Journal Pre-proof

Processed excipients for targeted drug delivery in cancer management: Enhancing efficacy and precision

Aditya Singh, Shubhrat Maheshwari, Vishal Kumar Vishwakarma, Saad Mohammed

PII: S2949-866X(23)00097-7

DOI: https://doi.org/10.1016/j.ipha.2023.10.006

Reference: IPHA 57

To appear in: *Intelligent Pharmacy*

Received Date: 30 September 2023

Revised Date: 16 October 2023

Accepted Date: 16 October 2023

Please cite this article as: Singh A, Maheshwari S, Vishwakarma VK, Mohammed S, Processed excipients for targeted drug delivery in cancer management: Enhancing efficacy and precision, *Intelligent Pharmacy* (2023), doi: https://doi.org/10.1016/j.ipha.2023.10.006.

Processed Excipients for Targeted Drug Delivery in Cancer Management: Enhancing Efficacy and Precision

Aditya Singh[1], Shubhrat Maheshwari[2*], Vishal Kumar Vishwakarma[3],

Saad Mohammed[1]

[1]Department of Pharmaceutics, Faculty of Pharmacy, Integral University, Lucknow-UP 226026 (India)

[2*]Faculty of Pharmaceutical Sciences Rama University Mandhana, Bithoor Road, Kanpur, Uttar Pradesh-209217(India)

[3]Department of Pharmacology, All India Institute of Medical Sciences, New Delhi , India.

Corresponding author

*Mr. Shubhrat Maheshwari, Assistant Professor, Department of Pharmacy, Faculty of Pharmaceutical Sciences Rama University Mandhana, Bithoor Road, Kanpur, Uttar Pradesh 209217,

Email: shubhrat.maheshwari@gmail.com

Abstract

Processed excipients (PEs) function in creating various dosage forms and need no introduction. For instance, recent studies have shown that PEs oleic acid, which is used with the breast cancer medicine Herceptin, functions both as a liquid delivery system for drugs and has the ability to suppress the breast cancer gene. Gamma-linolenic acid and omega-3 fatty acids, respectively, have some positive impacts on anticancer activity and cardiovascular advantages. PEs can transport other medications in liquid form, but they can also destabilise APIs. The physical interactions between excipients can alter how quickly a solid dosage form dissolves. The aim of the study is to investigate the crucial role of processed excipients (PEs) in creating diverse dosage forms, with a particular focus on their functions, effects, and interactions. The study also aims to explore recent research findings that demonstrate the potential of certain PEs, such as oleic acid, gamma-linolenic acid, and omega-3 fatty acids, in drug delivery and their potential therapeutic impact, including suppressing breast cancer genes and enhancing anticancer and cardiovascular activities. Furthermore, the study aims to delve into the dual nature of PEs, where they can both facilitate the delivery of drugs in liquid form and potentially influence the stability and dissolution characteristics of active pharmaceutical ingredients (APIs). It seeks to examine the intricate interplay between different excipients and their effects on drug bioavailability and functionality. The study acknowledges the global health burden posed by cancer and aims to highlight the application of traditional and emerging therapies, such as phytochemicals, in cancer treatment. It also intends to discuss the challenges associated with conventional chemotherapy, including the development of drug resistance. Additionally, the study aims to emphasise the continued relevance of PEs in the formulation of biologic medicinal products, particularly in the context of injection-based delivery methods. It aims to address the crucial considerations surrounding endotoxins and microbiological quality in these products. Overall, the study aims to contribute to a deeper understanding of the multifaceted roles and significance of PEs in pharmaceutical formulation and their impact on drug delivery, stability, and therapeutic outcomes.

Keywords: Processed excipients, Cancer, Oleic acid, Biologic medicinal products, pharmaceutical ingredients, bio

1. Introduction

Among the other complicated and hazardous illnesses that are still largely incurable, cancer is one of the leading causes of mortality. Nonetheless, there has been significant advancement in this field. To treat cancer and its effects, a number of techniques have been devised, including hyperthermia, phototherapy, gas therapy, chemotherapy, and radiotherapy [1]. Additionally, because conventional chemotherapy frequently fails to distinguish between cancerous and healthy cells, it is unable to treat cancer in a targeted manner. Most of the medications employed in this treatment have undesirable side effects instead of affecting the malignant tissue that is their intended target [2]. Controlled drug delivery systems are therefore strongly advised [3]. These new techniques add to existing ones, are more precise and efficient, and solely identify and target tumour cells. Processed excipients (PEs) are used for the formation of controlled and targeted drug delivery systems to target cancerous cells [4]. However, the adoption of PEs has been slow due to their classification as "novel" by regulators, even when prepared using compendial excipients [5]. Moreover, the use of PEs can provide an optimized product [6-9]. Lignin is a naturally occurring PE with many advantageous qualities, such as biodegradability and biocompatibility [10]. Lignin is now being used more frequently as a sustainable polymer for creating carbon fibres [11]. The PEs market is expected to reach its peak in 2028, according to a global study on COVID-19 impact, which analyses the market by type, therapeutic indication, functionality, application, and end user [12]. The market is divided into several types, including bioresorbable polymers [13]. The analysis includes clinical indications for gene treatments, metabolic and infectious disorders, cancer, dental and ophthalmic conditions, and other conditions. Functionality is divided into categories such as coating and colouring agents, sweeteners and flavours, preservatives, and antioxidants [14]. Parenteral and oral formulations, including tablets, capsules, liquids, and injectables, as well as topical applications, nutraceuticals, over-the-counter products, and other uses, are among the various applications of pharmaceutical excipients [15]. The study examines biopharmaceutical, pharmaceutical, animal health, and other end users, provides an in-depth analysis of the market while taking into account the impact of COVID-19, and projects market growth through 2028. According to Muley [16], it is ideal for the components used to make PEs to also interact in synergistic ways that improve functionality. In this way, the PEs not only have a simpler formulation but also deliver better performance [16].

According to Joshi [17], the PEs chosen should be able to be used in widely accessible commercial processes such as agglomeration and spray-drying, and they should perform consistently under these processing conditions. He also notes that they should have complementary and/or synergistic functions. Additionally, Muley [18] states that the ingredients used in PEs must be inert and nonreactive to prevent any chemical changes during manufacturing [19], depending on the intended use of the product; one or more fillers are typically treated with binders, glidants, or disintegrants. Additionally, single PEs may not offer the necessary physicochemical characteristics for the correct formulation of a certain API via direct compression [20]. In light of this, PEs have come to be regarded as a viable solution for the production of formulations and their combinations [21]. PEs are solid particle blends of organic or inorganic materials that are produced utilising a variety of methods, including spray drying, granulation, melting processes, crystallisation, and milling. Among these methods, spray drying is thought to be the most successful at producing PEs of superior quality [22]. In general, PEs have better physicochemical characteristics than straightforward physical mixes of components. PEs also have a lower sensitivity to lubricants, which can negatively affect the compressibility of the resulting mixture. Mannitol-based PEs are commonly used in the pharmaceutical market as oral disintegrate tablet (ODT) excipients [23]. These excipients are readily available and have similar compositions, but differences in fabrication methods and slight variations in their component characteristics can lead to different reactions after ODT formation. The drug release process of an ODT does not require patients or carers to drop them [24]. PROSOLV® EASYtab SP is an innovative, pre-mixed excipient composite designed to simplify the tablet manufacturing process. It consists of four distinct components that retain their unique chemical properties, working together synergistically to enhance tablet functionality. Using PROSOLV® EASYtab SP to create tablets offers several benefits. The tablets are durable and have excellent APIs and PEs compared to traditional blends. Additionally, using this composite can increase profitability through cost savings [25]. By using PROSOLV® EASYtab SP, manufacturers can also reduce their equipment capital, inventory, and analysis costs. Instead of buying and storing four separate excipients, they can purchase and store just one product, simplifying the manufacturing process and streamlining the supply chain [26].

