

A Delve into The Novel Field of Essential Oil-Based Silver Nanoparticles and Its Anti-Inflammatory Potential [†]

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Abstract: The overall interest in natural products is ever-increasing which clearly explains the involvement of various essential oils in different aspects of the day-to-day lives of common people. These pharmacologically relevant agents are categorised as secondary metabolites of plants extracted or distilled from different parts of plants, and that show pharmacological activities like anti-inflammatory, antioxidant, antimicrobial, larvicidal, etc. The synthesis of metal nanoparticles has been developed by including different polymers, capping agents, and metal sources in the reaction. With the advancement of research, biological capping agents are being used for synthesizing metal nanoparticles like plant extracts, algae, fungi, etc. Essential oil is a newly added member of this list of capping agents. In the case of other metallic nanoparticles produced from biological capping agents, it was seen that the therapeutic activity of the plant material is also present within the produced nanoparticle. Similarly, for essential oil-derived nanoparticles, the therapeutic efficacy of the oil will be present within the nanoparticle. So, essential oils derived from plants like Eucalyptus, Clove, Lavender, etc. can be used to create nanoparticles that can act as anti-inflammatory agents. With work initiating on cumin oil and other oils like turmeric oil, it can be understood that the field of essential oil-derived nanoparticles is gaining much traction. The poster will present an accumulation of knowledge and show the available literature related to the anti-inflammatory potential of essential oil-mediated silver nanoparticle.

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1. Introduction

Inflammation is seen within a tissue that is caused as a result of some kind of traumatic, toxic, infectious injury. It can also occur due to some kind of autoimmune injury or invasion of some microorganisms. After the occurrence of the injury, a complex set of reactions take and the end result of it is inflammation. After the inflammation occurs, the cells generally go for healing and recovering from the infections which means it is the defence mechanism of the body from unwanted changes. In worse-case scenarios, inflammation may lead to permanent damages within the body [1]. Additionally, inflammations may give rise to repeated instances of inflammation that would further develop into auto-inflammatory disorders like Familial Mediterranean Fever. Considering the global population, it can be said that chronic inflammation or diseases causing the same can be marked as one of the reasons for high mortality. According to the World Health Organisation (WHO), chronic inflammation should be identified as a threat to humankind. This can also be proven by the fact that 3 out of 5 patients expire because of chronic inflammatory diseases like heart disorders, strokes, obesity, cancer, etc. [2]. Systemic

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chronic inflammation can be caused by several factors other than the ones mentioned above like lifestyle and environmental factors [3]. Some of the ways to treat inflammation involve the usage of anti-inflammatory drugs. A few examples of such kinds of drugs are diclofenac, ibuprofen, paracetamol, etc. They work primarily by inhibiting the inflammatory mediators that are produced within the body as a part of the body's response. But they come with several side effects like gastrointestinal bleeding, damage in the gastric mucus layer, and many more. To avoid such kinds of side effects, natural anti-inflammatory agents can be used as they have higher potency and the number of side effects associated with natural drugs is very less. Additionally, they show biological activities by protein binding which also helps to increase their efficiency [4].

Nature has been a great source of inspiration for medicine and therapy; so, having plants as the primary source of medicine at the dawn of medicine is very much expected. Most of the ailments within human beings were cured of plants or plant products. They have been used not only for treatment but also for developing immunity against several microorganisms. To date, a lot of these herbs and plant products are waiting to be discovered and studied further to see their utilisation in daily life. In some cases, the remedies have stood the test of time and are continued to be used till now. The more nature was explored the more knowledge was gathered and they were implemented in medicine and treatment. With time, the effectiveness of the same was understood and this gave birth to valuable data which again added to the pool of knowledge. All these slowly but steadily gave birth to the different ancient systems of medicine like Ayurveda, Unani, Siddha, and others [5]. Most of the countries have their own systems of medicine which are largely composed of native plants or indigenous plants as their source of treatment and medicine. For this reason, the biodiversity of the local area was directly linked with the particular system of medicine under question [6]. These traditional systems of medicine serve as the example of the old tradition of healing and the rituals associated with the same. Despite the rich history and good success rate in the past, they are now identified as "alternative medicine" or "complementary medicine."

