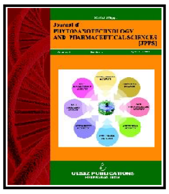
Journal of Phytonanotechnology and Pharmaceutical Sciences 1(2): 1-9, 2021

http://jpps.ukaazpublications.com

DOI: http://dx.doi.org/10.21276/jpps.2021.1.2.1

Journal of Phytonanotechnology and Pharmaceutical Sciences



Review Article : Open Access

Potential activities of nanoparticles synthesized from *Nigella sativa* L. and its phytoconstituents: An overview

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Article Info

Article history

Received 1 April 2021
Revised 7 May 2021
Accepted 8 May 2021
Published Online 30 June 2021

Keywords

Anticancer
Antibacterial
Antidiabetic
Medicinal plants
Nanocomposite
Nanoparticles
Nigella sativa L.
Phytochemicals
Thymoquinone

Abstract

Nanotechnology has been used since the ancient period in some or another way, either in the form of storing food or for medicinal purposes. Nanotechnology has allowed scientists to study an object in detail at its microscopic level which ultimately means discoveries and innovations leading towards development in various fields like pharmacy, medicine, electronics, engineering, *etc*. Nanotechnology can produce the material at the nanoscale called nanoparticles. When nanotechnology and the biological components are brought together, they can have a great impact on serving the medication and other environmental problems at a better level. *Nigella sativa* L. commonly known as black cumin, has been extensively used as a traditional medicine to treat a variety of ailments. It possesses several bioactive compounds like thymoquinone, thymohydroquinone, dithymoquinone, p-cymene, carvacrol, t-anethole, 4-terpineol, a-pinene, sesquiterpene longifolene, and thymol. Among which, thymoquinone plays a significant role in treating a wide range of diseases. Various nanoparticles like silver, gold, platinum, zinc oxide, copper, and gold are synthesized from the seeds, oil extracts, and the bioactive constituents of *N. sativa* and play an ameliorative effect enhancing the medicinal potential of this valuable plant. Comprehensive studies on *N. sativa* suggested various pharmacological activities like a diuretic, digestive, antihypertensive liver tonic, antidiarrheal, antibacterial, appetite stimulant, analgesic, and useful in skin disorders. Subsequently, *N. sativa* has also been largely studied for its biological activities such as antidiabetic, antiglycation, antimicrobial, anticancer, immunomodulatory, anti-inflammatory, analgesic, bronchodilator, renal protective, hepatoprotective and antioxidant properties. This review focuses on the medicinal effects of *N. sativa* and its collaboration to synthesize various nanoparticles and their applications in various processes.

1. Introduction

Nanobiotechnology represents an active area of research in clinical and medical domains and gaining popularity worldwide. It is an emerging field of study in the recent era due to its ability to form nanoparticles, *i.e.*, it has the capability of remodelling bulk compounds into smaller nanosized particles. The nanomaterials are defined as manufactured or natural material that poses unbound, aggregated, or agglomerated particles where external dimensions are between 1nm - 100 nm (Jeevanandam *et al.*, 2018). Because of its distinct design and synthesis process, the application of nanoparticles has grown into multidisciplinary areas such as biomedicine, environment, biotechnology, drug delivery, and nanomedicine. As the reason for the nanoscale, the nanoparticles behave differently giving the novel properties; for example, silver and gold nanoparticles show antibacterial activity. The synthesis of metal nanoparticles by physical and chemical methods is finite because of its negative impact on environmental factors and its need for expensive equipment. Green-approach technology is presently alluring due to its biogenic, non-toxic, and cheap approach that has become a main focusing area of research, leading to exploring various types of bioreducing agents. The involvement of phytochemicals of plants or seed extracts in the synthesis of nanoparticles has a distinctive part in the field of nanotechnology and nanomedicine as it supplies alternative therapeutic options (Prairna *et al.*, 2020). As herbs have been natural remedies since ancient times holding the framework of the Indian system of medicine. Also, herbal plants have been considered as the safest medicinal practice than modern allopathic medicines (Ahmad *et al*., 2013). The WHO has evaluated that most of the global population relies on herbal medicine for their health-related issues. The significance is largely based on scientific information, on the safety, efficacy, quality control/quality assurance, dosage, therapeutic uses, clinical trials, toxicity description of the plant species, and drug interactions amongst others. Effective application of *N. sativa* for remedial aim and for trade solely depends upon yield (raw plant product-seeds; bioactive compounds-essential oil) and its good quality. Currently, the seed and oil yields of black cumin have been given major importance. *N.sativa* is one of the medicinal herbs which have ample benefits because of its various active phytochemicals. Therefore, a combination of nanoparticles and *N. sativa* could give solutions to various clinical issues. The present review focuses on the medicinal properties of *N. sativa* seeds and their incorporation with various metallic or non-metallic nanoparticles and their use in various fields and medical treatments.