2. Processed Excipients

An increasing number of new APIs have been discovered due to advancements in high-throughput screening technology. However, approximately 75% of novel drug candidates suffer from poor aqueous solubility and inadequate bioavailability, which can be attributed to the growing structural complexity of therapeutic prospects [27]. To overcome this challenge, various tried-and-tested as well as cutting-edge approaches, such as cyclodextrin inclusion, microemulsion, nanocrystals, cocrystals, and amorphous dispersions, are utilised to enhance the delivery of class IV pharmaceuticals. Among these approaches, amorphization of pharmaceuticals has emerged as one of the most successful methods for increasing solubility and dissolution, thereby improving therapeutic bioavailability. Amorphous solids have higher internal energy than their crystalline counterparts and lack long-range order in molecular packing [28]. PEs used in the DC process must perform various functions, such as facilitating an excellent binding capacity, to produce tablets effectively. However, finding a single material with all these desirable attributes is a challenging task [29]. To overcome the limitations mentioned above and best suit the active ingredients, PEs manufacturers invest a lot of time and energy in researching and developing new multifunctional PEs, as per Figure 1. Many studies focus on chemically altering excipients to produce PEs, for example, alginate esters and cinnamyl-chitosan [30]. On the other hand, co-processing is a commonly utilised technique for producing new materials with various capabilities. This procedure involves physically combining two or more excipients already on the market using proper manufacturing techniques, such as spray drying, wet granulation, or hot melt extrusion. Processed blends typically combine disintegrants, binders, and fillers to create a final product with enhanced functional qualities as an excipient in direct compression. In the perfect-case scenario, the manufactured tablets would have enhanced powder flowability and bulk density [31]. Although many ready-to-use, multifunctional excipients are already available on the market, the large number and diversity of APIs require the development of novel multifunctional excipients. Cop AA-MCC is an excellent excipient created specifically for direct compression. It is suitable for the majority of directly compressible actives due to its acceptable bulk density, good flow, and high compatibility [32].

Additionally, it can be manufactured into orodispersible tablets because of its very fast breakdown, satisfying a variety of patients, including the elderly and children. From a business standpoint, Cop AA-MCC was created using only two natural excipients that are safe and widely

accessible at affordable prices: alginic acid and microcrystalline cellulose. Wet granulation, a traditional technology, was utilised in the co-processing step to produce Cop AA-MCC, which is less expensive than spray drying and easy for industrial workers to understand. Additionally, this industrial technique enabled a high yield [33]. The standard method of dosage modification involves tablet splitting, which frequently results in undesirable dose fluctuations or tablet coating disturbances [34]. Stereolithography (SLA), binder jetting, fused deposition modelling (FDM), and semi-solid extrusion (SLS) Digital light processing (DLP) is another tool with potential in this area. Successful production of tablets with different geometries and infill percentages, orodispersible films, gastroretentive tablets, modified release tablets, immediate-release caplets, and tablets with drug-loaded nanocapsules has been achieved using 3D printing. Other successful applications include the production of drug-loaded gyroid lattices, modified release tablets, tablets with different geometries, multi-layered polypills, and modified release tablets using DLP technology. The active polymerization of photosensitive resin used in SLA and DLP technologies is triggered by UV radiation and requires the presence of photopolymer and a photoinitiator [35].

3. Lipid based PEs used in Delivering Drug to the Targeted Site for the Management of Cancer

Chemotherapeutic drugs have a limited therapeutic window and a high potential for toxicity [36]. Consequently, reducing chemotherapy's negative effects by only administering it to tumour locations would boost its effectiveness and improve patient care. The subject of drug distribution has undergone a revolution thanks to nanotechnology [37]. The creation of several kinds of nanoparticles (NPs) with sizes ranging from 10 to 1000 nm has enhanced the transport of numerous pharmacological molecules, particularly chemotherapeutic drugs, and offered creative, alternative solutions to many of the problems relating to their efficiency and safety. NPs are ideal medication carriers due to a variety of unique characteristics they have. Generally, but not always, many different types of NPs utilised as medication carriers are formed of lipids or polymers [38]. Depending on the kind, there are various approaches to generating structured lipids. Some are made using conventional methods for making lipids, such as chemical hydrolysis, physical separation, chemical interesterification, or esterification. These techniques cannot be used to synthesise several additional structured lipids, particularly those that call for

particular arrangements of different fatty acids in particular places. In these situations, enzymes show particular advantages over conventional approaches. These formulations are made up of lipids, which are natural or synthetic compounds that are soluble in fats or oils. The main advantage of NP systems is that they can improve the solubility of poorly water-soluble drugs, thereby enhancing their absorption and distribution in the body [39]. Targeting needs a molecular recognition method to achieve "active targeting," another technique [40].

3.1.Liposomes

The words "liposome" (fat) and soma (body) are the birth of the "liposome. The term liposome refers to its structural constituents, the phospholipids, rather than to its size, and it can be created in a variety of sizes using either unilamellar or multilamellar construction [41]. a microscopic bubble (vesicle) that is constructed from the same substance as a cell membrane, as illustrated in Figure 1. Drugs for cancer and other disorders can be delivered using liposomes that have been loaded with medication. Phospholipids, which are molecules with head and tail groups, are typically the building blocks of membranes. Water attracts the head, which is made of hydrocarbons, while repelling the tail, which is made of long chains of hydrocarbons. When there is water present, the heads are drawn to it and form a surface that faces the water [42]. The tails align to form a surface distant from the water since water repels them. One layer of the head faces the exterior of the cell, drawn to the water in the surroundings. The water inside the cell has drawn a second layer of heads that are facing the interior. Large multilamellar vesicles are described in the case of numerous concentric bilayers, whereas tiny or big unilamellar vesicles are used to describe one bilayer encasing the aqueous core. The monolayer layers are known as micelles, while the bilayer ones are known as liposomes [43]. Biologically active substances can be easily delivered via liposomes, which are globular lipid bilayers with a diameter of 50–1000 nm. To lessen the harmful effects of the pharmaceuticals when administered alone or to lengthen the time the drugs are in circulation and be more effective, topical application of liposomes in dermatology and the delivery of anticancer agents have a lot of potential. By affixing amino acid fragments from proteins, antibodies, or other relevant pieces that target certain receptor sites, liposomes can be used to target exact cells. Future uses for liposomes include DNA vaccination and enhanced gene therapy effectiveness, to name a few [44]. Liposomal components include both structural and nonstructural elements. The phosphatidylcholine (PC) molecule is the most

prevalent phospholipid [45]. Due to their insoluble nature in water and aqueous conditions, phosphatidylcholine particles arrange themselves tightly. The majority of liposome formulations contain glycerol, including phospholipids [46]. These are phosphatidic acid derivatives. Some phospholipids include phosphatidyl ethanolamine (cephalin), phosphotidyl choline (lecithin), phosphotidyl serine (PS), phosphotidyl inositol (PI), and phosphotidyl glycerol (PG). Despite the fact that cholesterol does not naturally form a bilayer structure, it can be incorporated into phospholipid membranes at very high concentrations—up to a 1:1 or even 2:1 molar ratio of cholesterol to phosphatidylcholine. Cholesterol occupies a specific location in the membrane, with its hydroxyl group towards the aqueous surface and its aliphatic chain parallel to the acyl chains in the bilayer's middle [47].

