2

Review of Literature

Generally, a systematic literature search is performed for the past 10 to 15 years to start the research. The prior reports beyond fifteen years were also included in this literature review for the substantive research framework. Through the literature search, the research gap was identified and hypothesised. The following pages comply with the literature reports relevant to **"Development of Bioactive Drug Formulations Using Eco-friendly Metallic Nanoparticles for Sustained Drug Release Systems and Selected *In vitro* Biomedical Applications"**.

2.1 Review of Literature on Garlic

Garlic (*Allium sativum*, family: Liliaceae) is a plant that is known to be useful in the treatment of various ailments like chronic cough, constipation and toothache. In ancient Indian and Chinese medicine, garlic was recommended to aid respiration and digestion and to treat various bacterial and parasitic infections. It has been reported that garlic has many experimentally and clinically proven benefits like reduction of cancer, prevention of cardiovascular diseases and hepatoprotective activity **(Bayan *et al.*, 2014; Ozougwu and Eyo, 2010)**. In addition to the volatile oil, garlic also has 33 sulphur compounds, including Alliin, Allicin, Ajoene, S-allyl-L-cysteine, Diallyl disulfide, S-allyl mercapto cysteine, Diallyl trisulfide, Vinyldithiin, as well as several enzymes, 17 amino acids, and minerals **(Shang *et al.*,2019; and Omar *et al.*, 2009)**. Allicin (Diallylthiosulfinate), which is a thioester of sulfenic acid, was first isolated and identified by Cavallito and Bailey in 1944, and it remains the primary and most biologically active organosulfur compound in garlic. Allicin has a distinctive odour similar to freshly crushed garlic, when tissue damage occurs the enzyme Alliinase facilitates the conversion of the non-proteinogenic amino acid Alliin (S-allyl cysteine sulfoxide) to Allicin **(Marchese *et al.*, 2016; Tesfaye *et al.*, 2015).**

Allicin possesses advantageous lipophilic characteristics and a low molecular weight, which confers high permeability, easily traverse phospholipid bilayers and the blood-brain barrier **(Liu *et al.*, 2015)**. The biological half-life of Allicin is estimated to be approximately one year at 4º C. However, it should be noted that its half-life may differ when it is dissolved in different solvents **(Rahman *et al.*, 2007)**. Conventional extraction techniques have several drawbacks including the degradation of sensitive compounds due to the use of high temperature, the consumption of large amounts of solvent, the toxicity of some solvents, the long processing times and the low selectivity **(Angela *et al.*, 2014)**. ***The previous reports highlight the importance of garlic and its bioactive constituents, particularly Allicin, in contributing to a wide range of therapeutic effects. Despite***

these benefits, the stability and efficient extraction of Allicin remain challenging due to its sensitivity to environmental conditions and the limitations associated with conventional extraction methods. There is a growing need to explore improved, selective, and mild extraction techniques that can preserve Allicin and maximise its therapeutic potential. Further the objective of the present research to enhance their bioavailability through optimised drug formulations.

2.2 Review of Literature on Ionic liquid-based Extraction of Plants

Today much attention is given to the development of sustainable technologies to produce, extract and to purify a wide range of secondary metabolites and materials. The extraction methods used to carry out the isolation of target compounds from plants and other matrices are usually grouped as heat reflux, soxhlet, high pressure extraction, mechanical, microwave and ultrasonic assisted extraction. An extraction technique is more complex in nature when high yield and purity of target biomolecules are required. Generally, isolation and separation method are connected; where both methods should be merged and conducted in a single step. However, existing isolation, separation methods present several limitations like low extraction efficiencies, high costs of the final product, high energy consumption and time demands. In addition, toxic volatile organic solvents and harsh conditions are employed. Based on these limitations, researchers are working to develop alternative techniques which are greener and more sustainable **(Ullah *et al.*, 2018)**.

Owing to its remarkable characteristics, ionic liquids (ILs) has received greater attention. ILs have attracted much attention due to their unique properties as novel green solvents. ILs belongs to liquid molten salts that possess glass transition or melting points under 100º C and are made up of organic cations, as well as inorganic or organic anions. As alternative solvents, ILs are appreciated for their excellent and distinctive properties, which include low vapour pressure, high thermal stability, low volatility, non-combustibility, solubility in polar and non-polar chemicals, a wide electrochemical (conductivity) window, etc. These outstanding features led to their various applications within chemistry, analysis, electrochemistry, advanced materials, and environmental protection. They are especially popular in the extraction and separation field **(Gong *et al.*, 2023).**

