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GENUS *FAGONIA* MEDIATED NANOPARTICLES AND THEIR THERAPEUTIC POTENTIAL: A REVIEW

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Abstract

Medicinal plants have remained a major focus for scientists for thousands of years. The main reason for the importance of medicinal plants is the presence of different bioactive compounds such as flavonoids, saponins, terpenoids, alkaloids, cardiac glycosides etc. These bioactive compounds play important role in treating diseases like cardiac glycosides used to treat heart problems etc. In recent years with the development of nanotechnology, medicinal plants are now used to synthesize nanoparticles using different metallic salts. The main advantage of nanoparticles is their small size which helps them to enter the cell. Genus *Fagonia* of the family Zygophyllaceae has high therapeutic potential. In the traditional medicinal system, various diseases like fever, blood purification, and cancer have been treated using different species of the genus *Fagonia*. Many peer-reviewed articles have been published on nanoparticle synthesis from different species of *Fagonia* by using different metallic salts like silver nitrate, zinc oxide, gold, and manganese oxide. These nanoparticles have been checked for biological and pharmacological activities like antibacterial, anti-fungal, anti-diabetic, anticancer, and antileishmanial activity. To our knowledge, the current paper presents a review for the first time of *Fagonia* mediated nanoparticles, their types, properties, and applications in the environmental field.

Key words: Antibacterial, Anticancer, Bioactive compound, Dhamasa, Leishmaniases, Nanoparticles.

Introduction

Nanotechnology deals with synthesizing, examining, and applying nano-range particles of about 1 to 100 nm. The nanosized particles we call nanoparticles (NPs) are eco-friendly and safe to apply. Methods used to synthesize nanoparticles include physical, chemical, and biological methods (Ahmad *et al*., 2019). Chemical and physical methods increase the risk of toxicity in the environment. In contrast, the biological method, also called green synthesis, is significantly attractive because it can potentially reduce the toxicity of NPs (Parveen *et al*., 2016). Different biological sources like plant extract and micro-organisms (bacteria, fungi) secondary metabolites can be used to synthesize NPs. Nanoparticles can be synthesized extracellularly or intracellularly through biological methods.

Medicinal plants are rich in valuable chemicals or metabolites that can treat various diseases in different forms. They may be used raw or processed to synthesize drugs from these chemicals (Gusain *et al*., 2021. Bibi *et al*., 2023). Medicinal plants generally have therapeutic properties or pharmacological effects on the animal or human body. Different types of crude drugs have been derived from different parts of plants (stem, wood, leaves, bark, fruit, seeds, root) (Namdeo, 2018). Furthermore, the chemicals-rich extract of these plants is also used in nanotechnology to synthesize nanoparticles. Nanoparticles can be synthesized using different precursor salts like gold, silver, cobalt, copper, zinc etc. (Gour & Jain, 2019). Silver and gold nanoparticles have been rapidly and efficiently synthesized extracellularly from several plants in different reports. Different species of *Fagonia* are also used to synthesize different types of nanoparticles (Table 1).

Fagonia: *Fagonia* of the family Zygophyllaceae is a medium sized genus of almost 35 species (Table 2). Its local name is dhamasa (Puri & Bhandari, 2014). It contains a small, spiny, erect shrub. The flower of plants of this genus is purplish pink. Common species are *F. indica*, *F. cretica*, *F. arabica*, *F. schweinfurthii*, *F. bruguieri*, and *F. mollis*. The species of *Fagonia* have been reported for their high medicinal value, such as sores, fever, vomiting, dysentery, antiseptic, blood purifier, antioxidant, and analgesic (Puri & Bhandari, 2014). Some species of *Fagonia* are also reported for their effectiveness against cancer like *F. indica* against breast cancer. *Fagonia* species also contain saponins, alkaloids, terpenoids, sterols, flavonoids, proteins, and amino acids (El-Amier & Aisha, 2019) (Table 3).

