

Original Article: Investigation of Green Chemistry Approaches in the Synthesis of Pharmaceuticals

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ABSTRACT

During the last two decades, research on nanoparticles and their application in various fields has been developed. Nanoparticles have exceptional electronic, catalytic, optical, magnetic, and other physical and chemical properties that are completely different from the mass of matter. Unfortunately, many organic solvents used for the synthesis of metal nanoparticles, such as thiophenol, mercaptoacetate, etc., are toxic enough to lead to environmental pollution in the synthesis of nanoparticles on a large scale. Although gold nanoparticles are considered biocompatible, using a chemical method to produce them can lead to the absorption of chemical substances on the nanoparticle and cause side effects in medical applications. The synthesis of nanoparticles using microorganisms or plants can potentially be useful for making compatible bio-nanoparticles in order to solve this important defect. The use of plant extracts for the synthesis of nanoparticles makes the synthesis process easier and its progress faster. In fact, with the extracellular synthesis of nanoparticles, there is no need to cultivate and maintain cells for the synthesis of nanoparticles. The use of plant extracts in the synthesis of metal nanoparticles, especially gold, is very promising, and so far, the synthesis of nanoparticles has been done using different plants such as cinnamon, eucalyptus black tea, and sweet root.

Introduction

Green chemistry is actually a set of methods that design processes and chemical products that are not harmful to human health and the

environment, or use as little harmful substances as possible [1]. Huge parts of the products that we use daily are obtained through a chemical process and reaction. Green chemistry works alongside environmental

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chemistry and focuses on technological methods to reduce pollution and consumption of non-renewable resources [2].

The objectives of green chemistry are broad and most of these objectives related to the design of various molecules, materials, products and the design of efficient and safe processes. Today, the development of green chemistry has grown significantly in various industries of the world, especially pharmaceutical industries [3]. The strategy of green chemistry for chemists and industry is to use environmentally friendly and renewable primary raw materials. In recent years, ionic liquids have received attention in research centers and chemical industries, because they are part of green chemicals and as solvents, they play an important role in reducing the use of hazardous, toxic and environmentally damaging compounds. They are a suitable substitute for volatile organic solvents in industries. Because volatile organic solvents are the most important source of environmental pollution in chemical and pharmaceutical industries [4].

Synthesis of metal nanoparticles using medicinal plants by green chemistry method

One of the fields of research that has attracted the attention of scientists in various sciences in recent years is nanotechnology, which is related to materials with dimensions of 10 (90) nanometers and many applications in medicine, agriculture and the industry know that in the meantime, metal nanoparticles are more welcome for the treatment of infectious and cancer diseases due to their anti-bacterial and anti-tumor properties [5].

The use of medicinal plants for the synthesis of nanoparticles is an alternative path to the conventional physical and chemical methods, and the biological method, or green synthesis, has attracted the attention of many researchers

due to its simplicity, cheapness, compatibility with the environment [6], and antimicrobial activity. In green synthesis, biomolecules in plant extracts used to reduce metal ions to nanoparticles in a one-step reaction.

Development of green chemistry in the synthesis of amid alkyl naphtha anti-*Helicobacter pylori* biological compounds

The preparation of medicine in the treatment of *Helicobacter pylori* (*H. pylori*) is known as the most important cause of gastritis, gastric and duodenal ulcers, which increases the probability of contracting the above diseases by applying changes in the physiology of the stomach. Various compounds against *Helicobacter pylori* synthesized and evaluated, among which nitro furans have shown good effects [7].

Comparative study of acetaminophen drug synthesis methods

Acetaminophen, which is marketed under the brand name of Tylenol (Tylenol or based on the combination with other medicinal substances such as caffeine and ibuprofen under the name of Ashine), in addition to its pain and fever relief properties, as an active ingredient in allergy, cough, cold, Influenza and insomnia are also used [8].

Acetaminophen is produced in different medicinal forms (drops, suppositories, syrups, tablets) and due to its importance as a pain and fever reliever, it has been produced in different ways over the years. and has been used, but in recent years, with the introduction of the green chemistry category [9], it has caused drug manufacturers to bring new methods in the manufacture of drugs, in 2012, with different catalysts and in solvent-free conditions and produce amides during the Beckmann Rearrangement process, and acetaminophen is also a part of this group of drugs. The effect of

acetaminophen starts about 12 minutes after taking it orally [10].

The spinal cord reduces the production of this substance. Excessive consumption causes liver damage, but for this purpose and in 2014, the American Food and Drug Administration (FDA) announced to all doctors: in order to prevent liver damage from prescribing Avoid

acetaminophen pain reliever in an amount greater than 325 mg. In this regard, statistics have been announced that more than half of liver damage and failure in the United States is due to excessive use of acetaminophen along with drugs and drinking alcohol (Figure 1).