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1.1 *Nigella sativa* L.

N. sativa, a flowering plant belonging to the family Ranunculaceae, is annually found in native of northern parts of India, Pakistan, and the Middle Eastern Mediterranean region. This plant is widely distributed to the native of Arabia and Turkey. Its common name is kala jeera, kalonji, black cumin. Other names of this include black caraway seeds, habbatu sawda, and habatul baraka ("Blessed Seed") (Gali-Muhtasib *et al.*, 2005). *N. sativa* has valuable importance in the Arab countries and is mainly used in the preservation of food and as a spice and used in various healing treatments as medication as a traditional remedy. *N. sativa* has been studied extensively to know about its phytochemical properties and pharmacological activities. It is known for antibacterial, anticancerous, antifungal, antidiabetic activities (Gali-Muhtasib *et al.,* 2005).

Figure 1: Seeds of *N. sativa*.

2. Phytochemical constituents of *N. sativa*

Using *N. sativa* seeds, different active compounds have been isolated and identified. The supreme active compounds found are thymoquinone (30-48%), thymohydroquinone, sesquiterpene longifolene (1-8%), p-cymene (15%), thymol, carvacrol (6-12%), 4-terpineol (2%), t-anethol (1-4%). The herb also contains an anti-cancerous component, alpha-hederin which is a water-soluble pentacyclic triterpene and saponin. Two different types of alkaloids identified in black cumin are isoquinoline alkaloids (includes nigellicimine and nigellicimine N-oxide) and pyrazole alkaloids or indazole ring bearing alkaloids which include nigellidine and nigellicine. Seeds also contain a good amount of certain minerals like zinc, iron, lead, copper, *etc.* Seed is reported to have vanillic acid and also carotene. Some compounds like carvone, limonene, citronellol are found in trace amounts. It also contains proteins, fibers, carbohy-drates. These black seeds are high in oil containing unsaturated fatty acids linoleic acid (50-60%), oleic acid (20%), eicosadienoic acid (3%), and dihomo linoleic acid (10%). Saturated fatty acids (palmitic, stearic acid) amount to about 30% or less. α-sitosterol is a major sterol, which accounts for 44% and 54% of the total sterols in Tunisian and Iranian varieties of black seed oils, respectively followed by stigmasterol (6.57-20.92% of total sterols) (Ali, 2020).

3. Potential activities of *N. sativa* by pharmacological studies

There are multiple pharmacological studies conducted on various medical and pharmacological issues using black seeds as a treatment or observe their effect and understand the properties. Some of the properties (Figure 2) and studies carried are discussed below.

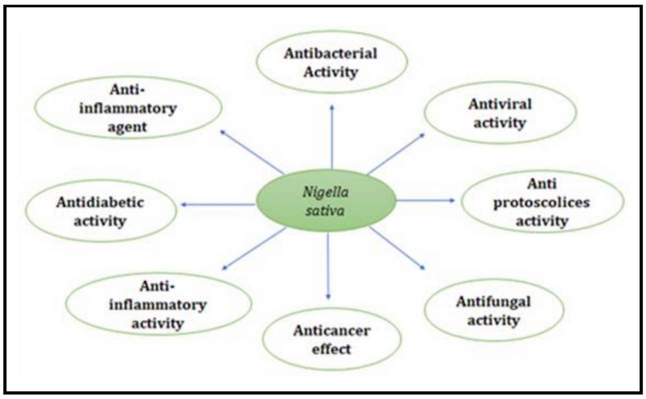

Figure 2: Potential activities of *N. sativa.*

3.1 Antibacterial activity

Increasing effects due to bacterial infections are ever-increasing and is a global concern to find the solution against it continuously and multiple kinds of research are carried out. According to the study conducted by Chaieb *et al.* (2011), *N. Sativa* has gained value for its potential effect in preventing formation of bacterial biofilm. Using *N. sativa* oil, antibacterial activity was carried against methicillin-resistant *Staphylococcus aureus* and methicillin-resistant coagulase-negative *Staphylococci* which showed an exceptionally low MIC range of <0.25-1.0 µg/ml (Ugur *et al.*, 2016). Thymoquinone, the most active compound of *N. sativa* has shown broader spectrum activity against multiple strains of both gram-positive and gram-negative bacteria like *Bacillus, Micrococcus, Staphylococcus, Pseudomonas, Escherichia, Salmonella, etc.* For bacteria like *Staphylococcus aureus and Staphylococcus epidermidis*, it has shown low biofilm inhibition at the concentration of 22 µg/ml and 60 µg/ml, respectively (Yimer *et al.,* 2019). Also, Monton *et al.* (2021) exhibited the antibacterial property of *N. sativa* against skin infecting bacteria, *i.e.*, *S. aureus* and *S. epidermidis*, hence it can be used in skin treatment. Recently, it has been reported that the bacterial strain *Bacillus subtilis and Bacillus licheniformis* were vulnerable to the phytochemicals of *N. sativa* seeds showing antibacterial activity (Habib *et al.,* 2021).