F. arabica: *Fagonia arabica* is a popular medicinal species of genus Fagonia, belonging to the family Zygophyllaceae. It is a tropical herb found in different geographic locations like deserts, South Asia, Middle East, Central Europe, and North Africa (Kanwal *et al*., 2021). *F. arabica* has been reported to have glycosides, flavonoids, triterpenes, saponins (Satpute *et al*., 2009), and sulfur compounds which are important medicinal constituents. Many different types of pharmacological actions have been reported like anti-inflammatory, anti-allergic, neuroprotective, endocrinological and antimicrobial (Shahid *et al*., 2022). A very important environmentally friendly activity of *F. arabica* has been reported is the use of its extract as a green corrosion inhibitor for Cu (Kanwal *et al*., 2021).

F. cretica: *F. cretica* has been used for different nanoparticle synthesis, like silver and gold, because this plant extract has a very good reducing and stabilizing power that helps synthesise nanoparticles (Zulfiqar *et al*., 2019). *F. cretica* is used for gynecological disorders. It is a small perennial, thorny herb. It is mostly seen in hot and barren places and distributed all over Pakistan and other continents except

Australia. Due to its antipyretic ability, demand is increasing, and it can also be used to prevent smallpox. In traditional medicinal systems, boiled parts of *F. cretica* are used to treat hepatitis (Yousaf *et al*., 2019). The formulations of these plants are also used in the Ayurvedic system, such as “Ardhabilva Kvatha Curna” (ADR), used for the treatment of constipation (Hamid *et al*., 2010).

F. indica: It is a spine-bearing small shrub found in arid and warm parts of the world. It is widely distributed in Asia and Africa (Anil *et al*., 2012). Silver NPs synthesized from the extract of the *F. indica* plant show efficient antibacterial activity (Adil *et al*., 2019). In addition to antibacterial activity, *F. indica* has also been reported to be used for different pharmacological purposes like asthma, toothache, and anti-cancer. Its aerial parts make an aqueous decoction for different skin lesions (Waheed *et al*., 2012). It is used for anti-inflammatory activity and antipyretic effects in folk medicine. It is also used as remediation for early-stage tumors (Rahman & Ansari, 1984). The zinc oxide nanoparticles of *F. indica* extract show a very high range of Total Flavonoid Contents (TFC) and Total Phenolic Contents (TPC) that indicate the high antioxidant activity of the plant extract (Hameed *et al*., 2021).

F. bruguieri: It is a biennial or perennial shrublet native to Saudi Arabia and found in different regions of the world. It is also called Shaoka tree because it yields honey called Shaoka honey which has been reported to have different medicinal important properties (Shawky & Alzmel *et al*., 2020). The Shaoka honey has been used as a remedy for gastrointestinal disorders, hepatitis and healing wounds (Adgaba *et al*., 2017). It is a widely used medicinal plant in Arabs culture. It shows high antimicrobial activity against certain gram-positive and gram-negative bacteria like *Staphylococcus aureus* and *Escherichia coli*. High antibacterial activity is due to different antibacterial peptides (Al-Dhafri & Ching, 2022). The methanolic extract of this plant also showed anti-fungal activity (Saleem *et al*., 2019).

Table 1. List of Fagonia- mediated nanoparticles.

Sr.#	Species	Nanoparticles	Size (nm)	characterization	Reported By
1.	*Fagonia cretica*	Ag NPs	16	UV-vis spectroscopy, TEM	Zulfiqar *et al*., 2019
2.	*F. cretica*	MnO_2 NPs	15.5	UV spectroscopy, XRD, SEM, FTIR	Faisal *et al*., 2022
3.	*F. cretica*	ZnO NPs	65-80	UV-vis spectra, SEM	Kiani *et al*., 2022
4.	*F. cretica*	Ag NPs	16	UV-vis spectra, TEM,	Yousaf *et al*., 2019
5.	*F. Arabica*	AgNPs CuO NPs	50-100 50-100	UV- vis spectra, SEM, XRD, EDX,	Shahid *et al*., 2022
6.	*F. indica*	Au NPs	10	XRD, FTIR, TEM, TGA	Mariam *et al*., 2021
7.	*F. indica*	ZnO_A NPs ZnO_s NPs	23.4 41	UV-vis, FTIR, EDS, SEM, TEM	Hameed *et al*., 2021
8.	*F. indica*	Ag NPs	12.09	UV- vis, XRD, DLS, SEM	Ullah *et al*., 2017
9.	*F. indica*	Ag NPs	22	UV-vis spectroscopy, XRD, FTIR	Khan & Ali, 2020
10.	*F. indica*	Ag NPs	27.2	UV- vis spectra, FTIR, XRD	Adil *et al*., 2019