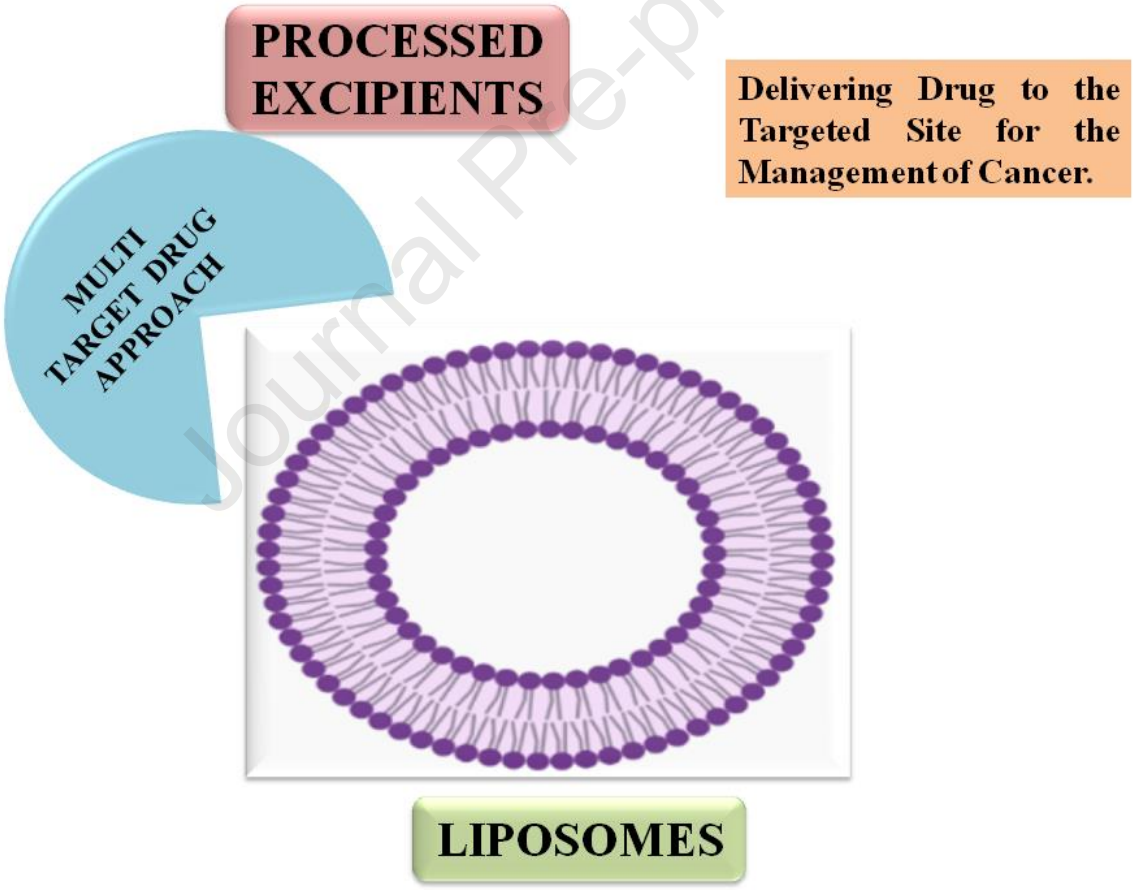

Figure 1. Multi targeting approach of Processed Excipients

3.2.The Solid Lipid Nanoparticles (SLNs)

SLN are an alternative drug carrier system for those seeking drug carrier formulations that increase bioavailability and contain well-tolerated excipients, as per Table 1. The particle matrix of SLNs is made up of solid lipids, unlike emulsions and liposomes. Lipid matrices have seen tremendous growth in recent years as a method of regulating medication release [48]. The physiological substances they include and the fact that they can be administered orally, topically, or by IV are all common characteristics of SLNs. They also have relatively affordable expenses. Another benefit is the simplicity of large-scale production using high-pressure homogenization, which is used, for example, to create parenteral fat emulsions. In addition, sonication, high-speed stirring, and the microemulsion technique can all be used to create SLNs. SLNs combine the advantages of o/w-type emulsions and polymer nanoparticles (solid matrix for controlled release). They may be made of lipids and surfactants that are typically found in pharmaceutical preparations, such as tablets or pellets, and they may also be made from lipids obtained from food sources [49].

Table 1: Types of PEs used in the formulation of lipid based carrier system [50].

Processed Excipients (PEs)	**Applications**
Glyceryl monostearate (ImwitorÒ900)	The glycerol ester of stearic acid is glycerol monostearate, also referred to as GMS. It is frequently utilised in food as an emulsifier.
Soy lecithin (LipoidÒ S 75, LipoidÒ S 100)	Purified soybean phospholipids, which begin as crude soybean lecithin, serve a variety of purposes in medical, cosmetic, and food applications. As wetting agents, solubilizers, emulsifiers, liposome builders, and technical aids, these carefully specified products exhibit remarkable performance. In addition, they provide choline and vital fatty acids. The majority of goods are accessible in non-GMO varieties.
Egg lecithin	The highly purified portions that come from hen egg yolks are called egg phospholipids. Egg phospholipids are ideal for parenteral applications because they closely resemble the makeup of human cells. They are primarily found in fat emulsions used in drug-containing formulations or for

	parenteral feeding.
Poloxamer 188	A nonionic block linear copolymer known as Poloxamer 188 (P188) has cytoprotective, antithrombotic. Once licenced by the FDA in the 1960s as a therapeutic agent to lessen blood viscosity prior to transfusions, P188 is no longer contained in any products that have received Regulatory approval. Owing to its sufactant qualities, P188 is also present in over-the-counter (OTC) items like toothpaste, bowel cleaners, and mouthwash and is employed in a variety of cosmetic, business, and pharmaceutical applications.
Phosphatidylcholine (Epikuron®®170, Epikuron 200)	Wetting and dispersion agent, suspension and emulsifying agent and dispersion agent, anti-crystallization agent, for tablets and powders

3.3.Nanostructured Lipid Carriers (NLCs)

NLCs are created by combining LL and SL in a way that prevents the oil molecules (also known as liquid lipids) from contributing to the crystalline structure of the latter and prevents the crystals of the latter from dissolving in the former [51]. Yet, at a temperature below their melting point, this lipid mixture should be uniform and devoid of phase separation; in other words, LL should be present as nanoscale compartments within the solid crystalline matrix. The components chosen for NLCs acting as carriers for chemotherapeutic drug molecules should be biocompatible, non-toxic, and appropriate for systemic administration [52]. Generally speaking, nanotechnology is utilized to enhance the effectiveness of drug delivery as well as to solve some of the constraints of cancer targeting. Chemotherapy, radiation, immunotherapy, and surgery are the only options for treating tumors. Yet, these methods are occasionally prohibited because they can be harmful to healthy cells, the immune system, or even because they can raise the chance of developing other malignancies. Hence, one of the primary objectives of therapeutic research is to find efficient remedies that can replace existing medications by increasing efficacy and reducing potential negative effects [53].