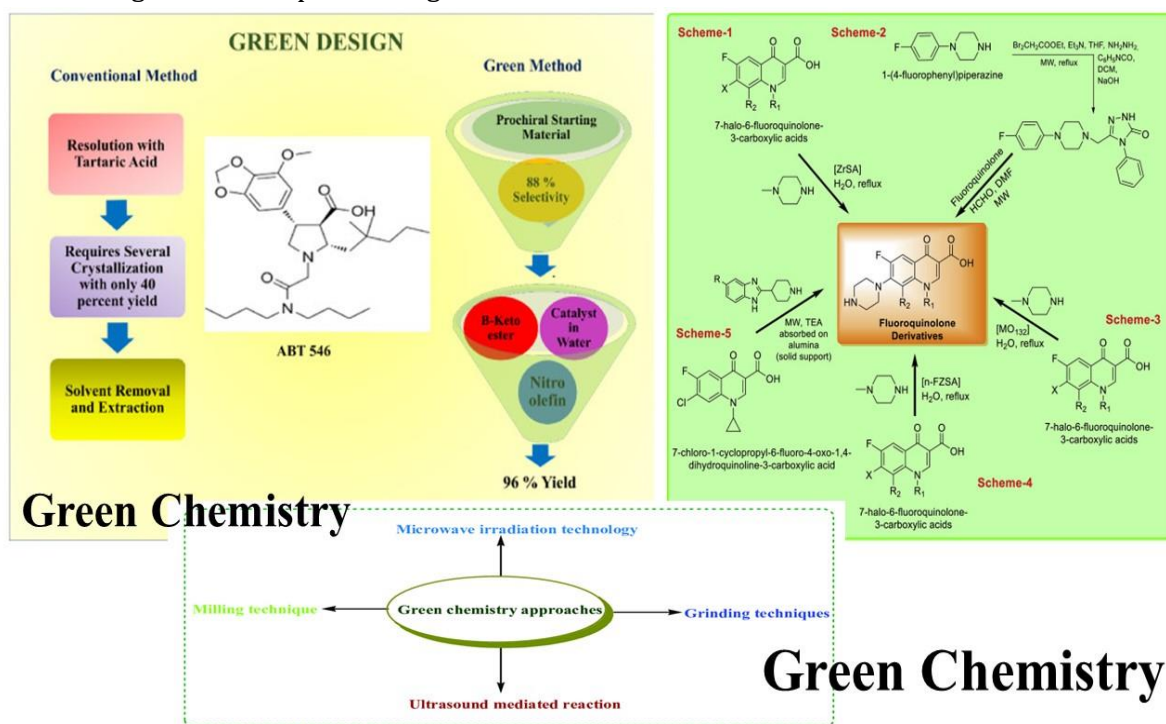


Figure 1. Investigation of Green Chemistry Approaches in the Synthesis of Pharmaceuticals

1- Synthesis by using 4-Aminophenol: In a two-mouthed flask, 50 mL, para-aminophenol (0.05mmol) (0.0 g and double distilled water 38mmol), (15 mL) was poured and then added to the above mixture. Acetic anhydride (63mmol), (6 mL) was slowly added. This experiment was performed several times with different amounts and temperatures, and the progress of the reaction was also confirmed by TLC test [11]. The sediment was washed and recrystallized with double distilled water under vacuum conditions, and then the product was weighed and efficiency was determined.

2- Synthesis using 4-hydroxyacetophenone and oxime formation: In this method, Beckman rearrangement is used to convert oxime into paracetamol. In a flask, 50 mL, 4-hydroxyacetophenone (36mmol), (5 g, hydroxylamine hydrochloride 42mmol), (3g and sodium acetate 45mmol), (75 g) was poured. This experiment was performed several times with different amounts Distilled water, ethanol solvent at different time and temperature were carried out under reverse distillation [12].

The progress of the reaction was also confirmed by performing a TLC test (1:1 ratio of ethyl acetate and -n hexane in the solvent

tank and ethanol + starting material in the control tank). It was formed in a rotary evaporator and dried after washing with 50% ethanol, the efficiency was measured, then it was confirmed by the IR spectrum and the melting point, which increased the efficiency in the fourth step according to the optimal conditions [13].

Green synthesis of gold nanoparticles by thyme medicinal plant

Today, the biosynthesis of gold nanoparticles has received attention. Plant extracts are environmentally friendly and are suitable for the synthesis of nanoparticles due to cost reduction and non-use of toxic substances. Aqueous extract was prepared from the leaves of Shiraz thyme medicinal plant. This extract was mixed with HAuCl₄ solution at different concentrations [14].

The synthesis of nanoparticles was investigated by changing the color of HAuCl₄ solution. Nanoparticle formation was studied using UV-Vis spectroscopy and the shape and size of nanoparticles were investigated with transmission electron microscopy. X-ray energy emission analysis was performed to confirm the presence of gold element in the samples. The color of HAuCl₄ solution changed from yellow to ruby red in combination with Shiraz thyme plant extract.