Table 2. Common species of *Fagonia.*

Fagonia acerosa Boiss	*F. harpago* Emb. & Maire	*F. pachyacantha* Rydb
F. arabica L.	*F. indica* Burm. f.	*F. palmeri* Vasey & Rose
F. bruguieri DC.	*F. laevis* Standl.	*F. paulayana* J. Wagner & Vierh.
F. californica Benth.	*F. lahovarii* Volkens & Schweinf	*F. rangei* Loes. ex Engl.
F. charoides Chiov	*F. latifolia* Delile	*F. scabra* Forssk
F. chilensis Hook. & Arn.	*F. latistipulata* Beier & Thulin	*F. schweinfurthii* Hadidi
F. cretica L.	*F. luntii* Baker	*F. scoparia* Brandegee
F. densa I.M. Johnst.	*F. minutistipula* Engl.	*F. spinosissima* Blatt. & Hallb.
F. densispina Beier & Thulin	*F. mollis* Delile	*F. subinermis* Boiss.
F. glutinosa Delile	*F. mahrana* Beier	*F. villosa* D.M. Porter
F. gypsophila Beier & Thulin	*F. olivieri* DC	*F. zilloides* Humbert
F. hadramautica Beier & Thulin	*F. orientalis* C. Presl	

Table 3. Bioactive compounds and pharmacological actions of *Fagonia* species.

Sr.#	*Species*	Pharmacological actions	Bioactive compound	Reported By
1.	*Fagonia cretica*	Androgenic activity Neuroprotective activity Antimicrobial activity Cytotoxic and antitumor activity	Saponins and flavonoids	Abhirami *et al*., 1996 Rawal *et al*., 2004 Anjum *et al*., 2007 Hussain *et al*., 2007
2.	*F. bruguieri*	Anti-allergic property	Tannins and flavonoids	Puri and Bhandari, 2014
3.	*F. indica*	Analgesic and Antimicrobial activity	Anticancer phenolics and flavonoids	Sharma *et al*., 2009
4.	*F. schweinfurthii*	Anti-inflammatory and wound healing property, skin problems	Alkaloids, flavonoids, tannins	Alqasoumi *et al*., 2011
5.	*F. Arabica*	Antibacterial Activity	Glycosides, saponins, flavonoids	Abobaker, 2017
6.	*F. mollis*	Free radical scavenging activity	Saponins	El-Amier & Aisha, 2019

***F. schweinfurthii*:** Another important species of the genus *Fagonia* is about 25 cm tall plant found in the desert. It is found in West USA, Chile, India, in Southern zone of Balochistan, and Tropical Africa (Alqasoumi *et al*., 2011). The stem of this plant is woody, the lower leaves trifoliate, the terminal leaves are unifoliate, and the flowers are pinkish (Taia *et al*., 2015). It produces flowers for almost a year (Sharma *et al*., 2013). It is commonly used in the Indian system of medicine as a treatment for various diseases like skin problems and fever (Sharma *et al*., 2013). Its anti-fungal lotion was prepared from its aqueous extract, which has a potential anti-fungal activity (Puri *et al*., 2013). It has an efficient anti-inflammatory activity (Rathore *et al*., 2012).

***F. mollis*:** *F. mollis* is a shrub with a woody base and stem is branched. The leaves are with leaflets, and fruits are obovoid (Alghanem, 2018). This species showed significant antimicrobial activity. The aerial parts are rich in secondary metabolites (Alghanem, 2018). Flavonoids and saponins were reported by Al-Wakeel *et al*., (1987) (Table 2).

Nanoparticle synthesis: The general steps to synthesize different types of nanoparticles using plant extract are as follows (Mariam *et al*., 2021) (Fig. 1).

Preparation of *Fagonia* extract: The plant extract can be prepared by adding 2g of *Fagonia* plant powder in 100 ml of distilled water and heating at 100°C on the hot plate for 30 min. and then filtered and stored for further use. The freshly prepared extract is used to reduce and stabilise nanoparticles.