3.4.Magnetic nanoparticles

Magnetic nanoparticles can be heated using an external magnetic field to induce hyperthermia in cancer cells. These nanoparticles can be targeted at cancer cells using antibodies or other targeting agents and can be loaded with anticancer drugs for combined hyperthermia and chemotherapy. Magnetic nanoparticles have been investigated for the treatment of a variety of cancers, including breast, prostate, and brain cancer [54].

3.5.Microwave ablation

Microwave ablation is a minimally invasive procedure that uses microwaves to heat and kill cancer cells. In this procedure, a small probe is inserted into the tumour, and microwaves are used to heat the tissue to temperatures above 60°C, leading to cancer cell death. Microwave ablation is commonly used to treat liver, lung, and kidney cancers [55].

3.6.Photothermal therapy

Photothermal therapy involves the use of light-absorbing nanoparticles that convert light energy into heat, leading to localised hyperthermia and cancer cell death. These nanoparticles can be targeted at cancer cells using antibodies or other targeting agents and can be loaded with anticancer drugs for combined photothermal and chemotherapy. Photothermal therapy has been investigated for the treatment of a variety of cancers, including breast, prostate, and brain cancer [56-60].

3.7.pH-sensitive PEs used in cancer management therapy

pH-sensitive liposomes, nanoparticles, hydrogels, and dendrimers that change their structure and release their contents in response to changes in pH These liposomes can be loaded with anticancer drugs and targeted at cancer cells using antibodies or other targeting agents. When exposed to the acidic pH of the tumour microenvironment, the liposomes release their contents specifically into the cancer cells, leading to localised drug delivery and cancer cell death [61-65].

4. The critical role of PEs through different pathways to the targeted site for the management of cancer

PEs are inert substances that are added to a drug formulation to facilitate its administration, stability, and efficacy. PEs plays a targeted role in the targeted delivery of formulations for the management of cancer. The unique characteristics of the tumour microenvironment can be exploited for passive targeting of drugs, while ligands or antibodies can be used for active targeting of tumour cells. Signal transduction pathways play a critical role in the targeted delivery of drugs for cancer management using PEs. These pathways are a series of chemical reactions that occur inside cells in response to extracellular signals, leading to changes in gene expression, protein activity, and cellular behavior [66-70]. PEs can exploit different signalling pathways and the unique characteristics of the tumour microenvironment for targeted drug delivery in cancer therapy. These strategies offer the potential to enhance drug efficacy and reduce toxicity, providing a promising approach for the development of more effective and less harmful cancer therapies. PEs can be functionalized with pH-sensitive moieties that enable drug release in response to the acidic pH of the tumor microenvironment. Alternatively, PEs can be functionalized with thermosensitive moieties that enable drug release in response to local heating, which can be achieved using external stimuli such as ultrasound or magnetic fields. A pathway that has been targeted using PEs is the Notch signalling pathway. One of the main challenges is the heterogeneity of cancer, which can lead to variability in the response to therapy among patients. Another challenge is the potential for off-target effects and toxicity, which can limit the efficacy and safety of PEs. Aberrant activation of Notch has been implicated in many types of cancer. PEs, such as liposomes and polymeric nanoparticles, can be functionalized with inhibitors of Notch activation to selectively target cancer cells and induce apoptosis. There are different pathways through which PEs can target the tumour site for cancer management, and some of these pathways are discussed below [71-75].

4.1. AGEs RAGEs Pathways targeted site for the management of cancer

The overexpression of the receptor for advanced glycation endproducts (RAGE) in many types of cancer cells has been linked to cancer development and progression. RAGE activation can promote cell proliferation, migration, invasion, and angiogenesis, which are essential for tumour growth and metastasis. Moreover, RAGE can activate signaling pathways such as PI3K/AKT, MAPK/ERK, and NF- KB, which can promote tumour growth and survival and contribute to resistance to chemotherapy and radiation therapy [76-80]. Additionally, RAGE activation has

been shown to regulate the tumour microenvironment by promoting the release of cytokines, chemokines, and growth factors that recruit immune cells, promote inflammation, angiogenesis, and tissue remodelling, ultimately creating a favourable environment for tumour growth and metastasis. Targeting RAGE using small molecule inhibitors, antibodies, or RAGE decoy receptors has shown promising results in preclinical studies, and clinical trials are currently underway to evaluate their efficacy in cancer treatment. Therefore, RAGE has emerged as a potential target for cancer therapy. PEs is the phosphatidylinositol 3-kinase (PI3K)/Akt pathway. This pathway is frequently activated in cancer and promotes cell survival, growth, and metastasis. PEs such as dendrimers and polymeric nanoparticles can be functionalized with inhibitors of PI3K or Akt to selectively target cancer cells and induce apoptosis [81-85]. NF- KB is activated in many types of cancer and promotes cell survival, angiogenesis, and metastasis. PEs such as liposomes and polymeric nanoparticles can be functionalized with inhibitors of NF-KB activation, such as curcumin, to selectively target cancer cells and induce apoptosis [86-100].

Conclusion

In conclusion, the use of Processed Excipients (PEs) in the field of cancer management represents a promising avenue for the development of more effective and targeted therapies. PEs, such as liposomes, nanoparticles, and other carrier systems, offer a wide range of possibilities for delivering drugs to the targeted site for cancer treatment. These excipients can be designed to exploit the unique characteristics of the tumor microenvironment, including its acidic pH and temperature variations, to release drugs precisely where they are needed. Additionally, PEs can be functionalized with various moieties and ligands to actively target cancer cells and enhance drug delivery and efficacy. Furthermore, PEs can play a crucial role in targeting specific signaling pathways involved in cancer development and progression. For example, the Notch signaling pathway and AGEs RAGEs pathways can be targeted using PEs to inhibit cancer cell proliferation, survival, and metastasis. As for future prospects, ongoing research in the field of PEs and cancer management is likely to yield even more innovative and tailored approaches. These might include the development of multifunctional PEs that can simultaneously target multiple pathways or deliver a combination of therapeutic agents. Additionally, advancements in nanotechnology and the use of smart materials may lead to more precise and controlled drug release systems, reducing off-target effects and improving the overall safety and efficacy of cancer treatments

Acknowledgement

The author expresses his gratitude towards Integral University and Rama University for providing a research environment and all necessary facilities for conducting research.