ILs are considered as the solvent of choice in the extraction process. Previous studies revealed that ILs could be an efficient solvent to extract bioactive compounds from medicinal plants. 1-alkyl-3-methyl imidazolium based ILs were the widely used and they were mostly combined with the anions such as Cl^-, BF_4^- and Br^-. ILs could possibly be applied as green solvent in solid-liquid extraction, microwave-assisted extraction, ultrasonic-assisted extraction, and solid-phase extraction **(Lim *et al.*, 2022)**.There are various reports related to the extraction of bioactive compounds such as cellulose from rice straw and buck wheat, lignin from *Populus albaglandulosa*, *Eucalyptus urophylla*, dry olive pomace and sugarcane, Norstictic acid, Depsidone was isolated from *Pertusaria*

pseudocorallina, Paeonol from *Cynanchum paniculatum* etc., has been extracted using various ILs as solvents **(Caputo *et al.*, 2021; Kim *et al.*, 2011; Jiang *et al.*, 2011; Bonny *et al.*,2011)**.

The previous reports highlight the importance of ILs as alternative solvent for the conventional solvent-based extraction. Thus, for extracting the bioactive compounds from plant materials, we utilised ILs as extracting solvent in this study.

2.3 Review of Literature on Sustained Drug Release Formulations

Drug therapy is one of the most important methods used to treat diseases. However, in the process of traditional drug therapy, there are series of problems, such as short drug action time, large fluctuations in drug concentrations, and the risk of side effects. For example, in conventional chemotherapy, commonly used in the treatment of cancer, the mechanism of action involves toxic chemotherapy molecules interacting with and damaging DNA, thereby inducing tumour cell death. This treatment has disadvantages of drug toxicity, a fast degradation rate, low specificity, and limited targeting. At present, the development of drug delivery systems (DDS), also known as new DDS, has attracted attention. This refers to the different methods of delivering various therapeutic drugs in the prevention and treatment of diseases, with unique advantages in terms of drug resistance, low toxicity, the possibility of double delivery, advances in chemotherapy, etc. New DDS have a short development cycle and relatively low cost, making them a good choice for drug development in the biomedical field. New DDS include slow- and controlled-release DDS, nano-DDS, targeted DDS, etc **(Ruan *et al.*, 2022)**.

Various formulation approaches have been applied for the last few decades in developing GRDDS with a vast array of drugs. Some of the approaches include floating DSS, swelling and expanding systems, high density systems, ion-exchange resin systems, bio/muco-adhesive systems, raft forming systems, super porous hydrogel systems, magnetic systems, bio adhesive liposomal systems, and modified shape systems. Among these approaches floating DDS has drawn huge interest as this system provides buoyancy action, which offers greater safety for clinical uses and is not affected by the peristaltic movement of the gastro intestinal tract (GIT). Low density (as compared to gastric fluid) achieved by this system inside the stomach fundamentally allows it to float in gastrointestinal (GI) fluid. Many floating dosage forms are currently doing well commercially and received positive feedback from the market. Several approaches of floating systems, as have been applied in the recent past, include hydrodynamically balanced system based on hydrophilic polymers, gas generating or effervescence system, low density system, propylene tubes containing tablets or multi-unit systems. Optimised tablets remained floating for more than 24 h with a floating lag time of less than 4 min. Based on best fitting method, optimised formulation was found to follow Korsmeyer-Peppas release kinetic. Accelerated stability study revealed that optimised formulation was stable for

three months without any major changes in assay, dissolution profile, floating lag time and other physical properties **(Senjoti *et al.*,2016)**.

Sustained-release drug carriers are an important type of DDS, with the aim of reducing or overcoming the problems caused by traditional drug therapy, and causing drugs to act slowly in the blood, which plays an important role in drug therapy. The term "sustained-release drug carrier" generally refers to a system in which the drug can slowly enter the blood, in order to reduce the concentration of the drug in the blood, thus providing drugs with a sustained long-term release. Sustained-release drug carriers include skeleton-type sustained-release preparations, film-coated sustained-release preparations, osmotic pump controlled-release preparations, and controlled-release microcapsules and microspheres **(Palva *et al.*, 2015)**.

Based on the significance of sustained drug delivery in chronic disease management, we focused on formulating sustained release floating tablets and microspheres to achieve prolonged therapeutic effect.

2.4 Review of Literature on Metallic Nanoparticles

In the field of nanotechnology, metallic NPs have shown number of properties and it has unlocked many new pathways in nanotechnology. Metallic NPs have speciality with appropriate functional groups. It can be synthesised and modified that it would allow them to bind with ligands, antibodies, and drugs. Metallic NPs is nanosized metals with the size range of 10-100 nm. Metallic NPs have unique characteristics such as Surface Plasmon resonance (SPR) and optical properties. Gold solution does have a golden yellow colour, for e.g., a solution of 20 nm gold nanospheres has red ruby colour where 200 nm nanospheres has bluish colour. The noble metals, especially silver and gold, have gained much attention to researchers in various branches of science and technology namely catalysis, photography, medical field as anticancer and anti-microbial agents. Faraday first recognised the existence of metallic NPs in solution and Mie gave the quantitative explanation of their colour.