3.2 Antiviral activity

Likewise, viral infection is also the main reason for apoptosis of the cell or death because of the infection. In an *in vitro* experiment, researchers found that when the alcoholic extract of *N. sativa* (50 µg/ml) was used as a treatment against Peste des Petits Ruminants (PPR) Virus, there is an increase in cell viability of infected cells and reduction in cytopathic effects of PPRV (Aqil *et al.,* 2018). According to Yimer *et al.* (2019), *N. sativa* along with the honey mixture showed effective results against HIV. In an *in vivo* experiment, a mouse that was infected using smith strain of Murine cytomegalovirus, it was observed that there was an increase in the number of CD-4 T helper cells and the number of macrophages which reduced the infection at an undetectable level in the spleen and liver of mice after their treatment with black seed oil was used as a treatment (Yimer *et al.,* 2019). According to the *in silico* studies, it has been displayed that the phytochemicals of *N. sativa* like dithymoquinone (DTQ) (Ahmad *et al.*, 2020), hederagenin, thymohydroquinone, thymoquinone (Kadil *et al.,* 2020), α-hederin, and nigelledine (Maideen, 2020) possibly have the ability to inhibit the SARS-CoV-2 replication and attachment to host cell receptors. These compounds have a moderate or high affinity towards the SARS-CoV-2 proteins (Koshak *et al.*, 2020). Recently also, it has been found that *N. sativa* can be an alternative therapy for curing COVID-19 (Islam *et al.*, 2021).

3.3 Antiprotoscolices activity

In an *in vitro* study, carried out on the protoscolices of hydatid cysts which causes hydatidosis or cystic echinococcosis due to the larva stage of parasitic cestode *Echinococcus granulosus.* It has been reported that the methanol extract of *N. sativa* at the concentration of 50 mg/ml has shown promising results by killing 100% of protoscoleces (Mahmoudvand *et al.*, 2014; Kohansal *et al.*, 2017). Recently, it has been discovered that *N. sativa* oil loaded on chitosan nanoparticles shows improved results on antihydatid properties by increasing the drug delivery to the tissues (Kishik *et al.*, 2021).

3.4 Antifungal activity

In vitro as well as an *in vivo* test was done using *N. sativa* extract as a treatment. In an *in vitro* study, *N. sativa* seeds have displayed the inhibitive growth effect against fungi species like *Aspergillus fumigatus, Aspergillus flavus, Cryptococcus laurentii, Candida parapsilosis, Cryptococcus albidus, Candida albicans, Candida tropicalis, and Issatchenki aorientalis* (Rogozhin *et al.*, 2011). In 2014, Mahmoudv *et al.* (2014) invented that *N. sativa* extract and its essential oil have effective antifungal activity against pathogenic dermatophyte strains like *Trichophyton mentagrophytes, Microsporum gypseum*, and *Microsporum canis.* In an *in vivo* experiment, the mice were infected by the fungal strain *Candida albicans* and were later treated with an aqueous extract of black seeds and the results showed to inhibit the effect of the fungal activity (Forouzanfar *et al.*, 2014). *N. sativa* seeds also showed inhibition in growth against *Fusarium solani fungi* (Taif *et al.*, 2019).

3.5 Anticancer effect

In this modern world, cancer is the second cause of death after a heart attack, which remains the first cause of death worldwide. The researchers have found that the most active compound of *N. sativa*, *i.e*., thymoquinone is the most effective component to have anticancer properties (Pu *et al.*, 2019). It has been extrapolated that TQ has anticancer activity by interfering with various cellular pathways like p53, NF-κB, PPARγ, STAT3, MAPK, and PI3K/AKT transducing signals (Diab-Assaf *et al.*, 2004). Other than thymoquinone, other phytochemicals of *N. sativa* like thymol, thymohydroquinone, dithymoquinone, nigellimine-N-oxide, nigellicine, nigellidine, and carvacrol have shown to have an anticancer effect (Satooka *et al.*, 2012). According to *in vitro* and *in vivo* studies performed, α-hederin has also had the anticancer activity on breast cancer cells (Cheng *et al*., 2014).