Informed consent

Not Applicable

Funding

No funding was received for conducting this study.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The authors declare no conflict of interest among themselves. The authors alone are responsible for the content and writing of this article.

Financial interests

The authors declare they have no financial interests.

References

1. Asmawi AA, Salim N, Ngan CL, Ahmad H, Abdulmalek E, Masarudin MJ, Abdul Rahman MB. Excipient selection and aerodynamic characterization of nebulized lipid-based nanoemulsion loaded with docetaxel for lung cancer treatment. Drug delivery and translational research. 2019 Apr 15;9:543-54.
2. Bowles BJ, Dziemidowicz K, Lopez FL, Orlu M, Tuleu C, Edwards AJ, Ernest TB. Co-processed excipients for dispersible tablets–part 1: Manufacturability. AAPS PharmSciTech. 2018 Aug;19:2598-609.

3. Benabbas R, Sanchez-Ballester NM, Bataille B, Sharkawi T, Soulairol I. Development and pharmaceutical performance of a novel co-processed excipient of alginic acid and microcrystalline cellulose. Powder technology. 2021 Jan 22;378:576-84.
4. Bhatia V, Dhingra A, Chopra B, Guarve K. PEs: Recent advances and future perspective. Journal of Drug Delivery Science and Technology. 2022 Apr 6:103316.
5. Chowdhury P, Nagesh PK, Hatami E, Wagh S, Dan N, Tripathi MK, Khan S, Hafeez BB, Meibohm B, Chauhan SC, Jaggi M. Tannic acid-inspired paclitaxel nanoparticles for enhanced anticancer effects in breast cancer cells. Journal of colloid and interface science. 2019 Feb 1;535:133-48.
6. Bin LK, Gaurav A, Mandal UK. A review on co-processed excipients: current and future trend of excipient technology. Int J Pharm Pharm Sci. 2019.
7. Yao K, McClements DJ, Xiang J, Zhang Z, Cao Y, Xiao H, Liu X. Improvement of carotenoid bioaccessibility from spinach by co-ingesting with excipient nanoemulsions: impact of the oil phase composition. Food & function. 2019;10(9):5302-11.
8. Ogawa K, Katsumi H, Moroto Y, Morishita M, Yamamoto A. Processing Parameters and Ion Excipients Affect the Physicochemical Characteristics of the Stereocomplex-Formed Polylactide-b-Polyethylene Glycol Nanoparticles and Their Pharmacokinetics. Pharmaceutics. 2022 Mar 4;14(3):568.
9. Markovic M, Ben-Shabat S, Aponick A, Zimmermann EM, Dahan A. Lipids and lipid-processing pathways in drug delivery and therapeutics. International Journal of Molecular Sciences. 2020 May 4;21(9):3248.
10. Pandey M, Choudhury H, Fern JL, Kee AT, Kou J, Jing JL, Her HC, Yong HS, Ming HC, Bhattamisra SK, Gorain B. 3D printing for oral drug delivery: a new tool to customize drug delivery. Drug delivery and translational research. 2020 Aug;10:986-1001.
11. Barkat MA, Das SS, Pottoo FH, Beg S, Rahman Z. Lipid-based nanosystem as intelligent carriers for versatile drug delivery applications. Current pharmaceutical design. 2020 Mar 1;26(11):1167-80. Buya AB, Beloqui A, Memvanga PB, Préat V. Self-nano-emulsifying drug-delivery systems: From the development to the current applications and challenges in oral drug delivery. Pharmaceutics. 2020 Dec 9;12(12):1194.

12. Geraldes DC, Beraldo-de-Araújo VL, Pardo BO, Pessoa Junior A, Stephano MA, de Oliveira-Nascimento L. Protein drug delivery: current dosage form profile and formulation strategies. Journal of drug targeting. 2020 Apr 20;28(4):339-55.

13. Collins MN, Nechifor M, Tanasă F, Zănoagă M, McLoughlin A, Stróżyk MA, Culebras M, Teacă CA. Valorization of lignin in polymer and composite systems for advanced engineering applications–a review. International journal of biological macromolecules. 2019 Jun 15;131:828-49.

14. Jacob S, Nair AB, Shah J. Emerging role of nanosuspensions in drug delivery systems. Biomaterials research. 2020 Dec;24:1-6.

15. Duan Y, Dhar A, Patel C, Khimani M, Neogi S, Sharma P, Kumar NS, Vekariya RL. A brief review on solid lipid nanoparticles: Part and parcel of contemporary drug delivery systems. RSC advances. 2020;10(45):26777-91.

16. Eleftheriadis GK, Katsiotis CS, Genina N, Boetker J, Rantanen J, Fatouros DG. Manufacturing of hybrid drug delivery systems by utilizing the fused filament fabrication (FFF) technology. Expert Opinion on Drug Delivery. 2020 Aug 2;17(8):1063-8.

17. Cho HJ. Recent progresses in the development of hyaluronic acid-based nanosystems for tumor-targeted drug delivery and cancer imaging. Journal of pharmaceutical investigation. 2020 Mar;50:115-29.

18. Garcia MA, Garcia CF, Faraco AA. Pharmaceutical and biomedical applications of native and modified starch: A review. Starch-Stärke. 2020 Jul;72(7-8):1900270.

19. Arévalo-Pérez R, Maderuelo C, Lanao JM. Recent advances in colon drug delivery systems. Journal of Controlled Release. 2020 Nov 10;327:703-24.

20. Crivelli B, Perteghella S, Bari E, Sorrenti M, Tripodo G, Chlapanidas T, Torre ML. Silk nanoparticles: From inert supports to bioactive natural carriers for drug delivery. Soft Matter. 2018;14(4):546-57.

21. Zhu YS, Tang K, Lv J. Peptide–drug conjugate-based novel molecular drug delivery system in cancer. Trends in pharmacological sciences. 2021 Oct 1;42(10):857-69.

22. Mouhid L, Corzo-Martínez M, Torres C, Vázquez L, Reglero G, Fornari T, Ramírez de Molina A. Improving in vivo efficacy of bioactive molecules: An overview of potentially antitumor phytochemicals and currently available lipid-based delivery systems. Journal of oncology. 2017 May 7;2017.

23. Shi C, Zhao H, Fang Y, Shen L, Zhao L. Lactose in tablets: functionality, critical material attributes, applications, modifications and co-processed excipients. Drug Discovery Today. 2023 Jul 5:103696.

24. Aziz A, Rehman U, Sheikh A, Abourehab MA, Kesharwani P. Lipid-based nanocarrier mediated CRISPR/Cas9 delivery for cancer therapy. Journal of Biomaterials Science, Polymer Edition. 2022 Sep 3:1-21.

25. Radmoghaddam ZA, Honarmand S, Dastjerdi M, Akbari S, Akbari A. Lipid-based nanoformulations for TKIs delivery in cancer therapy. NanoScience Technology. 2022:11-27.

26. Luiz MT, Dutra JA, Tofani LB, de Araújo JT, Di Filippo LD, Marchetti JM, Chorilli M. Targeted liposomes: a nonviral gene delivery system for cancer therapy. Pharmaceutics. 2022 Apr 8;14(4):821.