The most important feature of NPs is their surface area to volume ratio, which allows them to interact with other particles. In NPs, high surface area to volume ratio makes diffusion faster and is feasible at lower temperatures and this field has found more interesting, without disturbing and poisoning of healthy cells, we can directly treat affected cells and tissues. In fluorescence enhancement and Surface Enhanced Raman Spectroscopy and in environment refractive index sensing NPs have found additional application in the enhancement of field sensitive optical process. The optical properties of metal NPs play a key role due to the localised surface plasmon resonance wavelength in the visible region. GNPs and SNPs are effective in inhibiting growth of gram-positive and gram-negative bacteria **(Harish *et al.*, 2018)**. Currently, there are numerous chemical and physical methods available in the literature for production of nanomaterials, which deliver a higher

rate of production and well-controlled size and shape of nanomaterials but these approaches are discouraging due to higher loss of energy and capital, use of toxic chemicals, and production of large amount of bio-waste. These key factors influence the commercial level scale-up process of nanomaterials economically as well as environmentally. Additionally, the clinical use of nanomaterials prepared through chemical methods has been limited due to issues of biocompatibility, toxicity and stability. These components elevate requirement of eco-friendly, cheaper and biocompatible methods for production of nanomaterials. In comparison to conventional physical and chemical methods, greener route for NPs synthesis offers economical, environment-friendly and non-toxic approaches. Several studies have shown that metallic NPs characteristics (size, stability, physical, chemical properties, morphology) are strongly influenced by the experimental conditions, adsorption process of stabilising agent, and the kinetics of interaction of metal ions with the reducing agents **(Bhardwaj *et al.*, 2020; Thakkar *et al.*, 2010).**

Eco-friendly, plant mediated synthesis have been used for production of low-cost, energy-efficient, non-toxic and biocompatible metallic NPs.

2.4.1 Review of Literature on Eco-friendly Synthesis of Gold Nanoparticles

Nanotechnology has become a trending area in science and has made great advances with the development of functional, and engineered NPs. Various metal NPs have been widely exploited for a wide range of medical applications. Among them, GNPs are widely reported to guide an impressive resurgence and are highly remarkable. GNPs, with their multiple, unique functional properties, and ease of synthesis, have attracted extensive attention. Their intrinsic features (optics, electronics, and physicochemical characteristics) can be altered by changing the characterisation of the NPs, such as shape, size and aspect ratio **(Hu *et al.*, 2020)**.

Therefore, GNPs have attracted extensive scientific and technological attention in recent decades. The optical properties of GNPs are dependent on SPR, which is the fluctuation and interaction of electrons between negative and positive charges at the surface **(Ramalingam, 2019)**. SPR can also be described in terms of surface plasmon polarisation, which originates from propagating waves along a planar gold surface **(Gurav et *al.*, 2019)**. Due to their unique optical and electrical properties, and economic importance, GNPs have abundant applications in various interdisciplinary branches of science, including medicine, material science, biology, chemistry and physics **(Khan *et al.*, 2019)**. Especially, GNPs are widely employed across the medical field owing to their excellent biocompatibility, which respectively results from their high chemical and physical stability, easy to functionalise with biologically active organic molecules or atoms **(Pissuwan *et al.*, 2019)**. GNPs can directly conjugate and interact with diverse molecules containing protein, drugs, antibodies, enzyme, nucleic acids (DNA or RNA), and fluorescent dyes on their surface, for diverse medical applications and biological activities **(Slocik *et al.*, 2005;** and **Ramalingam, 2019).**

2.4.2 Review of Literature on Eco-friendly Synthesis of Silver Nanoparticles

Silver nanoparticles (SNPs) are one of the most vital and fascinating nanomaterials among several metallic NPs that are involved in biomedical applications. SNPs play an important role in nanoscience and nanotechnology, particularly in nanomedicine. Although several noble metals have been used for various purposes, SNPs have been focused on potential applications in cancer diagnosis and therapy **(Zhang *et al.*, 2016)**.