An important practice of the traditional medicine system is the implementation of essential oils within the treatment practice. These oils mostly have great therapeutic potential and are extracted or distilled from natural sources. They are highly potent but the implementation of the essential oils becomes difficult. This is mainly because of their volatile nature and high cost which makes it difficult for common people to use them in great abundance [7]. A similar issue is with the usage of herbal medicines. The most well-known problem is the low solubility of the components [8]. Many such similar issues constrict the usage of herbal medicine in abundance. But their high potency makes it difficult to completely avoid herbal medicines and rely only on modern medicines. To solve this issue, the scientific community has found ways to incorporate herbal medicine within modern therapy with the help of new technologies. This has caused the merge of nanotechnology and herbal medicines.

2. Anti-Inflammatory Potential of Essential Oils

Essential oils are complex mixtures of phenylpropanic derivatives or terpenes. They are naturally found within different parts of plants like flower, seed, leaves, bark, etc. Being volatile liquids, they need to be stored in specific environmental conditions. They have a characteristic order for which they are utilized in perfumery and the cosmetic industry [9].

Therapeutically, these oils can be used as antimicrobial, antidepressants, anxiolytic agents, antioxidant, and many more [10]. The therapeutic applications of essential oils are not only limited to treating humans. They also find its use in veterinary medicine [9]. Citronella oil extracted from *Cymbopogon citratus* is a well-known insect repellent. Similarly, essential oil extracted from *Eucalyptus* spp. and *Ocimum* spp. are also potent insect repellents that are utilized in day-to-day life [11]. As an anti-inflammatory agent, essential oils can be used. Some examples of such essential oils have been mentioned in Table

1. It is said that the phenylpropanoids that are present within the volatile oils are responsible for the anti-inflammatory activities of the oil. Although the exact mechanism of action differs from one essential oil to another but the compound responsible for the anti-inflammatory activity are the phenylpropanoids. So, these compounds are tested further to obtain a safe drug that can act as a therapeutic agent for the treatment of different inflammatory diseases [12].

Table 1. Essential oils as natural anti-inflammatory agents.

Sl. No	Name of the Plant	Part Used	Main Component	Experimental Model	Mechanism of Action	References
1	<i>Thymus carnosus, Thymus camphoratus</i>	Flowering aerial parts	<i>T. carnosus</i> [Borneol (29%), Camphene (19.5%)] <i>T. camphoratus</i> [Borneol (20%), 1, 8-cineole (29%)]	RAW 264.7 and HepG2 cell lines	Inhibition of nitric oxide production; <i>T. camphoratus</i> inhibits COX-2 & iNOS	[13]
2	-	-	Citronellol, α -terpineol, carvacrol	OVA induction in male Swiss mice	Reduction in leucocyte migration and TNF- α levels, modulates COX, PGE ₂ , & H1 receptors	[14]
3	<i>Citrus limon, Citrus aurantifolia, Citrus limonia</i>	Fruit peel	Limonene, β -pinene, γ -tripinene	In vivo anti-inflammatory tests: Hot plate test, Formalin test; Subcutaneous air pouch (SAP) model	Reduce increased levels of TNF- α , IL-1 β , IFN- γ	[15]
4	<i>Citrus aurantium</i> L.	Fresh blossoms	Linalool	Inflammatory paw edema test, cotton plate-induced granuloma	Inhibition of expression of prostaglandin synthesis through the COX pathway, inhibits formation or release of nitric oxide	[16]
5	<i>Boswellia ovalifoliolata</i>	Leaves and bark	Bark [β -Farnesene, caryophyllene oxide, etc.]; Leaves [spathulenol, caryophyllene oxide]	In vitro test: albumin denaturation assay	-	[17]

3. Nanotechnology

Nanotechnology is the technology that has developed from nanoscience that is based off of the nano size range (1–100 nm). This means all the byproducts of the technology has this size range and therefore, can be identified as a characteristic feature. As the dimension of the nanotechnology has been reduced in such lower numbers, the overall properties of the products also change and it affects the effectivity and efficiency. Primarily, the physicochemical properties of the materials that are reduced to the nanoscale are greatly affected. This technology is very important because the ratio of volume to surface area is increased and thus the potency of the products is enhanced. Due to the low size, it has no problem in crossing the cellular barrier for which the technology finds its uses in medicine. Many-a-time, the biological entities are of large molecular sizes

which limit their uses within the body as they cannot bind with any receptors. But nanotechnology helps to reduce these structures to the nanoscale which increases the potency. The production process of this technology can be primarily carried out through the Top-Down Approach and the Bottom-Up Approach. Among the two, the latter is the better and it involves self-assembly of the components [18-20].