27. Amin M, Seynhaeve AL, Sharifi M, Falahati M, Ten Hagen TL. Liposomal Drug Delivery Systems for Cancer Therapy: The Rotterdam Experience. Pharmaceutics. 2022 Oct 11;14(10):2165.

28. Khan MI, Hossain MI, Hossain MK, Rubel MH, Hossain KM, Mahfuz AM, Anik MI. Recent progress in nanostructured smart drug delivery systems for cancer therapy: a review. ACS Applied Bio Materials. 2022 Feb 28;5(3):971-1012.

29. Bigham A, Rahimkhoei V, Abasian P, Delfi M, Naderi J, Ghomi M, Moghaddam FD, Waqar T, Ertas YN, Sharifi S, Rabiee N. Advances in tannic acid-incorporated biomaterials: Infection treatment, regenerative medicine, cancer therapy, and biosensing. Chemical Engineering Journal. 2022 Mar 15;432:134146.

30. Van NH, Vy NT, Van Toi V, Dao AH, Lee BJ. Nanostructured lipid carriers and their potential applications for versatile drug delivery via oral administration. OpenNano. 2022 Aug 6:100064.

31. Rahman M, Almalki WH, Alrobaian M, Iqbal J, Alghamdi S, Alharbi KS, Alruwaili NK, Hafeez A, Shaharyar A, Singh T, Waris M. Nanocarriers-loaded with natural actives as newer therapeutic interventions for treatment of hepatocellular carcinoma. Expert Opinion on Drug Delivery. 2021 Apr 3;18(4):489-513.

32. Kurakula M, Gorityala S, Moharir K. Recent trends in design and evaluation of chitosan-based colon targeted drug delivery systems: Update 2020. Journal of Drug Delivery Science and Technology. 2021 Aug 1;64:102579.

33. Aanisah N, Wardhana YW, Chaerunisaa AY, Budiman A. Review on modification of glucomannan as an excipient in solid dosage forms. Polymers. 2022 Jun 23;14(13):2550.

34. Tranová T, Macho O, Loskot J, Mužíková J. Study of rheological and tableting properties of lubricated mixtures of co-processed dry binders for orally disintegrating tablets. European Journal of Pharmaceutical Sciences. 2022 Jan 1;168:106035.

35. Abdelhamid M, Koutsamanis I, Corzo C, Maisriemler M, Ocampo AB, Slama E, Alva C, Lochmann D, Reyer S, Freichel T, Salar-Behzadi S. Filament-based 3D-printing of placebo dosage forms using brittle lipid-based excipients. International Journal of Pharmaceutics. 2022 Aug 25;624:122013.

36. Gao Y, Li J, Zhao L, Hong Y, Shen L, Wang Y, Lin X. Distribution pattern and surface nature-mediated differential effects of hydrophilic and hydrophobic nano-silica on key direct compaction properties of Citri Reticulatae Pericarpium powder by co-processing. Powder Technology. 2022 May 1;404:117442.

37. Zupančič O, Spoerk M, Paudel A. Lipid-based solubilization technology via hot melt extrusion: Promises and challenges. Expert Opinion on Drug Delivery. 2022 Sep 2;19(9):1013-32.

38. Nakmode D, Bhavana V, Thakor P, Madan J, Singh PK, Singh SB, Rosenholm JM, Bansal KK, Mehra NK. Fundamental aspects of lipid-based excipients in lipid-based product development. Pharmaceutics. 2022 Apr 11;14(4):831.

39. Dhaval M, Vaghela P, Patel K, Sojitra K, Patel M, Patel S, Dudhat K, Shah S, Manek R, Parmar R. Lipid-based emulsion drug delivery systems—a comprehensive review. Drug Delivery and Translational Research. 2022 Jul 1:1-24.

40. Lazić I, Kučević S, Ćirin-Varađan S, Aleksić I, Đuriš J. Formulation of ibuprofen-modified release hydrophilic and lipid matrix tablets using co-processed excipients. Arhiv za farmaciju. 2022;72(4 suplement):S3400-401.

41. Singh A, Ansari VA, Ahsan F, Akhtar J, Khushwaha P, Maheshwari S. Viridescent concoction of genstein tendentious silver nanoparticles for breast cancer. Research Journal of Pharmacy and Technology. 2021;14(5):2867-72.

42. Telange DR, Bhaktani NM, Hemke AT, Pethe AM, Agrawal SS, Rarokar NR, Jain SP. Development and Characterization of Pentaerythritol-EudragitRS100 Co-processed Excipients as Solid Dispersion Carriers for Enhanced Aqueous Solubility, In Vitro Dissolution, and Ex Vivo Permeation of Atorvastatin. ACS omega. 2023 Jul 5.

43. Singh A, Ansari VA, Haider F, Akhtar J, Ahsan F. A Review on Topical preparation of Herbal Drugs used in Liposomal delivery against Ageing. Research Journal of Pharmacology and Pharmacodynamics. 2020;12(1):5-11.

44. Gao Y, Zeng Y, Liu X, Tang D. Liposome-mediated in situ formation of type-I heterojunction for amplified photoelectrochemical immunoassay. Analytical Chemistry. 2022 Mar 9;94(11):4859-65.

45. Liu P, Chen G, Zhang J. A review of liposomes as a drug delivery system: current status of approved products, regulatory environments, and future perspectives. Molecules. 2022 Feb 17;27(4):1372.

46. Chavda VP, Vihol D, Mehta B, Shah D, Patel M, Vora LK, Pereira-Silva M, Paiva-Santos AC. Phytochemical-loaded liposomes for anticancer therapy: An updated review. Nanomedicine. 2022 Apr;17(8):547-68.

47. Yanoff Z. The Effect of DNA Sequence on Oligonucleotide-Stabilized Lipid Micelles.

48. Moosavian SA, Kesharwani P, Singh V, Sahebkar A. Aptamer-functionalized liposomes for targeted cancer therapy. Aptamers Engineered Nanocarriers for Cancer Therapy. 2023 Jan 1:141-72.

49. Mohammadi M, Hamishehkar H, McClements DJ, Shahvalizadeh R, Barri A. Encapsulation of Spirulina protein hydrolysates in liposomes: Impact on antioxidant activity and gastrointestinal behavior. Food Chemistry. 2023 Jan 30;400:133973.

50. Chen M, Wang S, Qi Z, Meng X, Hu M, Liu X, Song Y, Deng Y. Deuterated colchicine liposomes based on oligomeric hyaluronic acid modification enhance anti-tumor effect and reduce systemic toxicity. International Journal of Pharmaceutics. 2023 Feb 5;632:122578.

51. Akbari J, Saeedi M, Ahmadi F, Hashemi SM, Babaei A, Yaddollahi S, Rostamkalaei SS, Asare-Addo K, Nokhodchi A. Solid lipid nanoparticles and nanostructured lipid carriers: A review of the methods of manufacture and routes of administration. Pharmaceutical Development and Technology. 2022 May 28;27(5):525-44.