In general, metallic NPs are produced by two methods, i.e., "bottom-up" (build-up of a material from the bottom: atom by atom, molecule by molecule or cluster by cluster) and "top-down" (slicing or successive cutting of a bulk material to get nano-sized particle) **(Husen *et al.*, 2014)**. The main demerit of the top-down approach is the surface structural defects. Such defects have significant impact on the physical features and surface chemistry of metallic NPs. Several methodologies are available for the synthesis of SNPs namely, chemical methods **(Zhang *et al.*, 2011; Roldan *et al.*, 2013; Sotiriou *et al.*, 2010; and Sotiriou *et al.*, 2011)**, physical methods **(El-Nour *et al.*, 2010; Tien *et al.*, 2008; Asanithi *et al.*, 2012)** and biological methods (**Siddiqi *et al.*, 2016a; and Siddiqi *et al.*, 2016b)**. Chemical method of synthesis can be subdivided into chemical reduction, electrochemical, irradiation-assisted chemical and pyrolysis methods **(Zhang *et al.*, 2007)**. SNPs synthesis in solution requires metal precursor, reducing agents and stabilising or capping agent.

Commonly used reducing agents are ascorbic acid, alcohol, borohydride, sodium citrate and hydrazine compounds. Sotiriou and Pratsinis have shown that the SNPs supported on nanostructured SiO_2 were obtained by flame aerosol technology, which allows close control of silver content and size **(Sotiriou *et al.*, 2010)**. Also, silver/silica NPs with relatively narrow size distribution were obtained by flame spray pyrolysis **(Sotiriou *et al.*, 2011)**. However, physical methods do not require lethal and highly reactive chemicals and generally have a fast-processing time. These methods include arc-discharge **(Tien *et al.*, 2008)**, physical vapour condensation **(El-Nour *et al.*, 2010)**, energy ball milling method **(Wright *et al.*, 2011)**, and direct current magnetron sputtering. Physical methods have advantage over chemical methods, SNPs have a narrow size distribution, while the main demerits are consumption of high energy **(Asanithi *et al.*, 2012)**. Thus, biological synthesis of SNPs from herbal extract and/or microorganisms has appeared as an alternative approach as these routes have several advantages over the chemical and physical methods of synthesis. It is also a well-established fact that these routes are simple, cost-effective, eco-friendly and easily scaled up for high yields and production of biosynthesised metal/metal oxide NPs using biological agents such as bacteria, fungi, yeast, plant and algal extracts has gained popularity in the area of nanotechnology **(Siddiqi *et al.*, 2016a)**. Plants and their parts contain carbohydrates, fats, proteins, nucleic acids, pigments and several types of secondary metabolites which act as reducing agents to produce NPs from metal salts without producing any toxic by-product. Similarly, biomolecules such as enzymes,

proteins and bio-surfactants present in microorganisms serve as reducing agents. For instance, in many bacterial strains, bio-surfactants are used as capping and/or stabilising agents **(Siddiqi *et al.*, 2018)**.

From the literature reports on GNPs and SNPs reveals, no reports related to the chosen bio reductants for this research work. This research gap related to the chosen bio reductants involved in synthesising the metallic NPs helps in framing one of the objectives of this research work.

2.5 Literature Reports on Chosen Bioreductants

2.5.1 Review of Literature on *Amphilophium paniculatum* and *Tristellateia australasiae*

Bignoniaceae plants are multipurpose herbal remedies with privileged chemical and biological profiles; nevertheless, some members in this family, e.g., Amphilophium species, have been scarcely investigated **(Samy *et al.*, 2021)**. The chemical composition of the methanol extracts and fractions from *Amphilophium paniculatum* (AP) against *Eisenia fetida*. A preliminary phytochemical analysis was performed to assess the presence of groups of secondary metabolites. The plants were extracted with methanol to obtain the crude extracts. The extracts were submitted to partition with solvents of increasing polarity to obtain the corresponding fractions. The methanolic extracts and the fractions obtained were tested for anthelmintic activity against *E. fetida*, using albendazole as a positive control. The phytochemical test demonstrated the presence of flavonoids, saponins, and steroids/triterpenes for AP methanolic leaves. The results obtained showed that the methanolic extracts of AP could possess anthelmintic activity. The isolation of the substances responsible for the observed biological activity could lead to the development of new drugs for treatment of helminth infections **(Bazan *et al.*, 2020)**. Four new triterpenoid glycosides, named Amphipaniculosides A-D, in addition to one new aliphatic glycoside, named Amphipaniculoside E, were isolated from the 1-butanol fraction of the leaves of *Amphilophium paniculatum* (L.) Kunth., together with five known compounds, *via.,* (+)-Lyoniresinol 3α-*O*-β-D-glucopyranoside, (-)Lyoniresinol 3α-*O*-β-D-glucopyranoside, Soacteos Verbascoside, Soacteoside (Isoverbascoside), and luteolin 7-*O*-β-D-glucopyranoside. **(Samy *et al.*, 2015)**.