Biosynthesis of *Nanoparticles* (NPs): To synthesize NPs, 100ml plant extract and molar solution (0.01M, 0.1M,1M, 1mM, 2mM, 3mM, 5mM etc.) of salt (silver/ gold/ zinc/ cobalt etc.) were mixed and stirred for 30 minutes. The change of color indicates the formation of NPs. Centrifugation and washing with distilled water can be done to separate the nanoparticles from the solution. The supernatant can be discarded, and pellet (NPs), after drying at room temperature, is crushed and used for characterization.

Characterization of NPs: Characterization of nanoparticles can be done by using different techniques such as UV spectroscopy, X-Ray Diffraction (XRD), Fourier Transform Infrared Spectroscopy (FTIR), Energy Dispersive X-ray (EDX), Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) etc.

Pharmacological actions: Several pharmacological actions of several types of NPs of Genus *Fagonia* have been reported. Major pharmacological actions of different nanoparticles have been listed in (Table 4).

Anti-fungal activity: Health and food are two major concerns for humans, and the main threat to both these concerns is pathogenic fungi which may be plant pathogens or human pathogens. Several types of chemicals have been applied for the remedial effect against fungal pathogens, but these remedies can cause environmental pollution and many health hazards (Akpinar *et al*., 2021). To avoid these bad effects, new advances and better approach has been used, which involves the synthesis of NPs from plant extract, which shows anti-fungal activity for example, MnO_2 NPs from *F. cretica* shows anti-fungal activity (Faisal *et al*., 2022).

Mechanism of action: Nanoparticles have been reported for their antifungal activity and studies have been done to explore the mechanism of action of NPs. According to previous studies, exact mechanism is not still known. The nanoparticles attached to the fungi and penetrate through it. After penetration it attaches to the DNA in the nucleus and stops cell division which leads to the death of fungal cell (Nasrollahi *et al*., 2011).

Anti-leishmanial activity: A major ignoring disease known as leishmaniasis worldwide is caused by a parasite which belongs to the genus *Leishmania* (Das *et al*., 2010). In Pakistan, people in villages are more affected by this disease. As Pakistan is a developing country, the prevailing treatment of this disease of using compounds such as amphotericin B is not cost effective and has side effects and causes toxicity to the normal cells. So, an alternative approach of synthesizing NPs using plant extract is being used (Ullah *et al*., 2017). *F. indica*-mediated zinc oxide nanoparticles have been reported for this activity (Hameed *et al*., 2021).

Mechanism of action: The mechanism of antileishmanial activity is also related to antifungal and antibacterial activity as silver nanoparticles have been reported for their production of ROS which cause death of bacteria due to protein damage. The leishmania parasites are also sensitive to these ROS. Silver nanaoparticles decrease the proliferation of parasites and also lessen their metabolic activity. Nanaoparticles also effect the infection capacity of the parasite (Allahverdiyev *et al*., 2011).

Alpha amylase inhibition activity: Diabetes is one of the major concerns about human health. About two million deaths were caused by diabetes in 2019 reported by WHO 2022. For this reason, the emerging field of nanotechnology is also tried to find a solution to this issue. The nanoparticles check the anti-diabetic activity by performing alpha-amylase and alpha-glucosidase inhibition activity. Alpha amylase and alpha-glucosidase are key enzymes in converting saccharides into glucose; glucose is the main reason for diabetes. Nanoparticles block the activity of these enzymes and inhibit the synthesis of glucose. ZnO nanoparticles show about 48% inhibition activity (Iqbal *et al*., 2019).

Anticancer activity: Various types of cancer cause mortalities all over the world. Breast cancer in all types of cancer causes significant number of women's death (Ullah *et al*., 2020). The reason behind its increasing number is the resistance of breast cancer cells to different chemotherapies. In recent years much work has been done on NPs to work against breast cancer as specifically silver NPs show a significant effect in killing breast cancer cells. This mechanism involves biological sources, so it is more ecofriendly and cost-effective than chemotherapeutic treatment (Ullah *et al*., 2020).