Various studies on *N. sativa* suggested that TQ has an anti-proliferative effect on Hela cancer cells by significantly reducing the number of viable cells (Butt *et al.*, 2019), in human myeloblastic leukemia HL-60 cells by inducing apoptosis in cancerous cell DNA laddering (Yimer *et al*., 2019) and pancreatic ductal adenocarcinoma by inducing the apoptosis of the cancer cells (Yimer *et al.*, 2019). Nanoemulsion of *N. sativa* seeds was prepared to test the cytotoxic effect using the MTT method against A2780 ovarian cancer and umbilical vein endothelial cells (HUVEC) as normal cells. According to the results, nanoemulsion notably reduced the bioavailability of A2780 cancerous cells by IC50 of 0.72 µg/ml; however, its toxicity against HUVEC cells was much lower ($IC_{50} > 25$ µg/ml) (Arazmjoo *et al.*, 2021).

3.6 Anti-inflammatory activity

Asthma is a chronic inflammatory respiratory disease. Asthma triggering factors can be environmental or non-environmental. At the initial stages of the asthma attack, the mast cells play a role. These mast cells have a high affinity to IgE receptors and this crosslinking with factors releases the mast cells. In an experiment, the prophylactic effect on asthma disease was studied where the boiled *N. sativa* extract was given to 29 asthmatic adults for 3 months and it has been found that the asthma symptoms of chest wheezing were significantly improved, and even the use of inhalers, oral beta-agonists were reduced by using *N. sativa* extract (Ahmad *et al.*, 2013). In another experiment, it has been displayed that *N. Sativa* serves as a potent analgesic and anti-inflammatory agent due to the presence of thymoquinone in the seeds (Amin *et al.*, 2016).

In carrageenan-induced paw edema in rats, *N. sativa* significantly reduced the inflammation compared to the control (p<0.001) and less than aspirin showing an anti-inflammatory effect. According to Pise *et al.* (2017), *N. sativa* also reduced the formation of granulomatous tissue in the cotton pellet-induced granuloma. Ethanolic extract of *N. sativa* unveiled that extract effectively inhibits the histamine from the peritoneal Wistar rat mast cells and acts as an effective anti-inflammatory agent which is nontoxic and good asthma therapy (Ikhsan *et al.*, 2018). In another *in vivo* study, it has been revealed that *N. sativa* also reduced adjuvant arthritis in the rats, and by providing a high dosage, *i.e.*, 1.82 ml/kg, it can also prevent the development of arthritis (Nasuti *et al.*, 2019).

3.7 Antidiabetic activity

Researchers revealed that when diabetes induced rat was treated with the *N. sativa* oil, it had been found that it suppressed the oxidative stress, the pro-inflammatory mediators, amyloidogenic pathway, lower the insulin receptor inhibitory effect of IOMe-AG538, and modifies the insulin-signaling pathway. Henceforth, it prevents neurotoxicity, amyloid plaque formation, and Tau hyper-phosphorylation, thereby restoring AD-related miRNA normal levels (Balbaa *et al.*, 2017). During the meta-analysis of glycemic and serum lipid profile, *N. sativa* supplementation improved fasting blood sugar, glycosylated hemoglobin, total cholesterol, and LDL-cholesterol in patients with type 2 diabetes (Daryabeigi-Khotbehsara *et al.*, 2017).

The outcome of diabetes leads to exposure to accumulation of glucose. The carbonyl group of glucose reacts with the amino acids of proteins, and this leads to various deleterious products called advanced glycation end products. The effect of *N. sativa* extract was also observed on glycation, the test performed using a glycated DNA sample and analyzed through agarose gel electrophoresis. The result showed that there was a significant decrease in glycation in the presence of *N. sativa* extract (Pandey *et al.*, 2018). Thymoquinone has shown potential effect as an antiglycation agent (Kumar *et al.*, 2020). According to certain studies, *N. sativa* can be given as an adjuvant for oral antidiabetic drugs (Hamdan *et al.*, 2019). *N. sativa* has a vital role in controlling diabetes-induced inflammation and oxidative stress in diabetic patients as it shows beneficial properties like the restoration of the antioxidant defense systems, the increase in the activity of antioxidant enzymes, the decrease of inflammatory biomarkers, the suppression of the production pro-inflammatory mediators, improvement of endothelial dysfunction, and hepatic, kidney, heart, and immune functions (Mahmoodi *et al.*, 2020).

Mohebbati *et al.* (2020) revealed that *N. sativa* and thymoquinone have protective effects on endothelial dysfunction induced by diabetes. Dose-dependent tests of *N. sativa* have shown to have inhibiting properties in AGE formation even at lower concentrations. It was observed that the thymoquinone was the primary compound to have an antiglycating property (Uzhir *et al.*, 2020).