Similarly, *Tristellateia australasiae* (TA**)** is a climber belongs to Malpighiaceae family and commonly called as Australian gold vine and the shower of gold climber. The leaves and stem of TA plant reports the presence of flavonoid, steroids and triterpenoids. The isolated phytochemical compounds present in TA are acyclic Hexitol, Dulcitol, Isorhamnetin, Friedelin, Epifriedelinol, β amyrin, Lupeol and Sitosterol **(Mo, 1996)**. To our knowledge, there are no other reports related to the pharmacological and biological activities of TA leaves extracts as well for the metallic NPs aided TA extract. ***Review of literature reveals, no reported work on Amphilophium paniculatum and Tristellateia australasiae aided metallic NPs and their biomedical and its pharmacological applications. This research gap prompted the synthesis of metallic NPs aided AP and TA extracts***

and exploring their biological applications.

2.5.2 Review of Literature on *Haematocarpus validus*

One of the promising and potential sources as fruit, medicine, nutrition and natural colourant is *Haematocarpus validus*, popularly known as 'Blood Fruit' (BF). Etymologically, the word *Haematocarpus* is derived from two words, *via*., haem meaning iron containing compound and carpus meaning fruit. It was first described by John Miers **(Singh and Bedi, 2016)**. Fruits are dark red in colour with full of copious blood red juice when ripe and densely fibrous and hence the name 'blood fruit'. *H. validus* is a dicotyledonous plant species included in the genus Haematocarpus and belongs to the family Menispermaceae. The family Menispermaceae is mainly restricted to tropics and subtropics; however, few species are also found growing in the temperate regions. The plants in the Menispermaceae family are known to be rich in different alkaloids and are famous for their traditional medicinal usages. Two species of the genus Haematocarpus, viz., *H. subpeltatus* Merr., and *H. validus* (Miers) Bakh.f.ex Forman has been reported from South Asia extending to Philippines, Borneo and Sulawesi and one species, *H. validus* from India. The importance and ethno-medicinal values of this fruit is well recognised and are utilised by few old members of the village people for its iron-rich fruit. But a little research has been done on identification, proper utilisation and the information available is scanty **(Momin *et al.*, 2018)**. The reports on the preparation of blended fermented beverages from BF to add quality analysis of wine to attract the consumers in terms of their health benefits, reduce the consumption of health deteriorating drinks and to avoid the seasonal glut of fruits in the market **(Rapunga *et al.*, 2023)**. Blood fruit is an excellent source of carbohydrate (6.99%), iron (0.57 g/100 g of fruit) and β-carotene (9.0 µg) and anthocyanins (8.76 mg/g) with Pelargonidin and Cyanidin as dominant **(Singh *et al.*, 2014; Bohra *et al.*, 2020)**. The pulp of the fruit along with peel contributes to about 58.72% of the fruit weight, single seed constituted to 41.28% indicating its potential in processing industry **(Sangma, 2017).**

The previous literature reports show the evidence of blood fruit as food colouring agent, antioxidant rich therapeutic and nutraceutical properties. However, there is no reports on BF aided metallic NPs synthesis and its pharmacological activity. This research gap inspired to utilise BF as a bio reductant to synthesise GNPs (Rajalakshmi et al., 2021a) and SNPs and its pharmacological applications.

2.5.3 Review of Literature on *Phoenix dactylifera*

Phoenix dactylifera is one of the most important and major economic food and crops of the Arab world. The date fruit seeds contain a large number of nutritionally important functional compounds, e.g., fatty acids, sugars, protein, fibres, ash, minerals, and vitamins as well as high amounts of phenolic and flavonoids **(Al-Farsi *et al.*, 2007)**. Date seeds are one of the major waste materials that constitute about 6.1–11.5% of the fruit **(Habib and Ibrahim, 2009)**. Date seeds have

antioxidant and free radical scavenging activity as they contain considerable amounts of alkaloids, flavonoids, anthraquinone, saponin, terpenoids, and tannin **(Adeosun *et al*., 2016)**. The date seeds are generally used as animal feed and are also potential sources of edible oils and pharmaceuticals. Date seeds are often used in alternative and folk medicine for the management of diabetes, hypertension, cancer, liver diseases, gastrointestinal, and cardiovascular disorders and also used to improve the functionality and integrity of the immune system **(Bouhlali *et al.*, 2017; El-Far *et al.*, 2016;** and **Adeosun *et al.*, 2016)**. Moderate antibacterial properties of acetone and ethanolic extract of date seed have also been reported against *Bacillus cereus*, *Staphylococcus aureus, Enterococcus faecalis, methicillin-resistant Staphylococcus aureus, Pseudomonas aeruginosa,* and *Escherichia coli* **(Ravi, 2017; Saleh and Najim, 2020)**. The green synthesis of GNPs, SNPs, zinc oxide NPs and gold-zinc oxide NPs were reported using *Phoenix dactylifera* seed extract and its anticancer effect against human lung adenocarcinoma (A^{549}) and breast cancer (MCF-7) cell lines (**Farshori *et al*., 2022; and Chamkouri *et al.*, 2023).**