This color change indicated the synthesis of gold nanoparticles. UV-Vis spectroscopy showed that the absorption peak is around 540 nm. Transmission electron microscope images showed that nanoparticles are spherical, irregular and pentahedral. Also, the sizes of different nanoparticles were determined between 1-50 nm. X-ray energy emission analysis shows the absorption peak at the limit of 2.3 kW due to the presence of gold nanoparticles [15].

The results show that environmentally friendly gold nanoparticles can be produced by Shiraz

thyme extract without using inappropriate and dangerous chemicals.

Dextrose and antimicrobial properties

In the construction of benign chemical methods for chemical products that reduce or eliminate the use and production of hazardous substances, the introduction of green chemistry has been emphasized in recent research techniques. In recent years, nanotechnology has successfully used the principles of green chemistry in the synthesis and various applications of nanomaterials [16]. In the green synthetic strategy for nanoscale materials, the use of non-toxic chemicals and environmentally friendly solvents has attracted considerable attention due to their advantage in reducing environmental hazards. Among the various metal nanoparticles, silver nanoparticles (Ag-NP) have attracted the attention of many researchers and companies for some time because of their extraordinary plasmatic activity, a wide range of antibacterial activities, chemical stability, good thermal and electrical conductivity. , it has been included in various applications [17].

Although the antibacterial activity of Ag-NPs has led to their wide application in various fields, especially biomedical research and incorporation into many products by various companies, their possible risks to health and the environment have caused concern. Another important challenge is to increase antibacterial properties while maintaining their biocompatibility. A scientific approach for this is the development of new nanomaterials of heterogeneous structure with new properties using non-toxic reagents through environmentally synthetic routes [18].

Green total synthesis from dextrose

We report here the green synthesis of highly dispersed, water-soluble, stable, and smaller-sized dextrose-reduced gelatin-coated silver

nanoparticles (Ag-NPs) via a completely green and environmentally friendly method. The synthesis includes the use of silver nitrate, gelatin, dextrose and water as silver material, stabilizing agent, reducing agent and solvent, respectively. By changing the reaction time, the time evolution of growth, optical properties, antimicrobial properties and Ag-NP assay were investigated as synthesis [19].

The nanoparticles were characterized using UV absorption spectroscopy, Fourier transform infrared spectroscopy (FT-IR), X-ray diffraction (XRD), transmission electron microscopy (TEM), and high-resolution transmission electron microscopy (HR-TEM). The maximum absorption of the as-synthesized material at different reaction times showed the peak characteristic of silver surface plasmon resonance (SPR) [20].

Synthesized Ag-NPs show better antibacterial effect than antibiotics. Ciprofloxacin and impanel against *Pseudomonas aeruginosa* with a minimum inhibitory concentration (MIC) of 6 µg/mL and better efficacy than impanel against *Escherichia coli* with an MIC of 10 µg/mL. The minimum antibacterial concentration (MBC) of synthetic Ag-NPs is 12.5 µg/ml [21].

The sensitivity of dextrose decreased the Ag-NPs coated with gelatin compared to hydrogen peroxide, which shows that the sensor has a very good sensitivity and a linear response in a wide concentration range of 10⁻¹¹-10⁻⁶ M H₂O₂. Raman spectroscopy analysis showed an increase in D/G ratio of Ag-MWCNTs hybrid nanocomposites compared to functional MWCNTs (F-MWCNTs) attributed to the presence of Ag-NPs on the surface of F-MWCNTs. Ag-MWCNTs nanocomposites as synthesized showed strong antibacterial effect against *Escherichia coli* compared to Ag-NPs and MWCNTs [22].

The catalytic potential of Ag-MWCNTs composite nanocomposite was investigated for

the first time by studying the reduction of 4-nitrophenol to 4-aminophenol in the presence of sodium borohydride at 299 K at different reaction times [23].

Medicinal plants and green synthesis of metal nanoparticles

The process of producing nanoparticles includes preparation of raw materials, synthesis of nanoparticles on a commercial scale and their use in many fields of medicine, health, agriculture, pharmacy, chemistry, etc. The economic and green production of metal nanoparticles with sizes less than 20 nm by medicinal plants under the influence of effective and optimized environmental factors is one of the main goals of the field of Nano biotechnology [24].

Different organs of medicinal plants can be used to produce nanoparticles. Various environmental factors such as pH, temperature, concentration of plant extracts, sample treatment time are among the factors affecting the economic and sustainable production of metal nanoparticles. In order to investigate different environmental treatments and investigate the mutual effects of multiple factors, a large number of conditions should be investigated.

Today, in order to reduce the number of investigated cases, the Taguchi method is used for the appropriate and effective selection of different cases. After choosing the optimal factors for the production of nanoparticles, to check the quantity and quality of the nanoparticles produced by different methods of Fourier transform infrared spectrometer analysis, including the results of color change and visible spectroscopy, ultraviolet, (FTIR), X-ray diffraction (XRD), zeta potential analysis, transmission electron microscope (TEM) and some other methods are used [25].

Nano is the science of studying materials and manipulating them on the scale of atoms,

molecules and macromolecules, in such a way that their characteristics are compared to the state in which the materials are in the bulk mode is changing considerably.

