photodynamic therapy and immune checkpoint blockade for colon cancer treatment. Molecular Biomedicine, 3(1), 26.

Haring, A. P., Thompson, E. G., Tong, Y., Laheri, S., Cesewski, E., Sontheimer, H., & Johnson, B. N. (2019). Process-and bio-inspired hydrogels for 3D bioprinting of soft free-standing neural and glial tissues. Biofabrication, 11(2), 025009.

Harun-Ur-Rashid, M., Jahan, I., Foyez, T., & Imran, A. B. (2023). Bio-Inspired Nanomaterials for Micro/Nanodevices: A New Era in Biomedical Applications. Micromachines, 14(9), 1786.

Hasan, S. (2015). A review on NPs: Their synthesis and types. Res. J. Recent Sci. ISSN, 2277, 2502.

Hong, S., Choi, D. W., Kim, H. N., Park, C. G., Lee, W., & Park, H. H. (2020). Protein-based nanoparticles as drug delivery systems. Pharmaceutics, 12(7), 604.

Huang, P., Wang, D., Su, Y., Huang, W., Zhou, Y., Cui, D., … & Yan, D. (2014). Combination of small molecule prodrug and nanodrug delivery: amphiphilic drug–drug conjugate for cancer therapy. Journal of the American Chemical Society, 136(33), 11748-11756.

Huo, Y., Hu, J., Yin, Y., Liu, P., Cai, K., & Ji, W. (2023). Self-Assembling Peptide-Based Functional Biomaterials. ChemBioChem, 24(2), e202200582.

Jiao, Y., Sun, Y., Tang, X., Ren, Q., & Yang, W. (2015). Tumor-Targeting Multifunctional Rattle-Type Theranostic Nanoparticles for MRI/NIRF Bimodal Imaging and Delivery of Hydrophobic Drugs. Small, 11(16), 1962-1974.

Jithan, A. V., Madhavi, K., Madhavi, M., & Prabhakar, K. (2011). Preparation and characterization of albumin nanoparticles encapsulating curcumin intended for the treatment of breast cancer. International journal of pharmaceutical investigation, 1(2), 119.

Karthikeyan, S., Prasad, N. R., Ganamani, A., & Balamurugan, E. (2013). Anticancer activity of resveratrol-loaded gelatin nanoparticles on NCI-H460 non-small cell lung cancer cells. Biomedicine & Preventive Nutrition, 3(1), 64-73.

Khalid, A., Mitropoulos, A. N., Marelli, B., Tomljenovic-Hanic, S., & Omenetto, F. G. (2016). Doxorubicin loaded nanodiamond-silk spheres for fluorescence tracking and controlled drug release. Biomedical Optics Express, 7(1), 132-147.

Khalid, A., Mitropoulos, A. N., Marelli, B., Tomljenovic-Hanic, S., & Omenetto, F. G. (2016). Doxorubicin loaded nanodiamond-silk spheres for fluorescence tracking and controlled drug release. Biomedical Optics Express, 7(1), 132-147.

Khalid, A., Mitropoulos, A. N., Marelli, B., Tomljenovic-Hanic, S., & Omenetto, F. G. (2016). Doxorubicin loaded nanodiamond-silk spheres for fluorescence tracking and controlled drug release. Biomedical Optics Express, 7(1), 132-147.

Koch, C., Dreavă, D. M., Todea, A., Péter, F., Medeleanu, M., Păuşescu, I., ... & Sîrbu, I. O. (2023). Synthesis, Characterization, and Antiproliferative Properties of New Bio-Inspired Xanthylium Derivatives. Molecules, 28(3), 1102.

Luo, J. Q., Liu, R., Chen, F. M., Zhang, J. Y., Zheng, S. J., Shao, D., & Du, J. Z. (2023). Nanoparticle-Mediated CD47-SIRPα Blockade and Calreticulin Exposure for Improved Cancer Chemo-Immunotherapy. ACS nano, 17(10), 8966-8979.

Lutz, T. M., Kimna, C., Casini, A., & Lieleg, O. (2022). Bio-based and bio-inspired adhesives from animals and plants for biomedical applications. Materials Today Bio, 13, 100203.

Miao, L., Guo, S., Zhang, J., Kim, W. Y., & Huang, L. (2014). Nanoparticles with precise ratiometric co-loading and co-delivery of gemcitabine monophosphate and cisplatin for treatment of bladder cancer. Advanced functional materials, 24(42), 6601-6611.

Mukherjee, A., Madamsetty, V. S., Paul, M. K., & Mukherjee, S. (2020). Recent advancements of nanomedicine towards antiangiogenic therapy in cancer. International Journal of Molecular Sciences, 21(2), 455.

Neubi, G. M. N., Opoku-Damoah, Y., Gu, X., Han, Y., Zhou, J., & Ding, Y. (2018). Bio-inspired drug delivery systems: an emerging platform for targeted cancer therapy. Biomaterials science, 6(5), 958-973.

Pedziwiatr-Werbicka, E., Horodecka, K., Shcharbin, D., & Bryszewska, M. (2021). Nanoparticles in combating cancer: opportunities and limitations: a brief review. Current Medicinal Chemistry, 28(2), 346-359.

Pericleous, P., Gazouli, M., Lyberopoulou, A., Rizos, S., Nikiteas, N., & Efstathopoulos, E. P. (2012). Quantum dots hold promise for early cancer imaging and detection. International Journal of Cancer, 131(3), 519-528.