The previous reports related to the green synthesis of GNPs and SNPs utilised using date palm seed extract possesses to have pharmacological applications. However, we have reproduced the metallic NPs synthesis using dates palm seed 75% aqueous ethanol extract. We utilised date palm seed aided SNPs as nanodrug formulation which are resistance against microbial strains (Rajalakshmi et al., 2023). Further the objective of the research is to evaluate their potential medicinal applications by encapsulating the NPs as nanodrug in microsphere formulation and in drug delivery applications.

2.6 Literature Reports on *In silico* Studies of Drug Discovery Approaches

The term "*in silico* drug discovery" describes the process of identifying and designing possible drug candidates using computer techniques. This strategy makes use of additional molecular modelling tools as well as computer-aided drug design methods such virtual ligand screening and profiling, *in silico* structure prediction, refinement, and optimisation. Because it cuts down on the time and resources needed to find and improve therapeutic candidates, *in silico* drug discovery has grown to be an essential component of contemporary drug research **(Chang *et al.*, 2022)**.

In order to maximise the likelihood of discovering viable drug candidates, *in silico* approaches are frequently combined with physical screening techniques **(Sadybekov *et al.*, 2023)**. Drug development benefits greatly from *in silico* research for a number of reasons. They facilitate the process of identifying prospective drug candidates by screening, design, and therapeutic potential prediction of new medications (**Nimgampalle *et al.*, 2021)**. Furthermore, *in silico* methods aid in toxicity prediction, enabling research groups to recognise potentially harmful effects early in the development process, thereby saving time and money. By predicting the binding modes of possible drug candidates and examining their interaction patterns, computational techniques like virtual ligand

screening, molecular modelling, and docking-based virtual screening help find novel and promising compounds **(Chang *et al.*, 2022; and Ekins *et al.*, 2007)**.

Additionally, *in silico* research makes early drug development more flexible and morally sound by utilising knowledge already in existence to guide future procedures. Many promising therapeutic candidates have been found in *in silico* drug discovery. For instance, *in silico* techniques were utilised to find the HIV treatment medication raltegravir **(Chang *et al.*, 2022)**. Melanoma medication vemurafenib, which was found by virtual screening **(Shaker *et al.*, 2021)**. Furthermore, prospective COVID-19 treatment candidates, such as the medication molnupiravir, have been found using *in silico* techniques **(Sadybekov *et al.*, 2023)**. For a number of reasons, *in silico* research is essential to the drug development process. The virtual ligand screening, molecular modelling, and docking-based virtual screening are computational techniques used to find new drug candidates, and anticipate how drug candidates would bind, and examine how they interact. By utilising these techniques in conjunction with conventional *in vitro* and *in vivo* investigations, the drug development process may be completed faster and with less resources. In the early phases of drug development, *in silico* approaches also help with toxicity prediction, process optimisation, and the discovery of potential compounds, eventually saving time and money. Although important, *in silico* techniques cannot completely replace necessary *in vitro* and *in vivo* procedures. To maximise the effectiveness of the drug discovery process, they are therefore utilised in combination with conventional experimental methodologies **(Chang *et al.*, 2022; and Ekins *et al.*, 2007)**. ***From the previous reports, there is clear evidence that in silico drug discovery plays a vital role in refining the process of identifying and developing promising therapeutic leads. By integrating computational methods such as virtual ligand screening, and docking-based studies with conventional experimental approaches, could efficiently predict drug efficacy and safety while reducing time and cost. However, there remains a notable absence of in silico studies investigating the bioactive compounds from Amphilophium paniculatum, Tristellateia australasiae, Haematocarpus validus, and Phoenix dactylifera against DPP-IV inhibitors. Further computational exploration of these species could provide valuable insights into their potential as source of novel antidiabetic agents.***