4. Nanoscience and nanoparticles

Nanoscience and nanotechnology have imparted themselves in today's research field and have shown flourishing development from past years. This field of science can produce the material at the nanoscale called nanoparticles. The nanoworld has attracted scientists to study any object's structure and characteristics at the nano level. Richard Feynman, in 1959 won the Nobel prize in physics for coming up with the idea of 'nano' and Norio Taniguchi was the first person to use the term 'nanotechnology' in 1974. The term nanoparticles are given to fine particles which have a dimension between 1 to 1000 nm. But nanoparticles ranging from 1 nm to 100 nm are best to be used in the research field. Nanoscience and nanotechnology can be differentiated. Nanoscience is the coordination of physics, material science, and biology. Where nanotechnology is the ability to observe, measure, manipulate, control the manufacture at nanoscale meters. Typically, nanoparticles consist of three layers: (a) surface layer: the layer consists of metal ions, polymers, and molecules, (b) shell layer: this layer differs chemically from the rest of two layers, and (c) core: core consists of the actual nanoparticles (Dontsova *et al.*, 2019).

4.1 Classification of nanoparticles

Nanoparticles are categorized into metallic nanoparticles and non-metallic nanoparticles.

4.1.1 Non-metallic nanoparticles

Non-metallic nanoparticles are used in certain cases and the majorly used non-metallic material is carbon and silicon which are liberal elements found on earth. Both elements are quite familiar to each other, both belonging to group IV of the periodic table and have valency 4. These borderline similarities between these two elements have application in diagnostic and therapeutic and electrical fields (Yu-Cheng *et al.*, 2013).

Carbon nanoparticles are an alternative form of graphene which are atom-thick sheets of graphite. Graphene has uses in biotechnology, in making electronic devices, and as surfactants (Han *et al.*, 2017). Graphene-associated carbon nanoparticles are of two types: (i) fullerene, and (ii) carbon nanotubes. These nanotubes possess remarkable properties which are commercially used in the production of the nanocomposite, efficient gas absorbent remediation, electric photodiodes, photo vault for solar panels, *etc.* (Khan *et al.*, 2019). Silicon nanoparticles: From the past few decades, extensive studies on solid silica nanoparticles (SiNPs) and mesoporous silica nanoparticles (MSNs) have been primarily carried and have shown many uses. The methods that have been put forward for synthesizing silica nanoparticles are sol-gel synthesis and water-oil microemulsion technique. The silicon nanoparticle with various metals collaboration is used for identifying and treatment of cancer and tumor cells (Chen *et al.*, 2013)

4.1.2 Metallic nanoparticles

The metal nanoparticle came into the picture of the modern era when it was first identified in a solution by Faraday (1857) and their properties were proved in his famous paper "experimental reactions of gold (and other metal) to light". But, the importance of metals in medicines was presumably known from the Vedic period of ancient India. The ayurvedic scholar of 1500 B.C, Acharya Charaka describes the medicinal properties of various metals like gold, silver, platinum, lead, and Mercury in his Charaka Samhita. Metals like gold which is the most primarily used noble metal to synthesize nanoparticles. Next to gold, silver is the second most metal to be widely used in synthesis, other than this metals like iron, copper, tin, lead, *etc.*, are used in the synthesis of nanoparticles. These metal nanoparticles show various properties like antibacterial, antioxidative, optical, *etc.* For example, gold nanoparticles showed antioxidant (Ahmed *et al.*, 2013), antibacterial, and antibiofilm (Manju *et al.*, 2016) activities while silver nanoparticles have antibacterial properties (Ranjan *et al.*, 2013) as shown in Table 1.

Table 1: Synthesis of metallic nanoparticles from *N. sativa* and their activities

Metallic nanoparticles synthesized from *N. sativa*	Applications	References
Silver nanoparticles	Anticancer Antibacterial Antiviral Antibiofilm Anti-inflammatory Antidiabetic	Usmani *et al.*, 2019 Al Matroudi *et al.*, 2020 Mahfouz *et al.*, 2020 Al Matroudi *et al.*, 2020 Rohini *et al.*, 2019 AlKhalaf *et al.*, 2020
Gold nanoparticles	Anticancer Antibiofilm Antidiabetic	Manju *et al.*, 2016 Manju *et al.*, 2016 Veeramani *et al.*,2021
Copper nanoparticles	Anti-inflammatory Anti-aggregation	Yan *et al.*, 2020 Istikhara *et al.*, 2016
Platinum nanoparticles	Anticancer Antibacterial	Aygun *et al.*, 2019 Aygun *et al.*, 2019
Zinc oxide nanoparticles	Antibiofilm	Al-Shabib *et al.*, 2016
Nickel oxide nanoparticles	Catalytic Property	Boudiaf *et al.*, 2021

4.2 Approaches of nanoparticles synthesis

The nanoparticles can be synthesized using two approaches: the (i) top-down approach, and (ii) bottom-up approach as shown in Figure 3.

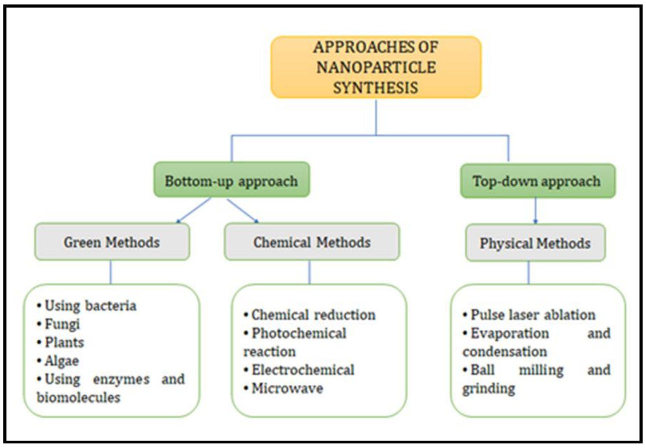

Figure 3: Different approaches to nanoparticle synthesis.

4.2.1 Top-down approach

Top-down approach is the destructive form where bulk material is decomposed or chopped into fine particles which are carried out using different size reduction techniques and synthesizes are carried out using physical methods. Physical methods include grinding pulse laser ablation, evaporation - condensation deposition (CVD), *etc*. A common physical method is an evaporation - condensation deposition (CVD). Physical methods are costly and are mostly followed when the nanoparticles are synthesized in a larger amount (Khan *et al.*, 2019; Chatterjee *et al.*, 2020).

4.2.2 Bottom-up approach

Bottom-up approach is carried out using smaller materials and it includes two methods: (a) chemical method, and (b) biological method. (a) In chemical methods, the nanoparticles are synthesized using reducing agents like sodium citrate, tollen's reagent, ascorbate, N, N - dimethylformamide (DMF), sodium borohydride. Capping agents are used for the additional stability of nanoparticles. The advantage of this method is that it can synthesize a greater number of nanoparticles in a limited period. Chemical methods tend to have disturbing effects on the environment because the chemicals used show hazardous effects. (b) The biological method is the most convenient, cost-effective, and environmentally friendly method. The biological method includes the synthesis of nanoparticles using biological materials like plants, microorganisms (bacteria, fungi, algae) biomolecules, *etc.* (Sharma *et al.*, 2019).

5. Synthesis of nanocomposites using *N. sativa*

5.1 Nanocomposite BC-GO@Fe_3O_4

This multipurpose nanocomposite was prepared by incorporation of ferric oxide nanoparticles by using *N. sativa* and later the graphene oxide was used to functionalize the nanocomposite. The purpose of making nanocomposite was for water treatment. Various chemicals like arsenic, dyes, and even microbes, and other pollutants from the industries or other sources cause water pollution (Wai *et al.*, 2019). The one cost-effective method used is the adsorption method that follows the phenomenon of attachment of pollutant molecules or ions to the solid surface which have many interaction sites with functional groups and high adsorbent capacity. The nanoparticles have many interaction sites, and when these metal nanoparticles get activated with carbon compounds and incorporated together with organic plant/cellulose compounds, form a framework that has more functional groups and interaction sites which make it good for adsorption. Nanocomposite BC-GO@Fe_3O_4 (Tara *et al.*, 2020) was used as treatment against gram-negative and gram-positive bacteria and it possessed antibacterial properties after that it was used in water treatment for the removal of arsenic and methylene blue dye. The results when compared with the previously studied adsorption of the nanocomposite BC-GO@Fe_3O_4 showed better results in the adsorption of arsenic and methylene blue (Sahoo *et al.*, 2020).

5.2 Nanocomposite Fe_2O_3-Sn_2O/BC

It was prepared using the co-precipitation method by using *N. sativa* as a cellulosic active compound that acts as a framework. The hydrogen bond and the electrostatic force between the nanoparticles and the cellulosic compound functional groups hold the iron and tin nanoparticles together and do not let them separate in the water. When the nanocomposite was tested with methylene blue dye, it was observed that 2 g/l Fe_2O_3 - Sn_2O/BC was enough to remove 95% of the methylene blue dye in 15 min (Singh *et al.*, 2019). Later for the confirmed results of interaction between nanoparticles and the dye, fourier-transform infrared spectroscopy (FTIR) analysis was carried out, and it was concluded that the adsorption capacity was more of Fe_2O_3-Sn_2O/BC than the previously studied $MnFe_2O_4$/BC Fe_2O_3-ZrO_2 /BC (Siddiqui *et al.*, 2018).

6. Synthesis of nanoparticles using *N. sativa*

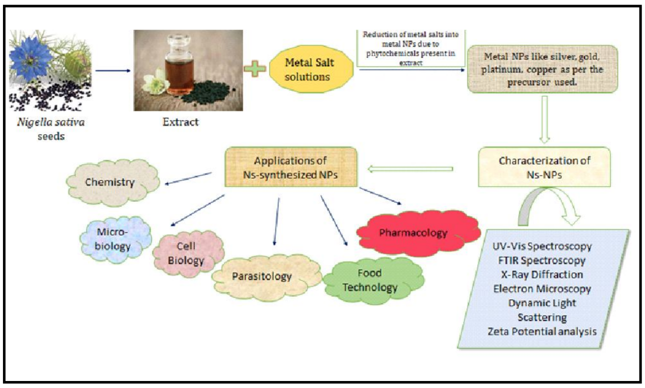

Figure 4: Synthesis, characterization and applications of *N. sativa* synthesized nanoparticles.

6.1 *N. sativa* synthesized silver nanoparticles (Ns-AgNPs)

Silver nanoparticles are known to destroy mitochondrial respiration and lead to apoptosis. The optimal test carried with the IC_{50} of 10 µg/ml Ns-AgNPs showed a 50% of reduction in cell viability. The treatment altered the expression of the Bax and Bcl-protein and COX-2 inflammatory markers. Therefore, it was observed that the AgNPs induced apoptosis in MCF-7 cells (Rohini *et al.*, 2019). Almatroudi *et al.* (2020) also supported the former study and suggested that Ns-AgNPs showed significant cytotoxic ability and substantially killed human breast cancer cell (HCC-712) viability. In an *in vitro* test carried out using Ns-AgNPs on hepatocellular carcinoma, it has been observed that these nanoparticles possess a cytotoxic effect of $p<0.05$ with a 7.16 µg/ml IC_{50} value (Usmani *et al.*, 2019). It has been observed that Ns-AgNP at an amount of 12.5 µg/ml showed antibiofilm activity by 88.42% for *Enterococcus faecalis*, 84.92% for *E. coli*, 81.86% for *Klebsiella pneumonia*, 82.84% for *Staphylococcus aureus*, and 49.9% for *Pseudomonas aeruginosa* (Almatroudi *et al.*, 2020). Ns-AgNPs have been used against dyslipidemia and DNA fragmentation in hydrogen peroxide-induced rats and it has been confirmed that silver nanoparticles control dyslipidemia and prevent DNA fragmentation (Ali *et al.*, 2019). Ns-AgNPs was used as an antiviral treatment against herpes simplex virus-1 and the viral load was decreased by 82.23% and mortality by 94.54% (Mahfouz *et al.*, 2020). For the photocatalytic effect of silver nanoparticles, the *N. sativa* extract amount plays a vital role in the preparation of well-dispersed and small-sized NPs. Once the nanoparticles are prepared, they act as a highly reducing and stabilizing agent with a porous structure (Chand *et al.*, 2021). The antidiabetic activity was tested on adult male albino rats using Ns-AgNPs and it has reduced oxidative stress characterizing anti-diabetic effect (AlKhalaf *et al.*, 2020).

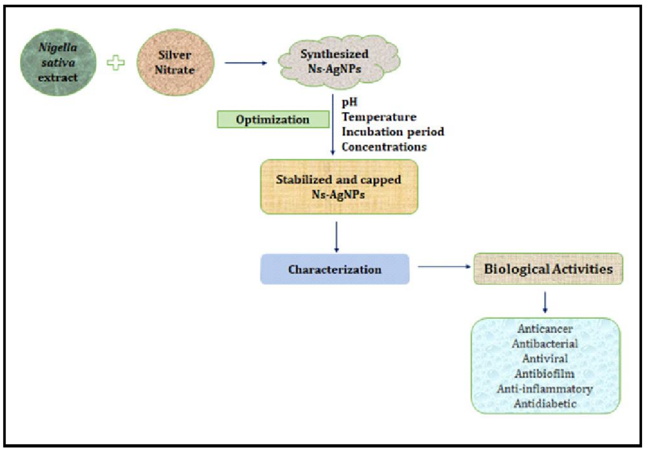

Figure 5: Ns-synthesized AgNPs and their properties.

6.2 *N. sativa* synthesized gold nanoparticles (Ns-AuNPs)

Using *N. sativa* essential oil, gold nanoparticles (NsEO-AuNPs) were synthesized, and an *in vitro* test was carried out on lung cancer cells. The MTT assay results confirmed the IC_{50} value of NsEO-AuNPs at 28.37 µg ml^{-1}. Thus, inhibiting the growth of lung cancerous cells. Along with that (NsEO-AuNPs) also inhibit biofilm-forming bacteria *S. aureus* and *Vibrio harveyi* by decreasing the hydrophobicity index by 78% and 46%, respectively (Manju *et al.*, 2016). Another experiment carried using gold nanoparticle synthesized by black seed, using-amylase activity confirmed that gold nanoparticles possess 78% antidiabetic property (Veeramani *et al.*, 2021).