Hence, the design, characterization, production and application of materials, tools and systems by controlling the shape and size at the nanometer scale are converging in recent years. Nanotechnology and biology have created a new field of nanotechnology, the science of using microorganisms such as actinomycetes, bacteria, viruses, and also plants in a number of biochemical and biophysical processes [26].

The introduction and use of nanoscale materials has become a focus in advanced biotechnology. Synthesis of nanometer scale particles through microorganisms as well as plants is the priority of the field of Nano biotechnology.

Nanoparticles are nanomaterials whose size in all three dimensions is similar and on the Nano scale. The small size and large surface-to-volume ratio of nanoparticles have led to significant changes in their properties. Nanoparticles are used in catalytic applications, chemical sensors, electronic components, diagnostic imaging, medicine, manufacturing and pharmaceutical protocols due to their electrical, optical, physical and chemical properties.

Metal nanoparticles of gold, silver, platinum and palladium are widely used in medicine, pharmaceutical and cosmetic industries. In general, the synthesis methods of nanoparticles are known as physical, chemical and biological methods. In physical methods with top-down strategy by mechanical pressure, high energy radiation, scratching by thermal or electric energy, melting and evaporation or condensation, nanoparticles are produced, which is a useful method due to the production of nanoparticles with uniform distribution [27].

The absence of solvent contamination, but the waste produced during the production process has turned this method into an expensive method. Chemical methods with a bottom-up strategy, such as micro emulsion technique, hydrothermal synthesis, etc., are not suitable due to the use of chemical solvents that are harmful to the environment [28].

The synthesis of nanoparticles through microorganisms such as actinomycetes, bacteria, fungi, viruses, algae, and also plants as biological factories is a clean, non-toxic and environmentally friendly method with specific physicochemical characteristics and with the ability to produce compared to microorganisms. Plants are different in size, shape and composition due to the lack of need. Special, complex and multi-stage processes such as purification, preparation and maintenance of culture medium are more efficient. Therefore, the synthesis of nanoparticles by plants is faster, cheaper and on a larger scale than microorganisms. The significant demand for the production of green nanoparticles has initiated a comprehensive study that shows that the use of plant extracts is the most effective way to produce environmentally friendly nanoparticles. Various plant organs, gum and secretions are used to prepare plant extract in the process of producing metal nanoparticles and metal oxide.

The stages of formation of nanoparticles include the formation of nuclei by reducing metal ions, the accumulation of atoms and the growth of nuclei after combining smaller particles and changing their shape and size under the applied conditions, and then the stability of nanoparticles with the help of plant compounds. Medicinal plants contain alkaloid active compounds, phenolic acid, polyphenol, proteins, terpenoids, flavonoids, terpenes and aromatic rings and sugar, which are responsible for the reduction of metal ions,

coating and stability of synthesized nanoparticles [29].

Hydroxyl, carbonyl, amine, and methoxides are the main functional groups responsible for reacting with precursors found in terpenoids, flavonoids, phenols, alkaloids, proteins, and carbohydrates.

The difference in the type and concentration of active compounds in medicinal plant extracts is the basis of the change in the size and shape of synthesized nanoparticles. Environmental factors such as pH, temperature, concentration and duration of treatment are other important and influencing factors on production amount, size and shape of produced nanoparticles. In this regard, the Taguchi test design approach with maximum accuracy and minimum number of investigated cases is very useful for determining the composition of environmental factors [30].

The final step in the process of producing nanoparticles is to ensure the production of nanoparticles, to determine the size and amount of produced nanoparticles.

To determine the stability and quality of nanoparticles, which is determined by various methods, including the results of Fourier transform infrared spectrometer (FTIR) analysis, X-ray diffraction (XRD), color and visible spectroscopy, ultraviolet and some other methods are done.

Optimization of green synthesis process of iron nanoparticles using fenugreek seed extract

Green synthesis of nanoparticles using plants has important advantages over other biological systems. Natural compounds in plant extracts can convert metal ions into nanoparticles in a one-step process. Fenugreek seeds with different compounds and antioxidant activity are suitable for this process. Fenugreek seed extract was extracted with distilled water solvent at ambient temperature and this

aqueous extract was used for the synthesis of iron nanoparticles [31].

Response surface method for optimizing the production of nanoparticles by considering three independent variables including the ratio of extract to metal ion (5.1 to 5.6), reaction time (30 to 90 minutes) and temperature (35 to 65°C). was used Mixing fenugreek seed extract and iron salt solution with a volume ratio of 1.5 at a temperature of 5.36 degrees Celsius for 90 minutes led to the optimization of the production of iron nanoparticles with the narrowest distribution. In optimal conditions, the size of nanoparticles was in the range of 20 to 40 nm. Iron nanoparticles were successfully synthesized by fenugreek seed extract.