Rezaie, J., Nejati, V., Mahmoodi, M., & Ahmadi, M. (2022). Mesenchymal stem cells derived extracellular vesicles: a promising nanomedicine for drug delivery system. Biochemical Pharmacology, 115167

Rong, P., Huang, P., Liu, Z., Lin, J., Jin, A., Ma, Y., ... & Chen, X. (2015). Protein-based photothermal theranostics for imaging-guided cancer therapy. Nanoscale, 7(39), 16330-16336.

Sang, S., Yang, C., Chai, H., Yuan, X., Liu, W., & Zhang, X. (2021). The sulfonated polyetheretherketone with 3D structure modified by two bio-inspired methods shows osteogenic and antibacterial functions. Chemical Engineering Journal, 420, 130059.

Schuh, C. M., Benso, B., & Aguayo, S. (2019). Potential novel strategies for the treatment of dental pulp-derived pain: pharmacological approaches and beyond. Frontiers in Pharmacology, 10, 1068.

Sheng, Z., Hu, D., Zheng, M., Zhao, P., Liu, H., Gao, D., ... & Cai, L. (2014). Smart human serum albumin-indocyanine green nanoparticles generated by programmed assembly for dual-modal imaging-guided cancer synergistic phototherapy. ACS nano, 8(12), 12310-12322.

Simonsen, J. B. (2016). Evaluation of reconstituted high-density lipoprotein (rHDL) as a drug delivery platform—a detailed survey of rHDL particles ranging from biophysical properties to clinical implications. Nanomedicine: Nanotechnology, Biology and Medicine, 12(7), 2161-2179.

Tampieri, A., Sandri, M., Iafisco, M., Panseri, S., Montesi, M., Adamiano, A., ... & Sprio, S. (2021). Nanotechnological approach and bio-inspired materials to face degenerative diseases in aging. Aging Clinical and Experimental Research, 33, 805-821.

Tarhini, M., Greige-Gerges, H., & Elaissari, A. (2017). Protein-based nanoparticles: From preparation to encapsulation of active molecules. International journal of pharmaceutics, 522(1-2), 172-197.

Tong, Q., Qiu, N., Ji, J., Ye, L., & Zhai, G. (2020). Research progress in bioinspired drug delivery systems. Expert Opinion on Drug Delivery, 17(9), 1269-1288.

Tortorella, S., & Karagiannis, T. C. (2014). Transferrin receptor-mediated endocytosis: a useful target for cancer therapy. The Journal of membrane biology, 247, 291-307.

Tripathi, D., Hajra, K., & Maity, D. (2023). Recent Advancement of Bio-Inspired Nanoparticles in Cancer Theragnostic. Journal of Nanotheranostics, 4(3), 299-322.

Von Storp, B., Engel, A., Boeker, A., Ploeger, M., & Langer, K. (2012). Albumin nanoparticles with predictable size by desolvation procedure. Journal of microencapsulation, 29(2), 138-146.

Wang, D., Li, Y., Tian, Z., Cao, R., & Yang, B. (2014). Transferrin-conjugated nanodiamond as an intracellular transporter of chemotherapeutic drug and targeting therapy for cancer cells. Therapeutic delivery, 5(5), 511-524.

Wang, L., Li, Z., Xu, C., & Qin, J. (2019). Bioinspired engineering of organ-on-chip devices. Biological and Bio-inspired Nanomaterials: Properties and Assembly Mechanisms, 401-440.

Watt, R. K. (2011). The many faces of the octahedral ferritin protein. Biometals, 24, 489-500.

Xiong, W., Qi, L., Jiang, N., Zhao, Q., Chen, L., Jiang, X., ... & Shen, J. (2021). Metformin liposome-mediated PD-L1 downregulation for amplifying the photodynamic immunotherapy efficacy. ACS Applied Materials & Interfaces, 13(7), 8026-8041.

Xu, J., Singh, A., & Amiji, M. M. (2014). Redox-responsive targeted gelatin nanoparticles for delivery of combination wt-p53 expressing plasmid DNA and gemcitabine in the treatment of pancreatic cancer. BMC cancer, 14, 1-12.

Xu, Y., Zhang, J., Liu, X., Huo, P., Zhang, Y., Chen, H., ... & Zhang, N. (2019). MMP-2-responsive gelatin nanoparticles for synergistic tumor therapy. Pharmaceutical Development and Technology, 24(8), 1002-1013.

Zaszczyńska, A., Niemczyk-Soczynska, B., & Sajkiewicz, P. (2022). A Comprehensive Review of Electrospun Fibers, 3D-Printed Scaffolds, and Hydrogels for Cancer Therapies. Polymers, 14(23), 5278.

Zhang, C., Zhou, L., Zhang, J., Fu, Y. Y., Zhang, X., Yu, C., ... & Yan, X. P. (2016). Green and facile synthesis of a theranostic nanoprobe with intrinsic biosafety and targeting abilities. Nanoscale, 8(36), 16204-16211.

Zhang, F., Wang, X., Xu, X., Li, M., Zhou, J., & Wang, W. (2016). Reconstituted high density lipoprotein mediated targeted co-delivery of HZ08 and paclitaxel enhances the efficacy of paclitaxel in multidrug-resistant MCF-7 breast cancer cells. European Journal of Pharmaceutical Sciences, 92, 11-21.