52. Li Z, Yin Z, Li B, He J, Liu Y, Zhang N, Li X, Cai Q, Meng W. Docosahexaenoic Acid-Loaded Nanostructured Lipid Carriers for the Treatment of Peri-Implantitis in Rats. International Journal of Molecular Sciences. 2023 Jan;24(3):1872.

53. Gugleva V, Andonova V. Recent Progress of Solid Lipid Nanoparticles and Nanostructured Lipid Carriers as Ocular Drug Delivery Platforms. Pharmaceuticals. 2023 Mar 22;16(3):474.

54. Wang H, Xue KF, Yang Y, Hu H, Xu JF, Zhang X. In situ hypoxia-induced supramolecular perylene diimide radical anions in tumors for photothermal therapy with improved specificity. Journal of the American Chemical Society. 2022 Jan 20;144(5):2360-7.

55. Hu H, Wang H, Yang Y, Xu JF, Zhang X. A Bacteria-Responsive Porphyrin for Adaptable Photodynamic/Photothermal Therapy. Angewandte Chemie. 2022 Jun 7;134(23):e202200799.

56. Li X, Yong T, Wei Z, Bie N, Zhang X, Zhan G, Li J, Qin J, Yu J, Zhang B, Gan L. Reversing insufficient photothermal therapy-induced tumor relapse and metastasis by regulating cancer-associated fibroblasts. Nature communications. 2022 May 19;13(1):2794.

57. Lei Q, He D, Ding L, Kong F, He P, Huang J, Guo J, Brinker CJ, Luo G, Zhu W, Yu Y. Microneedle patches integrated with biomineralized melanin nanoparticles for simultaneous skin tumor photothermal therapy and wound healing. Advanced Functional Materials. 2022 May;32(22):2113269.

58. Chang M, Hou Z, Wang M, Wen D, Li C, Liu Y, Zhao Y, Lin J. Cu single atom nanozyme based high-efficiency mild photothermal therapy through cellular metabolic regulation. Angewandte Chemie International Edition. 2022 Dec 12;61(50):e202209245.

59. Hu B, Cui Y, Yang X, Xu X, Janani BJ, Fakhri A. Fabrication of novel rational Ti-Sn doped Cu-ferrite nanoparticles for robust photocatalysis reaction, magnetic resonance imaging, and chemo-magneto-photo-thermal therapy. Surfaces and Interfaces. 2022 Oct 1;33:102226.

60. Mo Z, Qiu M, Zhao K, Hu H, Xu Q, Cao J, Luo Y, Liu L, Xu Z, Yi C, Xiong Z. Multifunctional phototheranostic nanoplatform based on polydopamine-manganese dioxide-IR780 iodide for effective magnetic resonance imaging-guided synergistic

photodynamic/photothermal therapy. Journal of Colloid and Interface Science. 2022 Apr 1;611:193-204.

61. Vila-Caballer M, Codolo G, Munari F, Malfanti A, Fassan M, Rugge M, Balasso A, de Bernard M, Salmaso S. A pH-sensitive stearoyl-PEG-poly (methacryloyl sulfadimethoxine)-decorated liposome system for protein delivery: an application for bladder cancer treatment. Journal of Controlled Release. 2016 Sep 28;238:31-42.

62. Ray P, Dutta D, Haque I, Nair G, Mohammed J, Parmer M, Kale N, Orr M, Jain P, Banerjee S, Reindl KM. pH-sensitive nanodrug carriers for codelivery of ERK inhibitor and gemcitabine enhance the inhibition of tumor growth in pancreatic cancer. Molecular Pharmaceutics. 2020 Nov 24;18(1):87-100.

63. Zhong H, Mu J, Du Y, Xu Z, Xu Y, Yu N, Zhang S, Guo S. Acid-triggered release of native gemcitabine conjugated in polyketal nanoparticles for enhanced anticancer therapy. Biomacromolecules. 2020 Jan 29;21(2):803-14.

64. Czupiel P, Delplace V, Shoichet M. Nanoparticle delivery of a pH-sensitive prodrug of doxorubicin and a mitochondrial targeting VES-H8R8 synergistically kill multi-drug resistant breast cancer cells. Scientific Reports. 2020 May 26;10(1):8726.

65. Cheng X, Zeng X, Zheng Y, Wang X, Tang R. Surface-fluorinated and pH-sensitive carboxymethyl chitosan nanoparticles to overcome biological barriers for improved drug delivery in vivo. Carbohydrate polymers. 2019 Mar 15;208:59-69.

66. Anandhan A, Dodson M, Schmidlin CJ, Liu P, Zhang DD. Breakdown of an ironclad defense system: the critical role of NRF2 in mediating ferroptosis. Cell chemical biology. 2020 Apr 16;27(4):436-47.

67. Lu J, Zhao Y, Liu M, Lu J, Guan S. Toward improved human health: Nrf2 plays a critical role in regulating ferroptosis. Food & Function. 2021;12(20):9583-606.

68. Ergul M, Aktan F, Yildiz MT, Tutar Y. Perturbation of HSP network in MCF-7 breast cancer cell line triggers inducible HSP70 expression and leads to tumor suppression. Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents). 2020 Jun 1;20(9):1051-60.

69. Hoter A, Naim HY. Heat shock proteins and ovarian cancer: important roles and therapeutic opportunities. Cancers. 2019 Sep 18;11(9):1389.

70. Yuan H, Pratte J, Giardina C. Ferroptosis and its potential as a therapeutic target. Biochemical pharmacology. 2021 Apr 1;186:114486.

71. Zhu Q, Wu Y, Mai J, Guo G, Meng J, Fang X, Chen X, Liu C, Zhong S. Comprehensive metabolic profiling of inflammation indicated key roles of glycerophospholipid and arginine metabolism in coronary artery disease. Frontiers in Immunology. 2022 Mar 8;13:829425.

72. Li D, Li Y. The interaction between ferroptosis and lipid metabolism in cancer. Signal transduction and targeted therapy. 2020 Jun 30;5(1):108.

73. Jiang X, Liu B, Nie Z, Duan L, Xiong Q, Jin Z, Yang C, Chen Y. The role of m6A modification in the biological functions and diseases. Signal transduction and targeted therapy. 2021 Feb 21;6(1):74.

74. Sun Y, Xue Z, Huang T, Che X, Wu G. Lipid metabolism in ferroptosis and ferroptosis-based cancer therapy. Frontiers in Oncology. 2022 Aug 1;12:941618.

75. Kennedy L, Sandhu JK, Harper ME, Cuperlovic-Culf M. Role of glutathione in cancer: From mechanisms to therapies. Biomolecules. 2020 Oct 9;10(10):1429.

76. Tang D, Kroemer G, Kang R. Ferroptosis in immunostimulation and immunosuppression. Immunological Reviews. 2023 Jul 9.

77. Song X, Long D. Nrf2 and ferroptosis: a new research direction for neurodegenerative diseases. Frontiers in neuroscience. 2020 Apr 21;14:267.

78. Liu X, Cui J, Gong L, Tian F, Shen Y, Chen L, Wang Y, Xia Y, Liu L, Ye X, Wang M. The CUL4B-miR-372/373-PIK3CA-AKT axis regulates metastasis in bladder cancer. Oncogene. 2020 Apr 23;39(17):3588-603.