Green chemistry and Nano catalyst design based on urea for use in chemical and pharmaceutical industry

The researchers of Bou Ali Sinai University of Hamedan have synthesized a Nano catalyst that can be used in catalytic acid chemical processes and increase the speed and efficiency of the process to an acceptable level. The designed Nano catalyst is based on urea and its manufacturing method is without the need for chemical solvents and according to the principles of green chemistry [32].

This Nano catalyst has been produced and evaluated on a laboratory scale. Catalysts are needed to carry out chemical reactions in industry and synthesis of pharmaceutical and biological compounds in order to reduce energy consumption.

Nano catalysts are usually a group of atoms, usually metal, metal oxides or organic compounds with changeable particle size between 1 and 50 nm, which can be used in various fields such as petroleum, chemistry, food processing, nuclear energy and environmental improvement.

These Nano catalysts represent a new frontier between homogeneous and heterogeneous

catalysts and are often referred to as quasi-homogeneous systems or soluble heterogeneous systems. According to Dr. Mahmoud Zarei, a postdoctoral researcher in organic chemistry at Boali Sina University in Hamedan, in this project, an acid Nano catalyst based on urea has been designed and synthesized, and its efficiency in the synthesis of heterocyclic compounds with biological properties has been investigated. Regarding the important features of this Nano catalyst, he said: the ability to recover and reuse, to perform the reaction without the need for toxic solvents and also without the use of auxiliary catalysts is one of the most important features of the synthesized catalyst [33].

Another noteworthy point in this project is the observance of the principles of green chemistry in the synthesis of this Nano catalyst. According to this researcher, according to the characteristics of the synthesized catalyst, it can be expected that if it is used in industrial or pharmaceutical processes, an increase in efficiency and a decrease in energy consumption can be achieved. On the other hand, the use of low-risk chemicals in the synthesis of materials and the reduction of pollution caused by chemicals will also lead to a healthy environment. Also, due to the selectivity of the desired catalyst, the formation of unwanted side products is prevented.

Green synthesis of gold nanoparticles using leaf and stem extracts of Anarijeh plant and investigating its toxicity on human breast cancer cells

Cancer is a destructive disease whose annual death rate is increasing and its treatment is one of the biggest challenges for mankind. Among the types of cancer, breast cancer is the most common cancer among women and the second leading cause of cancer-related deaths in women.

To date, the most common cancer treatments are limited to chemotherapy, radiation therapy, and surgery, which despite the many advances they have made, cancer treatment still has major disadvantages. The most important disadvantages that we face in current cancer treatments include: insufficient concentration of drugs to enter the tumor site, general and non-specific distribution of anti-tumor agents in the body, damage to healthy tissues, general toxicity and long-term side effects [34].

In total, all these factors limit the clinical application of the mentioned methods. Therefore, there is a need for more efficient and suitable treatment methods for the treatment of cancer in humans. The key issue in cancer treatment is to achieve the appropriate concentration of the therapeutic agent in tumor sites with the aim of destroying cancer cells and at the same time minimizing damage to normal cells. In this regard, cancer nanotechnology has created a new revolution for cancer treatment. Nanotechnology involves the manipulation and creation of nanoscale materials to produce products with new properties [35].

Recent developments show that nanotechnology will have a significant impact on the prevention, diagnosis and treatment of cancer. The main output of nanotechnology is the development of new materials on the nanometer scale, including nanoparticles. Nanoparticles are particles with sizes less than microns and usually between 10 and 100 nanometers.

The performance of nanoparticles depends both on their measurable values such as mass, volume and electric charge and on their internal characteristics such as reactivity. Among the main properties of nanoparticles, we can point out that they have great diversity, unique surface characteristics, very high reactivity, high solubility, low toxicity,

bioavailability, and the use of faster and cheaper methods for their production [36].

The use of nanoparticles provides a convincing solution for the gradual removal of cancer cells without serious damage to normal cells. Nanoparticles can be metallic or non-metallic particles. Metal nanoparticles have different geometric shapes, but they are usually spherical and form colloidal systems in the ionic state.

Among the various nanoparticles, gold metal nanoparticles (GNPs) are considered to be the most popular due to their unique properties such as strong photoelectric absorption coefficient, ease of synthesis, high surface-to-mass ratio, high atomic number ($Z=79$), high activity of gold nanoparticles and Their high affinity to bind to biomolecules and macromolecules in particular are used in many fields, including cancer treatment [37].

There are generally different physical and chemical methods for the production of nanoparticles and they are categorized into two main types: bottom-up methods and top-down methods. The main problem of the top-down method is the change in the surface chemistry and the physical and chemical properties of nanoparticles, and the nanoparticles are not synthesized with proper quality, and in general, most of the synthesis methods of nanoparticles are complex and time-consuming.

In addition, the synthesis of gold nanoparticles by chemical methods may cause adverse biological effects due to the adsorption of chemical species on the surface of the nanoparticles and ultimately be harmful to health, but the synthesis of nanoparticles using microorganisms or plants that are in the category the bottom-up synthesis of nanoparticles can potentially solve these problems.