2.7 Literature Reports on Biological Applications

2.7.1 Review of Literature on Antioxidant assay of Plant Extracts and Nanoparticles

The present study was undertaken for the antioxidant profiling of the lesser-known underexplored ethnic fruit crop *Haematocarpus validus* (Miers) Bakh.f. ex-Forman (Khoon phal). Reports on nutritional status and phytoconstituents of this plant are scanty and there is no scientific report on antioxidant potential of *H. validus* leaf even though, it is used as a hepatoprotective and anti-inflammatory agent in ethnomedicine. Methanolic extracts prepared from shade dried and powdered samples of both leaf and fruit were used in the study. *H. validus* methanolic leaf and fruit

extracts are found to be a potent source of natural antioxidants as evidenced by DPPH free radical scavenging activity and DNA protective properties (at 500 µg/mL) **(Alex *et al.*, 2018)**. Highly efficient antioxidant capabilities were proven with DPPH removal of 67.5% for *Zi*-GNPs and 92.34% for *Ziziphus spina-christi* extract **(Hosny *et al.*, 2022)**. The antioxidant properties of GNPs enhance its wide-ranging potential for use in healthcare applications including anti-aging, anti-inflammatory, and wound healing agents, as well as treatment for various diseases. This review highlights recent progress in the synthesis of GNPs as antioxidants and method for assessing their antioxidant capacity as well as delves into their mechanism of action and explores their potential health applications **(Suliasih *et al.*, 2024)**.

2.7.2 Review of Literature on Antimicrobial activity of Plant Extracts and Nanoparticles

Recently, the upsurge in hospital-acquired diseases has put global health at risk. Biomedical implants being the primary source of contamination, the development of biomedical implants with antimicrobial coatings has attracted the attention of a large group of researchers around the globe. Bacteria develops biofilms on the surface of implants, making it challenging to eradicate them with the standard approach of administering antibiotics. As nanotechnology continues to advance, various types of nanomaterials have been created, including 2D NPs and metal/metal oxide NPs with antimicrobial properties. Researchers from all over the world are using these materials as a coating agent for biomedical implants to create an antimicrobial environment **(Sahoo *et al.*, 2022)**. Total extract of *P. austroarabica* showed weak antimicrobial activity against *S. aureus, Staphylococcus epidermidis*, Methicillin Resistant *S. aureus* (MRSA), *B. subtilis, Streptococcus mutants, Enterococcus faecalis, Proteus vulgaris, Pseudomonas aeruginosa and, Cryptococcus neoformans*. The activity of the extract ranged from 33 to 67% relative to positive control, where the highest antimicrobial activity was shown against MRSA **(Khodeer *et al.*, 2022)**.

2.7.3 Review of Literature on Anticancer activity of Plant Extracts and Nanoparticles

GNPs have been widely used in biomedical fields such as imaging, diagnosis, and treatment because of their special characteristics. GNPs can be synthesised using several methods, including the biological method, also called green or eco-friendly synthesis. Recent studies have reported the anticancer activity of biosynthesised GNPs, especially in lung cancer **(Wang *et al.*, 2020)**. Vanadium NPs (VNPs) were green synthesised using the aqueous extract of *Salvia officinalis.* Anticancer activity evaluation of the treated cells with VNPs were assessed by MTT assay for 48 h. The cytotoxicity and anti-lung cancer properties on normal and lung cancer cell lines were examined. The IC_{50} of VNP were 213, 210, 297, 204, 160, and 125 µg/mL against EBC-1, LK-2, LU65, LU99, STC1 and RERF-LC-MA cell lines, respectively. The viability of malignant lung cell lines was reduced dose-dependently in the presence of VNPs. It appears that the anti-lung cancer effect of VNPs is due to their antioxidant effects **(Liu *et al.*, 2023)**.

2.7.4 Review of Literature on Antidiabetic activity of Plant Extracts and Nanoparticles

Allium sativum (*A. sativum*), a traditional medicinal plant with a huge amount of medicinal properties showed better hypoglycaemics activities in rats and humans. The antidiabetic activity of *A. sativum* was well documented in terms of reducing insulin resistance and blood sugar level. The sulphur-containing compounds (Alliin, Allicin, Ajoene, Diallyl disulfide, Diallyl trisulfide, Diallyl sulfide, S-allyl cysteine, and Allyl mercaptan) from *A. sativum* responsible for the pungent smell and possess anti-diabetic activity. The phytocompounds such as Sitagliptin, Vildagliptin, and Alogliptin from *A. sativum* were used to treat diabetes clinically. SNPs synthesised from *A. sativum* have prominent antidiabetic activity in terms of reducing the hyperglycaemia through the increased glucose utilisation, decreased hepatic glucose production, and the inhibition of α-amylase and α-glucosidase enzymes. So, it can be used as a promising nanomedicine for the treatment of diabetes **(Jini *et al.*, 2022)**. The aqueous *Physalis minima* extract and phyto fabricated GNPs suppressed the most α-amylase enzyme activity and had a 90–93% antidiabetic effect. The presence of phytochemicals such as flavonoids and polyphenols in GNPs resulted in highest amylase inhibitory property. The synthesised GNPs from *Physalis minima* had an excellent antioxidant activity because they minimise oxidative stress, and enhanced anti-diabetic activity. The aqueous extract of *Physalis minima* and phyto generated GNPs are promising anti-oxidant and anti-diabetic agents **(Sekar *et al.*, 2022)**.