79. Chang C, Lee SO, Yeh S, Chang TM. Androgen receptor (AR) differential roles in hormone-related tumors including prostate, bladder, kidney, lung, breast and liver. Oncogene. 2014 Jun;33(25):3225-34.

80. Xu G, Chhangawala S, Cocco E, Razavi P, Cai Y, Otto JE, Ferrando L, Selenica P, Ladewig E, Chan C, Da Cruz Paula A. ARID1A determines luminal identity and therapeutic response in estrogen-receptor-positive breast cancer. Nature genetics. 2020 Feb;52(2):198-207.

81. Li Y, Feng X, Zhang Y, Wang Y, Yu X, Jia R, Yu T, Zheng X, Chu Q. Dietary flavone from the Tetrastigma hemsleyanum vine triggers human lung adenocarcinoma apoptosis via autophagy. Food & function. 2020;11(11):9776-88.

82. Elmallah MI, Cordonnier M, Vautrot V, Chanteloup G, Garrido C, Gobbo J. Membrane-anchored heat-shock protein 70 (Hsp70) in cancer. Cancer Letters. 2020 Jan 28;469:134-41.

83. Clemente SM, Martínez-Costa OH, Monsalve M, Samhan-Arias AK. Targeting lipid peroxidation for cancer treatment. Molecules. 2020 Nov 5;25(21):5144.

84. Singh A, Ansari VA, Mahmood T, Ahsan F, Wasim R. Neurodegeneration: Microglia: Nf-Kappab Signaling Pathways. Drug Research. 2022 Sep 2.

85. Singh A, Ansari VA, Mahmood T, Ahsan F, Wasim R, Shariq M, Parveen S, Maheshwari S. Receptor for Advanced Glycation End Products: Dementia and Cognitive Impairment. Drug Research. 2023 Mar 8.

86. Wasim R, Mahmood T, Siddiqui MH, Ahsan F, Shamim A, Singh A, Shariq M, Parveen S. Aftermath of AGE-RAGE Cascade in the pathophysiology of cardiovascular ailments. Life Sciences. 2022 Aug 5:120860.

87. Maheshwari S. AGEs RAGE Pathways: Alzheimer's Disease. Drug Research. 2023 Mar 20.

88. Li Q, Chen X, Lin W, Guo X, Ma Y. Application of a novel multicomponent nanoemulsion to tumor therapy Based on the theory of "unification of drugs and excipients". Pharmaceutical Development and Technology. 2023 Apr 21;28(3-4):351-62.

89. Thompson SA, Gala U, Davis Jr DA, Kucera S, Miller D, Williams III RO. Can the Oral Bioavailability of the Discontinued Prostate Cancer Drug Galeterone Be Improved by Processing Method? KinetiSol® Outperforms Spray Drying in a Head-to-head Comparison. AAPS PharmSciTech. 2023 Jun 21; 24(6):137.

90. Awad A, Goyanes A, Basit AW, Zidan AS, Xu C, Li W, Narayan RJ, Chen RK. A review of state-of-the-art on enabling additive manufacturing processes for precision medicine. Journal of Manufacturing Science and Engineering. 2023 Jan 1;145(1):010802.

91. Zheng YD, Ma LM, Lu JJ, Chai T, Naghavi MR, Ma JY, Sang CY, Yang JL. Nardoguaianone L isolated from nardostachys jatamansi improved the effect of

gemcitabine chemotherapy via regulating AGE signaling pathway in SW1990 cells. Molecules. 2022 Oct 13;27(20):6849.

92. Huang J, Chen B, Wang H, Hu S, Yu X, Reilly J, He Z, You Y, Shu X. Dihydromyricetin Attenuates Depressive-like Behaviors in Mice by Inhibiting the AGE-RAGE Signaling Pathway. Cells. 2022 Nov 22;11(23):3730.

93. Kadonosono T, Miyamoto K, Sakai S, Matsuo Y, Kitajima S, Wang Q, Endo M, Niibori M, Kuchimaru T, Soga T, Hirota K. AGE/RAGE axis regulates reversible transition to quiescent states of ALK-rearranged NSCLC and pancreatic cancer cells in monolayer cultures. Scientific reports. 2022 Jun 14;12(1):9886.

94. Moulahoum H, Ghorbanizamani F, Khiari Z, Toumi M, Benazzoug Y, Tok K, Timur S, Zihnioglu F. Artemisia alleviates AGE-induced liver complications via MAPK and RAGE signaling pathways modulation: A combinatorial study. Molecular and Cellular Biochemistry. 2022 Oct;477(10):2345-57.

95. Lu D, Shang J, Guo X, Zhang Y. Assessing the mechanism of action of "Fructus Ligustri Lucidi-Cuscutae Semen" in prostate cancer treatment using network pharmacology and molecular docking. Computational and Mathematical Methods in Medicine. 2022 Oct 25;2022.

96. Waqas K, Muller M, Koedam M, El Kadi Y, Zillikens MC, van der Eerden BC. Methylglyoxal–an advanced glycation end products (AGEs) precursor–Inhibits differentiation of human MSC-derived osteoblasts in vitro independently of receptor for AGEs (RAGE). Bone. 2022 Nov 1;164:116526.

97. Holms RD. Long COVID (PASC) Is Maintained by a Self-Sustaining Pro-Inflammatory TLR4/RAGE-Loop of S100A8/A9> TLR4/RAGE Signalling, Inducing Chronic Expression of IL-1b, IL-6 and TNFa: Anti-Inflammatory Ezrin Peptides as Potential Therapy. Immuno. 2022 Sep 8;2(3):512-33.

98. Kinscherf NA, Pehar M. Role and therapeutic potential of RAGE signaling in neurodegeneration. Current drug targets. 2022;23(12):1191.

99. Ren L, Yan H. Targeting AGEs-RAGE pathway inhibits inflammation and presents neuroprotective effect against hepatic ischemia-reperfusion induced hippocampus damage. Clinics and research in hepatology and gastroenterology. 2022 Feb 1;46(2):101792.

100. Rowe MM, Wang W, Taufalele PV, Reinhart-King CA. AGE-breaker ALT711 reverses glycation-mediated cancer cell migration. Soft matter. 2022;18(44):8504-13.

ACKNOWLEDGEMENT

The author expresses his gratitude towards Integral University and Rama University for providing a research environment and all necessary facilities for conducting research. The Integral University has provided a communication number for further internal communication (IU/R&D/2021-MCN000337).

AUTHORS CONTRIBUTIONS

AS has written the manuscript, SM has communicated the manuscript, VKV has collected material, SM has made the paper according to journal instruction and prepared table and figure.

All data repository available within the manuscript.

Suggested Reviewer

1. Dr. Saad Mohamad
   BBAU , Faculty of Pharmacy, Lucknow
   msaad2757865@gmail.com
2. Dr. Jagat Pal Yadav
   Faculty of Pharmaceutical Sciences, Rama University
   j.p.yaduvansi@gmail.com
3. Aditya Varshney
   Varshney.aditya.1993@gmail.com

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: