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GREEN CHEMISTRY: A CONSERVATIVE APPROACH IN PHARMACEUTICAL SYNTHESIS

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ABSTRACT

Several conventional synthesis techniques include elements, such as abrasive or explosive liquids, gases, or explosives, that may be harmful to human beings or the environment when used in high proportions. Chemical reactions generate a significant amount of toxic waste, which is a serious barrier for the production of pharmaceuticals. Green chemistry is expanding dramatically, due to a greater awareness of environmental safety, and the development of new products, procedures, and services that meet the necessary societal, economic, and environmental goals is increasingly difficult for chemists. This article contains a brief discussion about green chemistry in nanotechnology as well as modern-day green chemistry along with its application in disease therapies. Moreover, it also covers the factors affecting the green synthesis of nanoparticles. The overview of this paper gives an idea about the current advancement of green chemistry as well as its role in pharmacology, toxicology, and pharmaceutical chemistry.

Keywords: Green synthesis, Pharmacology, Toxicology, And Pharmaceutical Chemistry

INTRODUCTION

Green synthesis seeks to eliminate energy waste, potentiate the use of recyclable energy sources, and optimize consumption [13].

Green chemistry is centred on the reduction or elimination of harmful solvents from chemical processes and analysis, as well as the avoidance of residue production [3, 8].

Green chemistry has transformed after social movements ever since the 1940s and brought about changes in industrial processes with improvements in environmental effects and awareness among businesses and the general public [30], Environmentally friendly approaches have been created in a variety of societal and scientific fields due to public and scientific concerns over environmental contamination. Due to the frequent use of toxic solvents, sample preparation, and Liquid Chromatography analysis require special consideration in green analytical chemistry. According to the European Medicine Agency (EMA), safe disposal or detoxification of the used or waste solvents is necessary due to their toxicity and hazardous nature which could result are all ways to get towards green liquid chromatography [5].

Professor Norio taniguchi of Tokyo Science University first used the word "nanotechnology" in 1974. Generally speaking, modifying a material to be between 1 and 100 nm in size is considered nanotechnology. It suggests that there are 109 meters in a billion. The size of human hair, the DNA molecule, protein molecule, and a flu virus is 10,000 nm thick, 2.5 nm wide, 50 nm long, and 100 nm respectively, and so on. The creation of nanoparticles by "green synthesis" minimizes or eliminates the use of potentially harmful substances

and solvents, promoting environmental safety. In many metallic nanoparticle syntheses, green materials like microorganisms, plants, fruits, and other food sources are routinely used. But the strain on the world's food supply and the shortage of natural resources raises concerns about the sustainability of the environment. In order to create highly effective, biocompatible, economical, and environmentally friendly metallic nanoparticles, bio-waste materials may be used. This approach could help trash be valued and promote environmental sustainability [6].

It is now common knowledge that food and the aquatic environment contain antibiotic residues. Antibiotic residue concentrations are normally minimal, however, there have been reported negative consequences on the environment and public health. As a result, an effective approach to identifying a variety of antibiotic residues should be straightforward, affordable, selective along with minimum demarcation line. Prior to chromatographic analysis, separation along the liquid is extensively utilized to immaculate and preconcentrate antimicrobials. Dangerous organic mixtures are swapped out with environmentally friendly mixtures to make processes greener and more environmentally sustainable [12].

Antioxidants, which are substances that stop distinct molecules from oxidizing one another, are primarily found in medicinal plants. Herbs include a significant amount chemical containing phenol, that function as antioxidants. Due to their redox characteristics, antioxidant chemicals counteract free radicals and break down peroxides to demonstrate how they work. In contrast to fabricated antioxidants, that should be averted because of their damaging effects on the normal physiology, natural antioxidants are regarded as harmless and beneficial. The creation of colloidal nanoparticles is the most dynamic and fascinating area of research (NPs). It demonstrates a strong influence in advancement of nanotechnology throughout the preceding decades. In nanotechnology, creation of nanoparticles using plant wrench outs is crucial. Since there are no harmful chemicals used, it is known as "green technology." The primary goal of green approaches is to produce biocompatible NPs by using benign macromolecules and these are rather expensive, easily decomposable, and subject to fraud. The salvia miltiorrhiza Bunge (Danshen) provides valuable antioxidant action and improves blood circulation [22]. revealed the compositions created using nanotechnology displayed higher activity than antioxidant qualities of composition made from conventional methods of grinding herbal plants [14].

Principles of green chemistry

Green chemistry revolves around ideas such as waste management, the use of non-toxic agents, use of Renewable resources, Enhanced atom efficiency, usage of environmentally benign solvent systems.

Following are the twelve fundamental principles of green chemistry: **(Figure 1)**.

Impact of green chemistry on the environment

During research and development of a new drug, various chemicals are used and are simultaneously disposed of in to the laboratory (in the sink or the outlet pipe) which ultimately goes to the major water sources such as rivers, and even after various purification processes the harmful residues still reside within the water. This leads to the accumulation of toxicity within the human body and can cause serious medical conditions. Green synthesis seeks to eliminate energy waste, increase the use of renewable energy sources, and optimize consumption [13]. Before being released back into the surrounding, the remnant produced during the drug analysis ought to first undergo pre-treatment. Nevertheless, the expense of this technique varies depending on how toxic and dangerous the solvent is. For instance, when acetonitrile is burned, trash is produced that leads to acid rain [3].

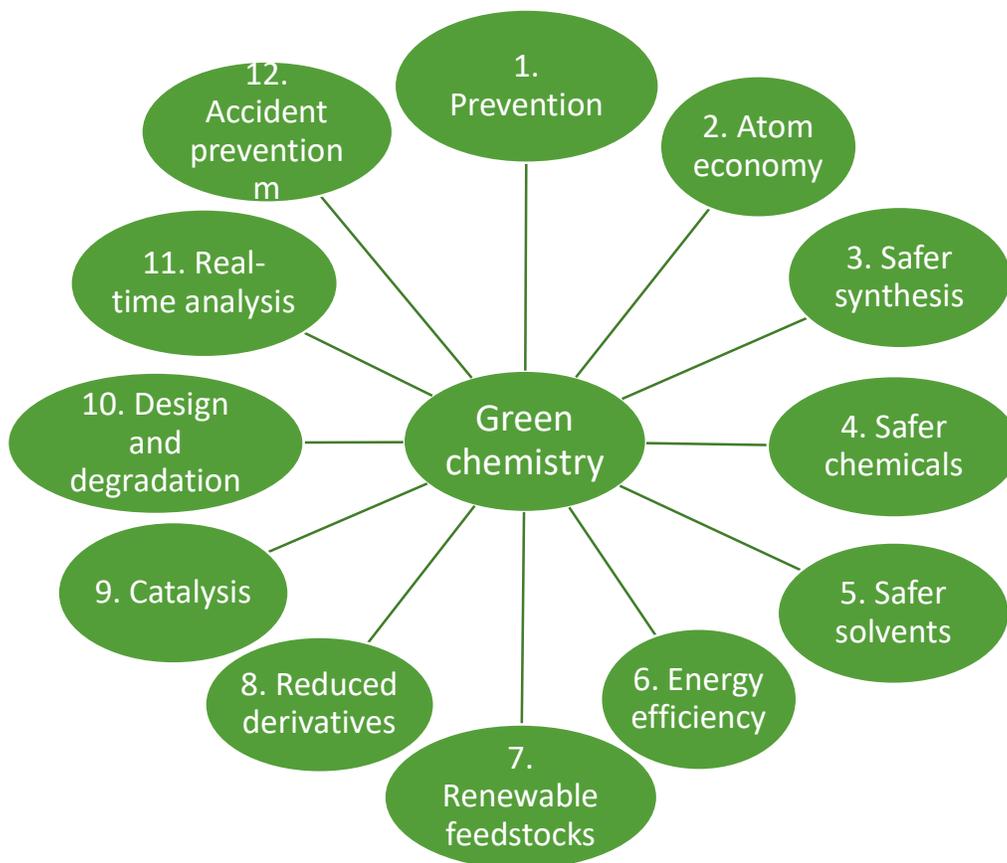


Figure 1: Principles of green chemistry

GAC (Green Analytical Chemistry)

The discussion of pharmaceutical synthesis of drugs is incomplete without the intervention of analytical chemistry. If the idea of green synthesis is collaborated with analytical chemistry, it can be of great use in pharmaceutical industry. The creation of analytical techniques, which gave rise to the term "Green Analytical Chemistry," is the first and foremost fields in experimentation in sustainable chemistry [3]. Luckily, sustainable chemistry has advanced in other disciplines, especially analytical chemistry, which is now referred to as GAC when the concern regarding surrounding wellbeing as

well as protection is taken into account throughout its operations [9].

A very significant area of research is the development of green sample preparation techniques, and numerous applications, including those for pharmaceutical analysis, are continually being suggested [9]. The primary methods for greening analytical chromatography are reducing column dimensions, lowering analysis times (by raising pressure or temperature), finding sustainable mixtures for mobile phase components [4].

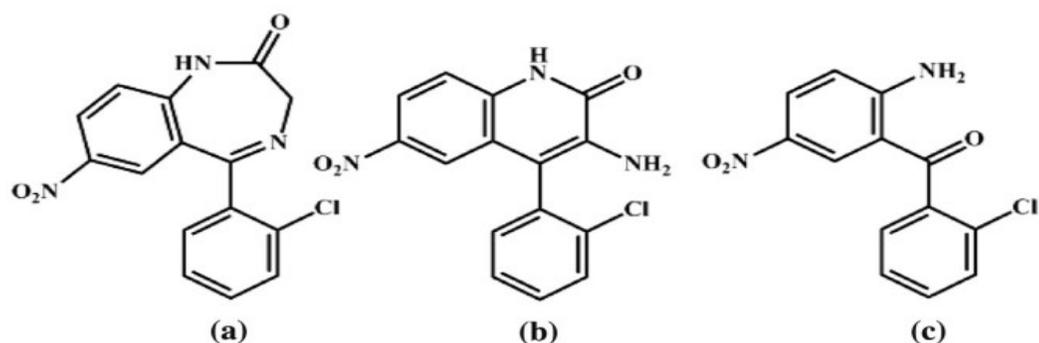
Unlike mixtures that have some danger, like organochlorine, drawn a significant amount

of interest lately, interchangeable polar solvents, which were found in 2010, are superior substitute. These mixtures are distinguished by their capacity to change the system's polar and non-polar state in water with a quick and free shift [9].

For example: the primary uses of clonazepam are as an anticonvulsant, spasmolytic as well as minor tranquilisers. One benzodiazepine ring is included in the chemical structure of clonazepam, making it susceptible to deterioration. In attempts to establish a firm stipulating RP-HPLC procedure for identifying drug along with their associated compounds in medicinal composition, a green analytical chemistry approach has been used. Since clonazepam is being sold both domestically and abroad, its related compounds A and B can be produced instead of using quality control

labs in dosage forms for drugs risky, poisonous liquids [5].

For reasons of sustainability, non-toxicity, and safety, there has been a lot of focus in recent years on using H₂O as a means in organic production. However, the effects of the solvent or moisture are frequently quite sensitive to organic reactions and reagents. Before employing water as a medium for organic transformations, make the assumption that the solubility of the starting materials and the reagents, as well as the physical features of the combination, are sufficient for transformations. Professor Lipshutz's team formed the micelles using the non-ionic surfactant TPGS-750-M in H₂O that can "solubilize" hydrophobic materials to a limited extent in a polar medium, thereby facilitate the reaction in order to address these significant problems [17].



Figures of clonazepam with its associated compounds (a) clonazepam (b) clonazepam related A and (c) clonazepam related B [5]

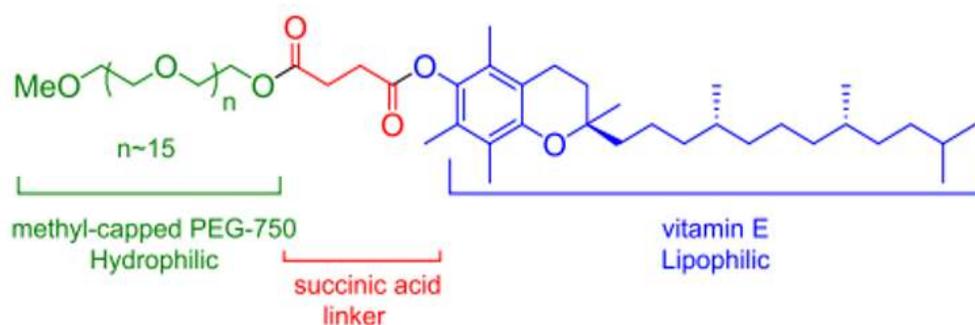


Figure 2: TPGS-750-M surfactant's structure [17]

Green chemistry in a modern-day scenario

Today's green chemistry goes beyond the notion of being a pure laboratory inquiry into extensive manufacturing of drugs. Nevertheless, because they are among the most vibrant areas, industries are every time at the forefront of any significant developments. It appears exciting to implement these modifications in terms of creative concepts, traditional feedstocks, healthier raw resources, and different techniques tested on a small scale in laboratories [13].

Following are a few of the cutting-edge final products and technologies of green chemistry for drug production that have recently gained popularity and recognition:

Green solvent

Sertraline hydrochloride is manufactured using chemical reagents such as methyl benzene, tetrahydrofuran, hexane, and TiCl₄ with the goal of replacing dangerous mixtures with additional green sustainable

solvents. These solvents were swapped out for greener solvents like water, and the removal of the Pd/C catalyst and metal salts resulted in a more environmentally friendly process.

Biocatalysts

The overall production was nearly twice as high as the previously employed traditional method, resulting in a greener, quicker, and more affordable alternative. The use of the protease enzyme, which regioselectivity hydrolyzed an ester group, was the most crucial step [13]. During the development of green chemistry, it is important to put a glance on biocatalysis. Enzymes excel in this field since they can transform simple compounds under mild aqueous conditions. For well over a century, enzymes have been utilized in the production of organic compounds. A biocatalytic procedure was replaced with recombinant protein synthesis because it is less expensive and time-saving, and enzymes are also changed at their amino acids level. The promising requirement of

sustainable synthesis techniques, together including developments in enzyme technologies, have encouraged the use of these techniques in chemical and pharmaceutical manufacturing [7].

Green chemistry in nanotechnology

When using green synthesis to create nanoparticles for the medical field, the process is both affordable and advantageous for people.

Carbonaceous materials

The scientific community has been interested in carbon-based nanomaterials due to their wealth of beneficial features, which has led to their use in a variety of research areas. Despite the fact that carbonaceous materials have many benefits, it should be kept in mind that they cannot be regarded as entirely green sorbents because of the potential risks associated with their synthesis and other intrinsic qualities to the environment and human health. It must be remembered, nevertheless, that these qualities can significantly minimize the need for sorbent and solvents during the extraction process, making the usage of such materials a net plus. New approaches to lessen their impact will also be developed and put into practice as research into these materials develops, aiding careful use and treatment [9].

Carbon nanotubes

One of the carbonaceous substances such as carbon nanotubes (CNTs) almost always

utilized in green pharmaceuticals analysis (alone or in combination with additional resources) due to characteristics such as bigger surface area (150-1500 m²/g) [9].

Nanotechnology in anticancer therapy

Researchers in the field of nanotechnology has recently made significant efforts to clarify the potential of multifunctional nanocarriers for the treatment of cancer. The general operating principles of various types of green nanocarriers (*i.e.*, the use of biological agents to minimize the usage of solvents), such as polymers nanoparticles (micelles, dendrimers, vesicles, hydrogel), solid lipid nanoparticles, porous nanoparticles, in addition, both quantum dots as well as gold nanoparticles used as inorganic nanoparticles [22].

The pharmacodynamics profile of different flavonoids is influenced by their different pharmacokinetic characteristics. The bioavailability of flavonoids may be enhanced by the use of new drug delivery methods and nanotechnology. Chrysin has been used for consumption because of its beneficial pharmacological properties in a number of research. Since chrysin is obtained naturally from *Passiflora caerulea*, Chrysin has been shown to have anticancer properties in cases of bladder, pancreatic, liver, tongue, gastric, colorectal, and breast cancer [20].

For example: the synthesis of 5-fluorouracil series compounds used as anticarcinogenic

agents can be done by green synthesis. Methanol is used as green solvent for the synthesis of 5-FU, Aspirin and Acetanilide. A solid-state grinding protocol was used to combine drugs with excipients while another fabrication approach made separate solutions for each component and combined them. The accepted methodologies provide simple fabrication protocols, no need for expensive solvents, no temperature management needs, practically any apparatus required, and purification and separation of the required products. Additionally, no by-products are produced; rather, circumstance encompassing the objectives of green technology occurs [10].

Another example of anticancer therapy using nanotechnology as a green approach:

Sorafenib tosylate has been given the US FDA's approval with the aim of curing hepatocellular carcinoma, thyroid cancer, and kidney cancer. Sorafenib tosylate's standard preparations have difficulties with different pharmacokinetic properties including cancer resistance. The nanotechnology-based specific anticancer approach has shown to be efficient and proved to be an asset in treating these recognized cancer indications. Additionally, there are promising results from studies looking at Sorafenib tosylate's innovative formulations for certain signs, such as

hepatocellular cancer, renal cancer, and cholangiocarcinoma [18].

To minimize unwanted effects and resistance to antimicrobial and antiviral drugs, among other things, and to successfully deliver nanoparticles carrying various drugs, including those for tumours as well as for different pathogenic and non-pathogenic conditions, it is necessary to overcome barriers in drug delivery, especially in special structures. These obstacles have been surmounted using a variety of nanotherapeutic tactics. Instances include using substances that can be absorbed by particular elements of the tissue's microenvironment, developing biomaterials that respond to stimuli, developing nanoparticles of substances with faceless friction to move across the unique structure, and utilizing external mechanical or physical energy to support particle delivery across the unique structure [11].

Nanotechnology in antidiabetic therapy:

Diabetes mellitus is a chronic metabolic illness that raises blood sugar levels mostly as a result of insufficient insulin secretion or as a result of the body's failure to react to insulin released by pancreatic cells. In the world, diabetes ranks behind cancer and cardiovascular illnesses as the third leading cause of mortality. Since nanoparticles are said to boost the productiveness of medications generated from natural products via a green biosynthetic approach

through their target-specific activity, nanotechnology is a developing field in pharmaceutical sciences. The nanoparticles created from plant resources have the ability to regulate the prepotency of specific disorders with little to no toxic undesirable effects [2].

Gold nanoparticles:

Due to their improved qualities for use as molecular nanoprobe, diagnostic instruments, and therapeutics, gold nanoparticles (AuNPs) are the focus of extensive research. Gold has emerged as one of the key metals utilized in the production of nanoparticles due to its dependence on size, electrical, and optical properties. AuNPs distinguish themselves from other metallic nanoparticles primarily because of their controllable Surface Plasmon Resonance, which is used in biosensor devices for bacteria and virus detection, drug delivery, bio-labelling methods, neoplasms and tissue imaging, photothermal therapy, and pathogenic identification in clinical specimens by the immune-chromatographic method. Gold nanoparticles have been found to be biocompatible, nontoxic, and easily interact with a variety of biomolecules (proteins, enzymes, DNA, and amino acids), and they also provide a large surface area for these molecules [2, 21].

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another, are primarily found in medicinal plants. Plants contain a significant amount of chemicals containing phenol, that function as antioxidants. Due to their redox characteristics, antioxidant chemicals counteract free radicals and break down peroxides to demonstrate how they work. In contrast to manmade antioxidants, which should be circumvented owing to their damaging effects on the biological system, natural antioxidants are regarded as harmless and beneficial. The creation of colloidal nanoparticles is the most dynamic and fascinating area of research (NPs). It demonstrates a strong influence of the advancement of nanotechnology throughout the previous era. In nanotechnology, the extraction of nanoparticles from plants is crucial. Since there are no harmful chemicals used, it is known as "green technology." The main aim of sustainable approaches is to design biocompatible NPs by using innocuous macromolecules; nevertheless, these biomolecules are rather expensive, easily decomposable, and subject to fraud. The *Salvia miltiorrhiza* Bunge (Danshen) provides valuable antioxidant action and improves blood circulation [22]. suggested that the preparation of nanoparticles having antioxidant activity greater than preparations made from conventional methods of grinding herbal plants [14].

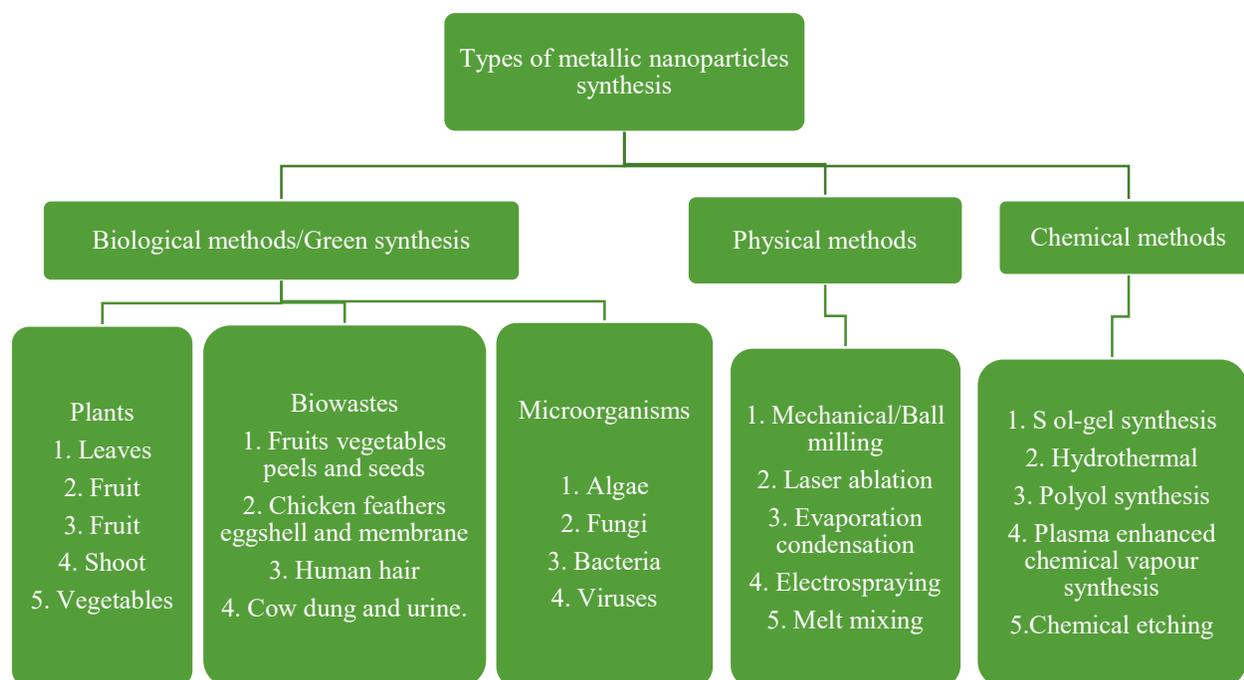


Figure 3: Numerous synthetic techniques for the production of metallic nanoparticles [6]

Factors influencing the production of nanoparticles:

pH

The creation of green nanoparticles depends heavily on pH, a crucial component. It affects the different texture and size characteristics during nanoparticle formation.

Temperature

The next crucial element in the creation of green nanoparticles is temperature. The physical approach calls for a temperature of at least 350°C.

Less than 350°C is needed for the chemical approach, and less than 100°C or a temperature close to that is needed for the biological method. As a result, the creation of nanoparticles depends on temperature.

The morphology and their rate are influenced by temperature.

Reaction time

In the synthesis of green nanoparticles, reaction time plays a crucial part in deciding the kind, quality, and morphology of the nanoparticles. Reaction time does have an impact on it [19].

Importance of green chemistry in organic reaction workups

Water could surely be considered as an ideal solvent option in case of any chemical reaction from the perspectives of accessibility, price, as well as surrounding greenness. Although, a large number of organic molecules react to H₂O and the majority of them are insoluble in it. Despite these challenges, water has been shown to significantly affect numerous organic

reaction outcomes, as well as reaction speeds and selectivity, most likely as a result of hydrophobic effects. The introduction of Green Chemistry in the 1990s steadily altered how chemistry is conceptualized and taught. Since then, various initiatives have been made to promote the concepts of ecologically friendly and sustainable ways to conduct chemistry, while amongst the primary problems is to ensure the simplification of concepts of reaction workups [1].

CONCLUSION

Green chemistry is a revolutionary advancement specifically in the field of pharmaceutical synthesis, pharmacology, toxicology, etc as it carries out synthetic reactions in an environmentally benign manner. Furthermore, with the enforcement of nanotechnology, the foundation of green chemistry becomes even stronger. Green nanotechnology is a concept used to refer to Nanoparticles produced utilizing various biotechnological methods from natural sources including bacteria, fungi, or plant-based extracts. The produced nanoparticles are advantageous for the environment and free of toxic chemicals. Green nanotechnology (nanoparticles) aids in various therapeutic processes such as antidiabetic therapy, and anticancer therapy. By altering and incorporating nanomaterials, multifunctional cancer microenvironment-targeted drug delivery

systems were developed to address the unique characteristics of the tumour microenvironment. As a result, the development of novel targeted nanomedicines has great potential for use in the treatment of cancer. These nanomedicines offer several advantages, including the ability to target tumour tissues directly and low toxicity to healthy tissues, which ensures the safety of drug administration.

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REFERENCES

- [1] Andrade, C. K. Z, Dar, A.R., Applying green processes and techniques to simplify reaction work-ups. *Chem. Inform*, 47(50), (2016).
- [2] Bhardwaj, M, Yadav, P, Dalal, S, Kataria, S. K., A review on ameliorative green nanotechnological approaches in diabetes management. *Biomed. Pharmacother*, 127:110198, (2020).
- [3] De Marco, B. A, Rechelo, B. S, Tótolí, E. G, Kogawa, A. C, Salgado, H. R. N., Evolution of green chemistry and its

- multidimensional impacts. Saudi Pharm J, 27(1):1-8, (2019).
- [4] Dogan, A, Tobiszewski, M., Optimization of liquid chromatographic separation of pharmaceuticals within green analytical chemistry framework. Microchem. J, 152:104323, (2020).
- [5] Eldin, A. B, Shalaby, A, Abdallah, M. S, Shaldam, M. A, Abdallah, M. A., Applying green analytical chemistry (GAC) for development of stability indicating HPLC method for determining clonazepam and its related substances in pharmaceutical formulations and calculating uncertainty. Arab. J. Chem, 12(7):1212-1218, (2019).
- [6] Gowda, B. J, Ahmed, M. G, Chinnam, S, Paul, K, Ashrafuzzaman, M, Chavali, M, Gupta, P. K., Current trends in bio-waste mediated metal/metal oxide nanoparticles for drug delivery, J Drug Deliv Sci Technol, 71:103305, (2022).
- [7] Hammer, S. C, Knight, A. M, Arnold, F. H., Design and evolution of enzymes for non-natural chemistry. Curr. Opin. Green Sustain. Chem, 7:23-30, (2017).
- [8] Haq, N, Iqbal, M, Alanazi, F. K, Alsarra, I. A, Shakeel, F., Applying green analytical chemistry for rapid analysis of drugs: Adding health to pharmaceutical industry, Arab. J. Chem, 10:777-785, (2017).
- [9] Jiménez-Skrzypek, G, Ortega-Zamora, C, González-Sálamo, J, Hernández-Borges, J., Miniaturized green sample preparation approaches for pharmaceutical analysis. J Pharm Biomed Anal, 207:114405, (2022).
- [10] Jubeen, F, Liaqat, A, Sultan, M, Iqbal, S. Z, Sajid, I, Sher, F., Green synthesis and biological evaluation of novel 5-fluorouracil derivatives as potent anticancer agents. Saudi Pharm J, 27(8): 1164-1173, (2019).
- [11] Khan, M.I, Batool, F, Kalsoom, F, Gao, S, Ali, R, Wang, W, Bilal, M., Trends in Nanotechnology to improve therapeutic efficacy across special structures. Open Nano, 7:100049, (2022).
- [12] Khataei, M. M, Epi, S. B. H, Lood, R, Spégel, P, Yamini, Y., Turner, C., A review of green solvent extraction techniques and their use in antibiotic residue analysis. J. Pharm. Biomed. Anal, 209: 114487, (2022).
- [13] Mishra, M, Sharma, M, Dubey, R, Kumari, P, Ranjan, V., Pandey, J., Green synthesis interventions of pharmaceutical industries for sustainable development. Curr. Opin. Green Sustain. Chem, 4:100174, (2021).
- [14] Mishra, Y, Amin, H.I. M, Mishra, V, Vyas, M, Prabhakar, P. K, Gupta, M, Kanday, R, Sudhakar, K, Saini, S, Hromić-Jahjefendić, A, Aljabali, A. A. A, El-Tanani, M, Serrano-Aroca, Ñ, Bakshi, H., Tambuwala, M. M.,

- Application of nanotechnology to herbal antioxidants as improved phytomedicine: An expanding horizon. *Biomed. Pharmacother*, 153:113413, (2022).
- [15] Ning, J, Zhang, G, Balash, M, Li, H, Zhu, L., Current nano-strategies to target tumor microenvironment to improve antitumor efficiency. *OpenNano*, 7:100042, (2022).
- [16] Parmentier, M, Gabriel, C. M, Guo, P, Isley, N. A, Zhou, J., Gallou, F., Switching from organic solvents to water at an industrial scale. *Curr. Opin. Green Sustain. Chem*, 7:13-17, (2017).
- [17] Raut, H, Jadhav, C, Shetty, K, Laxane, N, Nijhawan, H. P, Rao, G. K, Yadav, K. S., Sorafenib tosylate novel drug delivery systems: Implications of nanotechnology in both approved and unapproved indications. *OpenNano*, 8:100103, (2022).
- [18] Sharma, P, Kaushal, A., Green nanoparticle formation toward wound healing, and its application in drug delivery approaches. *Eur. J. Med. Chem*, 6:100088, (2022).
- [19] Talebi, M, Talebi, M, Farkhondeh, T, Kopustinskiene, D. M, Simal-Gandara, J, Bernatoniene, J, Samarghandian, S., An updated review on the versatile role of chrysin in neurological diseases: Chemistry, pharmacology, and drug delivery approaches. *Biomed. Pharmacother*, 141:111906, (2021).
- [20] Thipe, V. C, Karikachery, A. R, Cakilkaya, P, Farooq, U, Genedy, H. H, Kaeokhamloed, N, Katti, K. V., Green nanotechnology—an innovative pathway towards biocompatible and medically relevant gold nanoparticles. *J Drug Deliv Sci Technol*, 103256, (2022).
- [21] Xu, X, Liu, C, Wang, Y, Koivisto, O, Zhou, J, Shu, Y, Zhang, H., Nanotechnology-based delivery of CRISPR/Cas9 for cancer treatment. *Adv. Drug Deliv. Rev*, 176:113891, (2021).