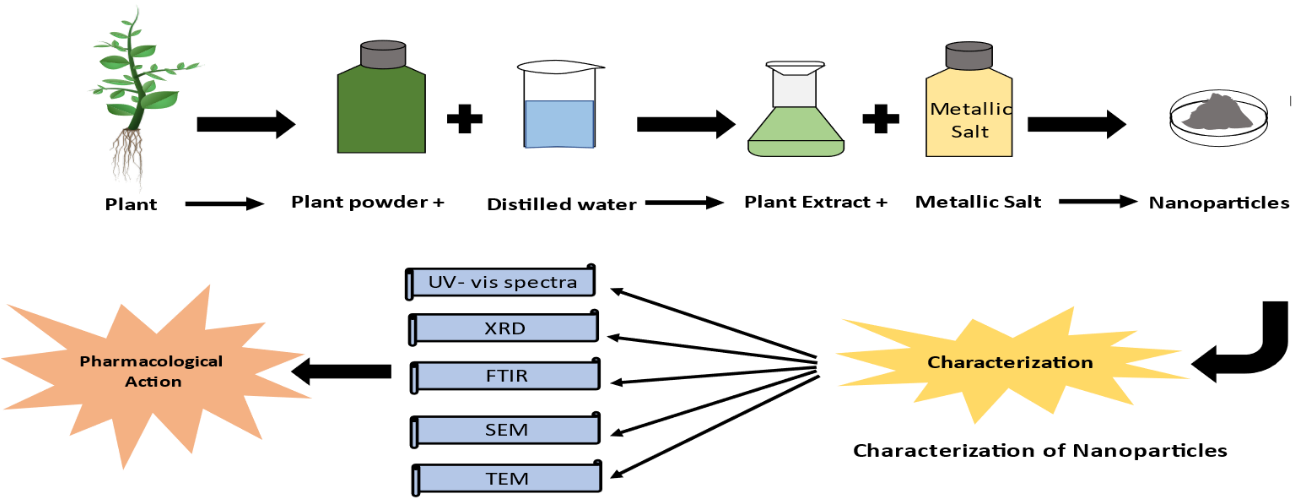

Fig. 1. Diagrammatic View of General Steps to Synthesize Nanoparticles from Plant.

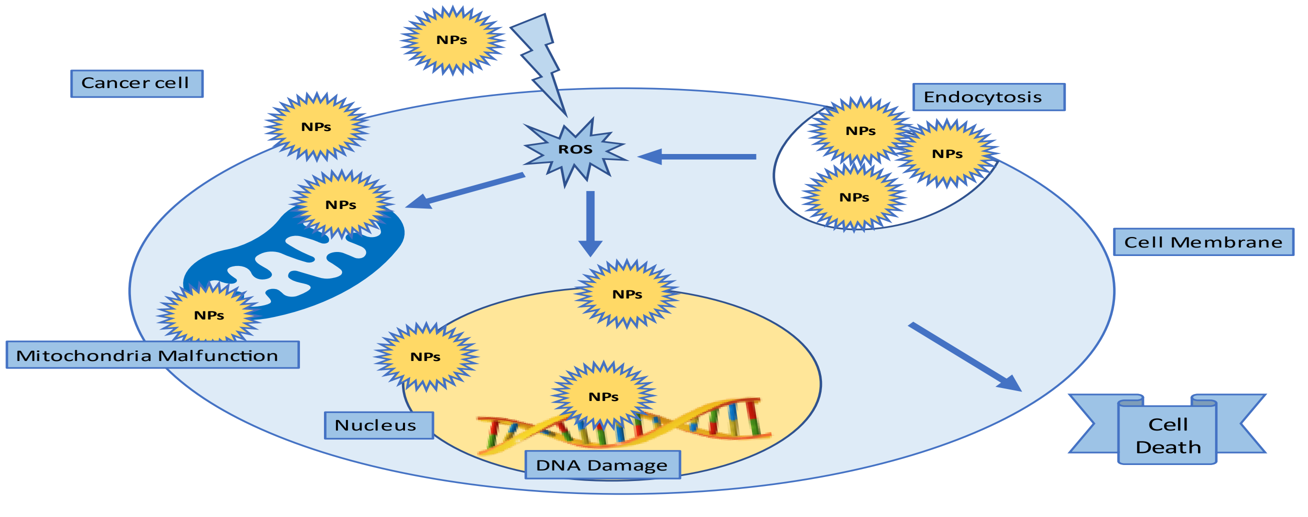

Fig. 2. Mechanism of Anti-cancer activity of NPs is diagrammatically represented: Nanoparticles cause morphological changes in cell wall, condensation of nucleus and attachment to the DNA causes damage, the endocytosis of nanoparticles produce ROS which create stress in cell and disturb the normal functioning of the mitochondria resulting in the death of cell.

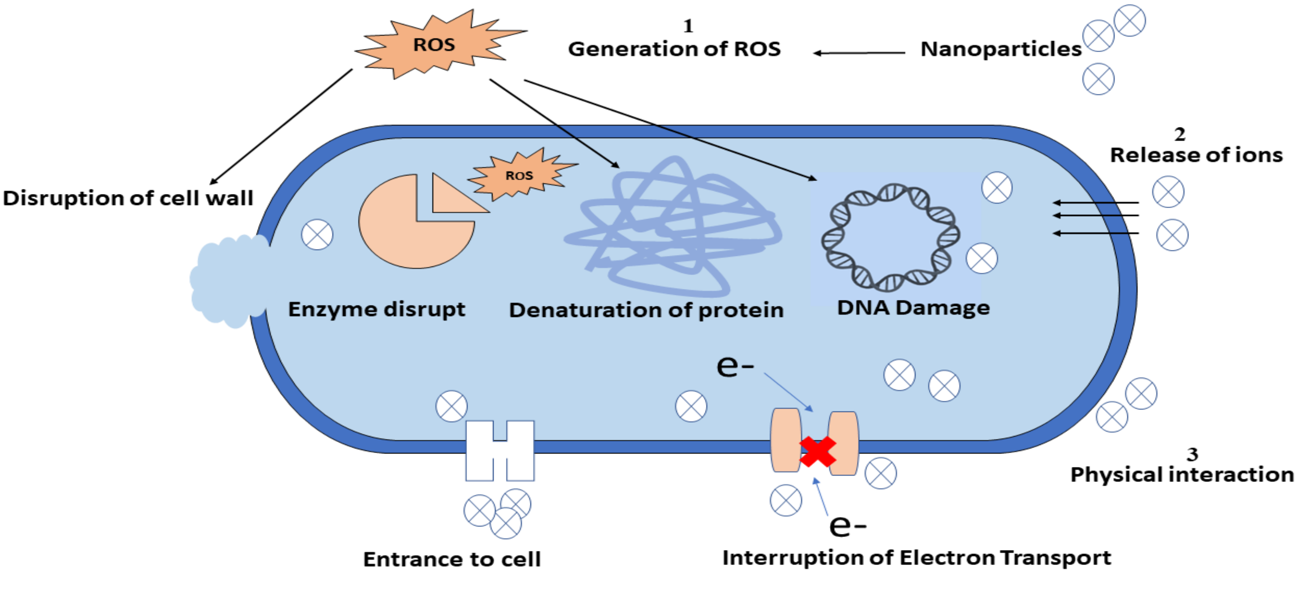

Fig. 3. Mechanism of Antibacterial activity of NPs: Different mechanisms include 1. Generation of ROS 2. Release of ions. 3.Physical interaction with the wall. The nanoparticles cause blockage of channels, the ROS cause enzyme, protein and DNA damage which results in the death of cell.

Table 4. Pharmacological actions of *Fagonia*- mediated nanoparticles.

Sr. #	Pharmacological actions	Plant species	Nanoparticles	Reported by
1.	Anticancer	*Fagonia indica*	Ag NPs	Ullah *et al*., 2020
2.	Antibacterial	*F. cretica*	Zn NPs	Kiani *et al*., 2022
		F. cretica	Ag NPs	Zulfiqar *et al*., 2019
		F. indica	Au NPs	Mariam *et al*., 2021
		F. indica	ZnO NPs	Hameed *et al*., *2021*
		F indica	Ag NPs	Adil *et al*., 2019
3.	Anti-fungal	*F. cretica*	Zn NPs	Kiani *et al*., 2022
		F. indica	ZnO NPs	Hameed *et al*., *2021*
4.	Anti- leishmanial	*F. indica*	Ag NPs	Ullah *et al*., 2017
		F. indica	ZnO NPs	Hameed *et al*., *2021*
5.	Antioxidant	*F. cretica*	Zn NPs	Kiani *et al*., 2022
		F. cretica	Ag NPs	Yousaf *et al*., 2019
		F. cretica	MnO_2 NPs	Faisal *et al*., 2022
		F. indica	ZnO NPs	Hameed *et al*., *2021*
6.	Protein kinase activity	*F. cretica*	Zn NPs	Kiani *et al*., 2022
		F. indica	ZnO NPs	Hameed *et al*., *2021*
7.	Alpha amylase activity	*F. cretica*	Zn NPs	Kiani *et al*., 2022
8.	Anti-urease activity	*F. cretica*	Ag NPs	Yousaf *et al*., 2019
9.	Anti-tyrosinase activity	*F. cretica*	Ag NPs	Yousaf *et al*., 2019
		F. cretica	MnO_2 NPs	Faisal *et al*., 2022
10.	Dye degradation activity	*F. indica*	ZnO NPs	Hameed *et al*., *2021*

Mechanism of action: The silver nanoparticles create morphological changes in the membrane of the cancer cell and lead to condensation of the nucleus, which causes cell apoptosis or cell death. Reactive oxygen species also produce due to the silver nanoparticles that generate stress in the cell. As a result, NPs cause the death of cancer cells (Patil & Kim, 2017) (Fig. 2).

Antibacterial activity: Several pathogenic bacteria cause many infectious diseases in humans, animals, and plants. Some common pathogenic bacteria include *Escherichia coli* and *Klebsiella pneumonia, Staphylococcus epidermidis, Bacillus subtilis, and Pseudomonas aeruginosa* cause problems like urinary tract infection, wound and nosocomial infections (Zulfiqar *et al*., 2019). So, the NPs synthesized from different species of *Fagonia* have been checked for promising antimicrobial activity against different pathogenic bacteria.

Mechanism of action: Nanoparticles show antibacterial activity via three different mechanisms, including the generation of Reactive Oxygen Species (ROS), ions release, and interaction with the cell wall. The nanoparticles cause several changes in the bacterial cell, i.e., blockage of transport channels, DNA, protein damage due to ROS, enzymes become inactive because of the attachment of metallic atoms. All these changes cause the death of the bacterial cell (Shahzadi *et al*., 2018) (Fig. 3).

Limitations of using nanoparticles: Nanoparticles are potential source of biological activities and have a major role in treatment of various diseases like cancer and diabetes etc. but on the other hand metallic nanoparticles also have few limitations of their uses and their synthesis as well. Metallic nanoparticles may cause toxicity in living healthy cells. Kidneys and liver can be effected by the toxicity of zinc oxide nanoparticles in high concentration (Espanani *et al*., 2015). Specifically silver nanoparticles have been reported for their effective antimicrobial property, but the detailed study has revealed that the method of synthesis of nanoparticles and selection of pathogenic microbes contain heterogeneity. So, for the purpose of developing nanoparticles an effective antimicrobial agent, the method of synthesis should be homogenized (Duval *et al*., 2019). As nanoparticles are small in size so they can enter the nervous system by penetration through olfactory bulb and cause threats to human (Elder *et al*., 2006). So, an in depth research is also needed to determine the possible threats of using nanoparticles.

Conclusion

Concludingly, *Fagonia* species have high therapeutic potential, and also contain a high degree of metabolites that helps in the synthesis of nanoparticles. *Fagonia* mediated nanoparticles showed very efficient biological activities, including antibacterial, anti-fungal, anti-cancer, and antileishmanial. Some nanoparticles also exhibit inhibition activity like alpha-amylase and alpha-glucosidase inhibition activity. So, *Fagonia* mediated nanoparticles can be used as a significant source for treating different diseases, including diabetes and cancer, by using these nanoparticles in drug delivery as well. Moreover, out of 35 species, only a few have been explored for their pharmaceutics effect. A lot more research work is required to explore the remaining species for more pharmaceutical products.

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