In recent years, plants, algae, fungi, and bacteria have been used to produce metal nanoparticles, which is called green synthesis and is cheaper, simpler, and non-toxic than other methods [38].

Among the various living organisms that are studied, plants are of particular importance in the synthesis of metal nanoparticles due to the advantage they have over other biological processes, and that advantage is the elimination of the complex step of cell culture maintenance.

In addition, the synthesis of nanoparticles using plants has become very important due to its simplicity, non-pathogenicity and compatibility with the environment. In addition, the presence of plant compounds in nanoparticles prevents the harmful effects of environmental factors such as pH fluctuation, enzymatic attack and possible biochemical degradation. On the other hand, evidence shows that various structural compounds obtained from plants are able to prevent and treat cancer [12].

The therapeutic activity of these agents belongs to different structural classes such as alkaloids, terpenoids, organosulfur compounds and polyphenols. Folic acids and flavonoids are the most common natural polyphenols. Flavonoids make up about two-thirds of polyphenolic compounds.

A wide range of anti-tumor properties have been attributed to these plant-derived agents and include antioxidant, anti-proliferative, anti-allergic, anti-metastatic and anti-inflammatory properties. On the other hand, most chemotherapy drugs that are currently used in clinical settings are natural products or semi-synthetic derivatives of these compounds found in plants, but despite their important health benefits, the effectiveness of natural products is low due to their low solubility in water, low absorption, low availability, and short-term persistence in the biological system

are weakened, and to eliminate these weaknesses, Nano formulations are used as drug carriers for treatment [19].

As a result, the integration of herbal medicine and nanotechnology in the goals of clinical treatment can bring a better drug response and clinical outcome for patients. Until now, the synthesis of gold nanoparticles has been carried out using many plants inside and outside of Iran. including the synthesis of gold nanoparticles using the extracts of plants Magnolia Kobus, Hibiscus, Punica granatum, coriander, Pelargoniumgraveolens, Nasturtium nasturtium and Sambucus ebulus fruit, some of which have been investigated in terms of the anti-cancer properties of the synthesized gold nanoparticles, such as the synthesis of gold nanoparticles Using extracts of Couroupita guianensis, Curcumae Kwangsiensis and beets.

Green synthesis of silica nanoparticles from horsetail plant

Silica nanoparticles are mostly produced from silicate precursors such as silicon lakesides and using different methods such as chemical processes including vapor phase and sol-gel reactions. These processes consume a lot of energy due to the need for high temperature and pressure [14].

They are also not environmentally friendly. Therefore, efforts are being made to find sources and new methods of producing amorphous silica nanoparticles with high quality and at lower costs with the help of environmentally friendly processes. Some plants, algae and animals can collect silica in their tissues mainly in the form of nanostructures. This type of silica is called biogenic silica.

Plants and animals obtain silica through the absorption of orthosilicic acid in water or soil with a concentration range of less than 0.1-0.6mM and at a pH less than 9. Despite the fact that silica is not necessary for the normal

growth of all plants, but it seems to be useful for some secondary effects such as the structural and functional role as a mineral barrier to prevent the attack of pathogens. On the other hand, biomass has the ability to accumulate a large amount of silica, and therefore plant biomass can be used to produce silica nanoparticles. There are several reports that refer to the production of silica nanoparticles from biomass [39].

The main sources of biomass used to date for the production of silica nanoparticles are: different parts of the stem, skin and fibers of plants such as banana, hemp, pineapple leaves, sisal and agricultural and industrial waste such as rice bran, sugarcane pulp and coffee husk. Eco stoma species are known as plants with high accumulation of silica. Compared to many other plants, these plants store silica in the form of hydrated amorphous silica.

Due to the presence of silica protrusions on the stems of these plants, the species of Ecostum were used in the past to polish metal plates and tin products. Silica can be observed in all parts of the Arons ecoestome. Holzötter et al showed that most of the silica is deposited as a thin layer on the inner surface of the plant cell wall, where the thickness of the surface layer varies from a few nanometers to about 7 μm . Silica layers are composed of dense particles with a size of 25-40 nm [17].

These layers can be used to produce silica nanoparticles. It is possible to obtain silica in about 25% of the dry weight of the plant in these plant species, and its amount depends on the weather conditions and the soil used for plant growth. Since the horsetail plant, in addition to being a suitable material for extracting silica nanoparticles, creates a hydro alcoholic extract with several analgesic, anti-inflammatory, hepatic protection, antifungal and antimetotoxic properties, it has also received attention from this point of view. Also, more than 70% of horsetail biomass contains

carbohydrates that can be converted into useful substances such as liquid fuels, organic acids, biopolymers and other green chemicals during the fermentation process.

Discussion

At the end of the 19th century, medicinal chemistry underwent a tremendous transformation with the discovery of "Paul Ehrlich", who is called the father of new chemotherapy, in connection with the fact that chemical compounds show selective toxicity against specific infectious agents [12].