2.7.5 Review of Literature on Toxicity Studies of Plant Extracts and Nanoparticles

Increased usage of GNPs in biomedicine, biosensing, diagnostics and cosmetics has undoubtedly facilitated accidental and unintentional release of GNPs into specific microenvironments. The significant genotoxicity in *Allium cepa* root meristematic cells (an off target bioindicator) treated with high concentration (≥100 μg/ml) of green-synthesised vanillin capped GNPs (VGNPs). In contrast, protein-coated VGNPs of similar concentrations had negligible genotoxic effects. This could be attributed to the change in physicochemical characteristics due to surface functionalisation of proteins on VGNPs and differential bioaccumulation of gold ions in root cells. Genotoxic risk associated with GNPs is due to the enhanced utility, which are emerging as new pollutants **(*Arya et al.*, 2022)**.

The study evaluates the cytogenetic effects of both GNPs and SNPs on the root cells of *Allium cepa*. In this study, the root cells of *Allium cepa* were treated with both GNPs and SNPs of different concentration (1 mg/L, 5 mg/L and 10 mg/L) along with control for 72 h. The experimental results revealed that after 72 h of exposure, a significant decrease in mitotic index (MI) from 68% (control) to 52.4% for 1 mg/L, to 55.8% for 10 mg/L for SNPs. It was observed that some specific chromosomal abnormalities such as stickiness of chromosome, chromosome breaks, nuclear notch, and clumped chromosome at different exposure conditions were noted. Therefore, present

results clearly suggesting that *A. cepa* root tip assay could be a viable path through which negative impact of both GNPs and SNPs can be demonstrated over a wide range of concentrations **(Debnath *et al.*, 2018)**. ***There are no previous reports are available on the in vitro biological evaluation and nano encapsulation studies involving GNPs and SNPs synthesised from these selected plants. These research gap highlights the need for their pharmacological and therapeutic potential in drug discovery and delivery.***

2.8 Literature Reports on Textile applications of Antibacterial and UV protection

Cotton accounts for a substantial portion of natural textiles. Fabrics made of cotton are a common choice in modern society. Cotton is known for its comfort, smoothness, hydrophilicity, biocompatibility, and optimum mechanical strength. Cotton is more susceptible to microbial attacks due to its higher moisture retentive capacity and porosity. This can lead to unpleasant smells, skin allergies, and other illnesses. Thus, the finishing of cotton textile products with antibacterial protection properties has become crucial in the textile industry. Antibacterial fabrics can prevent the growth and propagation of microbes like bacteria and fungi **(Seetharaman *et al.*, 2022)**.

Biologically synthesised SNPs were found to be effective against six hospital prevalent bacterial species. SNPs were deposited on the fabric and surgical blades using layer-by-layer and electrochemical deposition methods. Coated fabric samples and blades were tested against six above mentioned bacterial species were found to be effective for all of them. Furthermore, washing durability test revealed that SNPs were strongly attached to the surface of fabric even after 20 cycles of hospital laundering **(Tahir *et al.*, 2024)**. Harmful portion of ultraviolet (UV) radiation is one of the significant physical carcinogens in our natural environment. The damage caused by UV exposure to our body is cumulative and builds up over the years. UV protective textiles have been used to protect the wearer from harmful UV radiation. UV blocking effect of textile depends on various parameters *via*. fiber type, yarn structure, weave, fabric construction factor, finishes, dyes etc. Further, UV protective property of textiles can be improved by incorporating UV blocking agent in the textile matrix. Several nanomaterials possess excellent UV blocking effect and these could be incorporated into the textile matrix to improve the UV blocking properties of textiles **(Mondal, 2022)**. Titanium dioxide NPs are shown to be very resistant to ultraviolet light and have a high UV protection factor. Cotton fabric's UV-protection factor (UPF) and crease recovery characteristics were also assessed. The obtained findings demonstrate strong UV-ray blocking characteristics (UPF 30 +) as well as good wrinkle recovery in cotton fabric to develop face-covering properties **(Madhu *et al.*, 2022b)** ***From the literature reports, nanomaterial functionalisation of cotton fabrics significantly enhances their antibacterial and UV-protective properties. However, there is an absence of reports on the utility of nanoparticle synthesised from selected plants for multifunctional textile applications.***