6.2.1 *N. sativa* synthesized platinum nanoparticles (Ns-PtNPs)

Ns-PtNPs were used to see its antibacterial and anticancer effect. These NPs were also used to test the cytotoxicity effect on MDA-MB-231 and Hela cells of cervical cancer. Higher cytotoxic effect against MDA-MB-231 breast and HeLa cervical cancer line with the increasing concentration of these NPs from 25 µg to 150 µg after 24 h compared to control cell lines was observed, 150 µg of Pt NPs stabilized with black cumin seed extract had the highest anti-proliferative effect, 93 % and 96 % on MDA-MB-231 and HeLa cell lines, respectively. The Pt NPS also showed an ameliorative effect against gram-positive and gram-negative bacteria (Aygun *et al.*, 2020)

6.2.2 *N. sativa* synthesized zinc oxide nanoparticles (Ns-ZnONPs)

Ns-ZnONPs have been used for biofilm formation to prevent the contamination of food. In a study conducted by Zaidi *et al.* (2016), these nanostructures of zinc oxides were treated against four biofilm-forming pathogens and demonstrated broad-spectrum QS inhibition in *Chromobacteri umviolaceum and Pseudomonas aeruginosa* biosensor strains. ZnNPs at sub-inhibitory concentrations inhibits the biofilm formation of four-food pathogens *viz., C. violaceum, P. aeruginosa*, *Listeria monocytogenes* and *E. coli* (Al-Shabib *et al.*, 2016). Therefore, it was envisaged that these zinc oxide nanoparticles can be used as food packaging material. Later in 2018, this report was also supported by Alaghemand *et al.* (2020) concluded that it can be used in the growth of yield and growth of height of branches and enhancing the properties of plants.

6.2.3 *N. sativa* synthesized copper nanoparticles (Ns-CuNPs)

Ns-CuNPs were tested to see their effect on methadone-induced cell death in adrenal pheochromocytoma (PC12) cells. Methadone is an opioid, which is used as a pain-relieving medication. CuNPs-treated cell cutlers significantly increased cell viability and mitochondrial membrane potential and decreased inflammatory cytokines concentrations, caspase-3 activity, and DNA fragmentation in the high concentration of methadone-treated adrenal pheochromocytoma (PC12) cells (Yan *et al.*, 2020). Copper nanoparticles have also been reported to show anti-aggregation properties in protein. The thymoquinone-based copper nanoparticles were synthesized and more efficiently restricted the aggregation of the protein. Therefore, the study provides the result of competitive binding of the quaternary amine of diethylaminoethyl rosin ester (QRMAE) and copper nanoparticles and protein (BSA) aggregation at higher temperature induced by QRMAE, the presence of copper nanoparticles and thymoquinone inhibits the aggregation process (Istikhara *et al.*, 2016).

6.2.4 *N. sativa* synthesized nickel oxide nanoparticles (Ns-NiONPs)

Ns-NiONPs were synthesized and developed as a stabilizing agent. The total reduction of 4-nitrophenol to 4-aminophenol corresponding to the catalytic activity of NiONPs occurred at pH7, pH9, and pH11 in 60 min, 10 min, and 45 min, respectively and the catalytic activity was best observed at pH 9 showing better electrocatalytic activity (Boudiaf *et al.*, 2021).

7. Conclusion

N. sativa has numerous health benefits and remarkable use in traditional medicine to treat various diseases. Nanotechnology is one of the modern technologies which is universally used in the pharmacological and medicinal field and has worldwide popularity. The incorporation of *N. sativa* and various metal nanoparticles have shown many benefits in various medical research especially in the treatment of cancerous cells and have good results on environmental aspects. Therefore, if herbs as well as nanotechnology, can be collaborated, it can benefit humans as well as the environment in many factors.

Future perspectives

Furthermore, research is required to study the nanoparticles using *N. sativa* and see their effects on different other diseases or disorders. Different metals or non-metal nanoparticles can be used in other environmental protection in terms of pollution control. This review focuses on the search of *N. sativa* and the study of nanoparticles. This review would help the researcher interested in nanoparticles and conduct studies on further clinical or pharmacological studies.

Conflict of interest

The authors declare that there are no conflicts of interest relevant to this article.

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Citation **Prairna Balyan, Shruti Shinde and Ahmad Ali (2021). Potential activities of nanoparticles synthesized from *Nigella sativa* L. and its phytoconstituents: And overview, J. Phytonanotech. Pharmaceut. Sci., 1(2):1-9. http://dx.doi.org/10.21276/jpps.2021.1.2.1**