At the same time, "Emil Fischer" presented the theory of lock and key, which was a logical change for the mechanism of action of drugs. Subsequent research by Ehrlich and his colleagues led to the discovery of a large number of new chemotherapeutic agents, among which antibiotics and sulfamides were the most prominent [22].

In addition, medicinal chemistry includes the isolation, diagnosis, and synthesis of compounds that can be used in medical science to prevent, cure, and treat diseases, and in this way, medicinal chemistry provides the chemical principles of substances in the field of drug therapy [31].

Researchers from Maragheh university and Payam Noor university in Tehran succeeded in building a smart drug delivery system for cancer treatment. This system is made of non-toxic raw materials compatible with the body. Also, the preparation steps of the drug delivery system are based on green chemistry and do not lead to the production of hazardous waste. This research has been done on a laboratory scale [38].

One of the most popular branches in nanoscience is the design of intelligent drug delivery systems, which has found a special place in the discussion of treating diseases, including cancer. One of the most important features of these systems is the guidance,

delivery and release of drugs at the target site and cancerous tissue, thus reducing the side effects caused by the use of drugs [39].

In this research work, an attempt has been made to design and synthesize a smart drug delivery system using non-toxic polysaccharides. This smart drug delivery system is designed using non-toxic polysaccharides, the anti-cancer drug sunitinib is loaded in magnetic chitosan nanoparticles and coated with carrageenan.

Sunitinib is used in the treatment of advanced or progressive cancers of the stomach, intestines, gastrointestinal tract, pancreas, kidneys, esophageal tumors, and breast cancer. Considering the acidic pH of the environment of cancer cells and the reduction of drug release in non-cancerous environments, the most important point in the design of drug delivery systems for anticancer drugs is their ability to release drugs in acidic environments. Therefore, according to the chemical structure of sunitinib, it has been tried to use magnetic chitosan as a carrier of sunitinib, so that this feature can be easily achieved. Examining the effect of pH on drug release showed that as the pH decreases, the percentage of drug release increases [19].

This drug delivery system can be used for many cancer drugs. On the other hand, the most important innovation of this research is the design of drug delivery system in a completely green way and a completely green system. In fact, in the construction of this system, non-toxic and compatible raw materials have been used, while the steps of preparing the drug delivery system do not lead to the production of hazardous waste.

Also, the cost of this system due to the cheapness of the raw materials can be the strength of the work done, but unlike the complex systems used, the most important advantage of this system is the easy and in-situ preparation method of magnetic nanoparticles

in the presence of chitosan, which leads to the production of nanoparticles with sizes less than 50 nm [14].

Also, for high loading of sunitinib in chitosan nanoparticles, the resulting nanoparticles were coated with carrageenan. It should be noted that the preparation of chitosan-carrageenan complex nanoparticles is not easily achieved. However, in this system, when the nanoparticles were prepared in the presence of chitosan, they were easily covered by carrageenan and complexed. The system designed in the pharmaceutical and medical industries can be evaluated and used to load anticancer drugs [29].

Also, the removal of colored pollutants and heavy metal cations from water environments is one of the other applications of the designed system. Of course, this research is currently carried out on a laboratory scale, but due to the simplicity of the system, no special technology is needed for its mass production, and despite the use of cheap raw materials available in the country, this plan has the potential to be commercialized, but the most important part of the work is the experiments related to the investigation of the drug delivery system in living organisms, the results of which must be evaluated [15].

Green synthesis of nanoparticles applied in medical sciences

The researchers of Mashhad University of Medical Sciences, in cooperation with the researchers of the country's universities, succeeded in producing uniform nanoparticles of zinc oxide (ZnO) with the help of a simple and environmentally friendly method. In the production of zinc oxide nanoparticles, it is very important to use cost-effective and at the same time simple methods that are able to produce nanoparticles with uniform particle size [32].

On the other hand, considering that one of the problems that threatens the environment and human health today is the use of dangerous substances and reagents in the preparation of various materials, including nanomaterials, hence the presentation of synthetic methods based on the principles of green chemistry on a laboratory scale [38].

And industry is an inevitable necessity for related scientific and manufacturing communities. In this research project, the researchers tried to observe the principles of green chemistry and expand it in the synthesis of nanoparticles as a new approach to synthesize, characterize and investigate the cytotoxicity of zinc oxide nanoparticles.

Also, marking these nanoparticles with radioactive materials such as ^{99m}Tc and using them in research-applied studies in the field of nuclear medicine such as identifying and treating cancer cells has been another goal of this research work. Zinc oxide nanoparticles, which are native materials of the country and available, are used in various fields such as medicine in terms of having photocatalytic and antimicrobial properties [40].

These nanoparticles can be used in wound sites due to their antibacterial and antimicrobial properties, as well as in the field of drug carriers in the discussion of targeted drug delivery and especially in the preparation of cosmetics and sun creams. Since in this research, zinc oxide nanoparticles of different sizes were prepared by sol-gel method and following the twelve principles of green chemistry, it is predicted that this method can be used for many other oxide nanoparticles as well. Therefore, by carrying out such projects, it is somehow possible to take advantage of the richness of the diversity of medicinal and indigenous plants of Iran in the preparation of nanomaterials and in this way bring them forward in the international arena.

Green synthesis of TiO₂ nanoparticles from papaya peel/proof of antifungal properties of these nanoparticles

Recently, an article has been published in the journal Scientific Reports that focuses on the biosynthesis of TiO₂ nanoparticles using papaya peel extract.

The researchers also conducted an antifungal effect study using different fungi to test the antioxidant activity of the TiO₂ nanoparticles produced in this project. TiO₂ nanoparticles produced using biological organisms such as plants, fungi and bacteria are more stable and environmentally safer than chemically synthesized TiO₂ nanoparticles. Therefore, they can be used for many biomedical applications.

Nanomaterials are widely used in medicine, energy production, agriculture and communication due to their significant physical, chemical and biological properties. Metal oxide nanomaterials, such as TiO₂ nanoparticles, have recently attracted research attention due to their interesting thermal, electronic, magnetic, and photonic properties. TiO₂ is an odorless and white powder that is hydrophobic under normal conditions. Nanoparticles of this material are very stable and can act as matting. TiO₂ nanoparticles have excellent antimicrobial and antifungal effects. Because they can produce free radical oxides with strong antioxidant activity and wide reactivity against many pathogens. Many studies have confirmed the effect of TiO₂ nanoparticles on the germination and growth of plants [9].

Titanium as a valuable element helps plant growth. It increases the productivity of the plant by 10 to 20% and increases the production of free radicals in the propagated seeds. The most common methods for producing TiO₂ nanoparticles are chemical vapor deposition (CVD), electrodeposition, hydrothermal deposition, and chemical

coagulation. However, these methods are time-consuming and expensive, and require high temperature, pressure, and potentially hazardous materials, which limit their pharmaceutical applications [30].

As a result, green synthesis is a popular method for producing TiO₂ nanoparticles. Green synthesis is a natural, environmentally friendly and cost-effective approach to produce large quantities of nanoparticles.

Among different biological organisms, plants or their extracts are of great importance in the production of nanoparticles due to their abundance, large-scale application, and minimal waste production. Plant-based TiO₂ nanoparticles can be valuable in various industries including pharmaceutical, food, catalytic, and cosmetic. Papaya *Carica* belongs to the Salicaceae plant family and is used in various therapeutic methods, especially in humid and subtropical regions of the world. Papaya peel extract contains biomolecules that can convert metal ions into nanoparticles in a one-step green manufacturing process [11]. This bioactive conversion of metal ions to the base metal is relatively fast, can be performed at ambient temperature and pressure, and can be easily scaled up. The production of nanoparticles with plant extracts is also environmentally friendly and reduces the risk of creating waste. In this study, researchers synthesized TiO₂ nanoparticles using papaya peel extract. The results of the researchers' findings showed that TiO₂ nanoparticles produced using papaya peel extract are hemispherical and monoclinic. Antifungal studies using pathogenic fungi showed that biosynthesized TiO₂ nanoparticles have excellent antifungal properties [41].

Conclusion

Today, due to the widespread use of nanoparticles in various industries, their synthesis has been given attention, but the

existence of environmental hazards due to various chemical and physical processes used in the production of nanoparticles has caused researchers to make great efforts to synthesize nanoparticles through compatible processes with the environment using microscopic organisms and plant extracts. The advantages of the green synthesis method include high production scale, faster speed and lower cost. Gold, silver, and copper nanoparticles are common Nano metals. According to the results obtained from the review of various scientific sources, nanoparticles synthesized by the green method have various applications in disease diagnosis, drug delivery, medical imaging, and elimination of infectious microorganisms, absorption and removal of pollutants in the environment.

In today's world, researchers need to produce environmentally friendly nanoparticles using synthesis methods without using toxic and dangerous chemicals. Environmental pollution such as chemical and physical pollution can be caused by various chemical and physical processes.

Therefore, researchers have made many efforts to synthesize nanomaterials by an environmentally friendly process using enzymes, microscopic organisms, and plant extracts. In recent years, along with the use of genetic engineering and the production of pest-resistant transgenic plants, the synthesis of Nano metals using plant extracts has attracted the attention of researchers due to its low risk to the environment and biological safety. Plant extracts contain reducing agents that reduce metal salts to metal ions when exposed to them. Also, the synthesis of nanoparticles using plant extracts is a simple, cheap and environmentally friendly method. Nanoparticles have attracted the attention of researchers due to their wide application in various sciences.

Therefore, the synthesis methods of nanoparticles are very important. Using

chemical methods to synthesize nanoparticles causes environmental pollution. Researchers are looking for synthetic methods with the least amount of pollution for the environment. The use of plant extracts is one of the methods of green (biological) synthesis to produce nanoparticles. Plants cause less pollution than chemicals, and the use of plant extracts for the synthesis of nanoparticles is a simple, cheap and cost-effective method.

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