Some of the different byproducts of nanotechnology are nanoparticles, nanofibers, nanocomposites, nanoplate, etc. [21]. Among the examples given, nanoparticles are unique due to their agglomeration state, morphology, and dimension. The nanoparticles like liposomes, metal, and metal oxide nanoparticles, can be used in different areas like medicine, electronics, environment, etc. Further applications have been described in Figure 1. As far as medicine is concerned, uses are found in drug delivery systems, biosensors or diagnosis, DNA-transfecting agents, and therapeutic agents [22]. Clinical trials are carried out with the aim of marketing the nanoparticles as therapeutic agents. Some of the approved formulations are VYXEOS, Patisiran/ONPATPRO, and NBTXR3/Hensify [23]. Therefore, it can be understood that nanoparticles have a promising future.

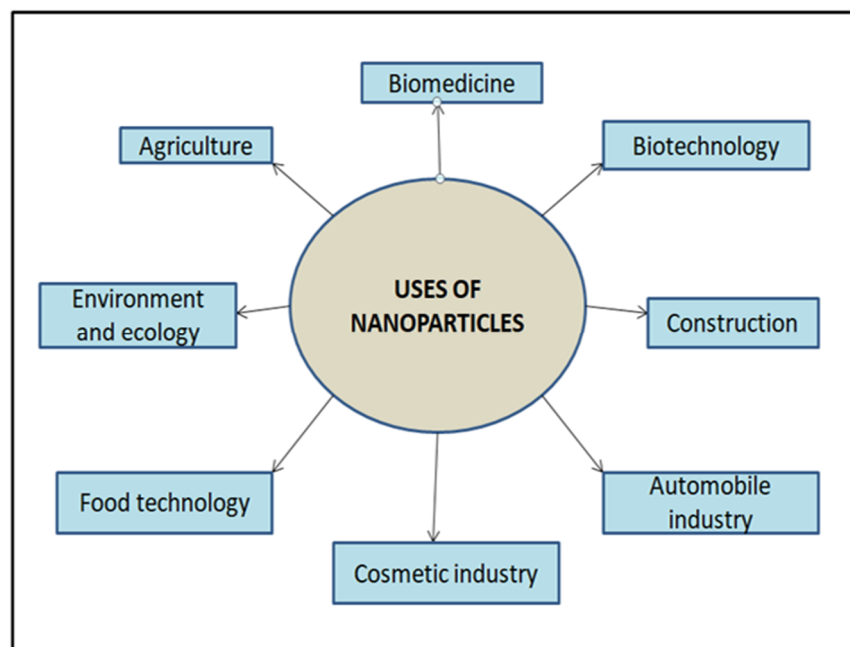


Figure 1. Application of Nanoparticles in different aspects of human life.

3.1. Metal Nanoparticles

Metal or metallic nanoparticles utilize metals like gold, silver, zinc, etc. for added health benefits. These metal ions acts as reducing agents and help in the formation of the nanoparticle. Production of metal nanoparticles can be carried out by methods like mechanical milling, sputtering, green synthesis, electrochemical decomposition, microwave assisted preparation, etc. The different methods have different pros and cons. For instance, the advantage of using green synthesis method is that it is economical, flexible, and the final product is homogeneous which shows the effectively of the process. The disadvantage of the same is that there is a safety risk as bacteria, fungi, etc. are used [24].

3.1.1. Silver Nanoparticles

Silver nanoparticles utilized the silver ion which is then reduced with the help of a reducing agent. The green synthesis method is often utilized for the synthesis of silver nanoparticles. This bio-method is overall an ecofriendly approach, which is also cost effective [25]. As shown in the work carried out by Shaik et al., where the extract of *Organum vulgare* plant was used as a bioreducing agent and thus prepared silver nanoparticles [26]. These nanoparticles have excellent electrical conductivity and thermal con-

ductivity which increases its utility in the physical world. At a larger scale it is utilized for being a good antibacterial agent who also possesses less toxicity [27]. Also, adding the plant extract rich in antibacterial components for the synthesis of silver nanoparticles increase the efficiency of the final product. Like, *Lysiloma acapulcensis* when used for preparation of silver nanoparticles shows a higher potency than the chemically produced silver nanoparticles along with less cytotoxicity [28].

4. Anti-Inflammatory Potential of Silver Nanoparticles

One of the essential biomedical applications of the nanoparticle is as an anti-inflammatory agent. Sole metallic nanoparticles containing silver have intrinsic anti-inflammatory effects [29]. This activity has been explained in Figure 2. When it is produced along with plant materials or biological materials, like the antibacterial activity mentioned before, the anti-inflammatory effect also shows synergistic action. Some examples have been presented in Table 2.

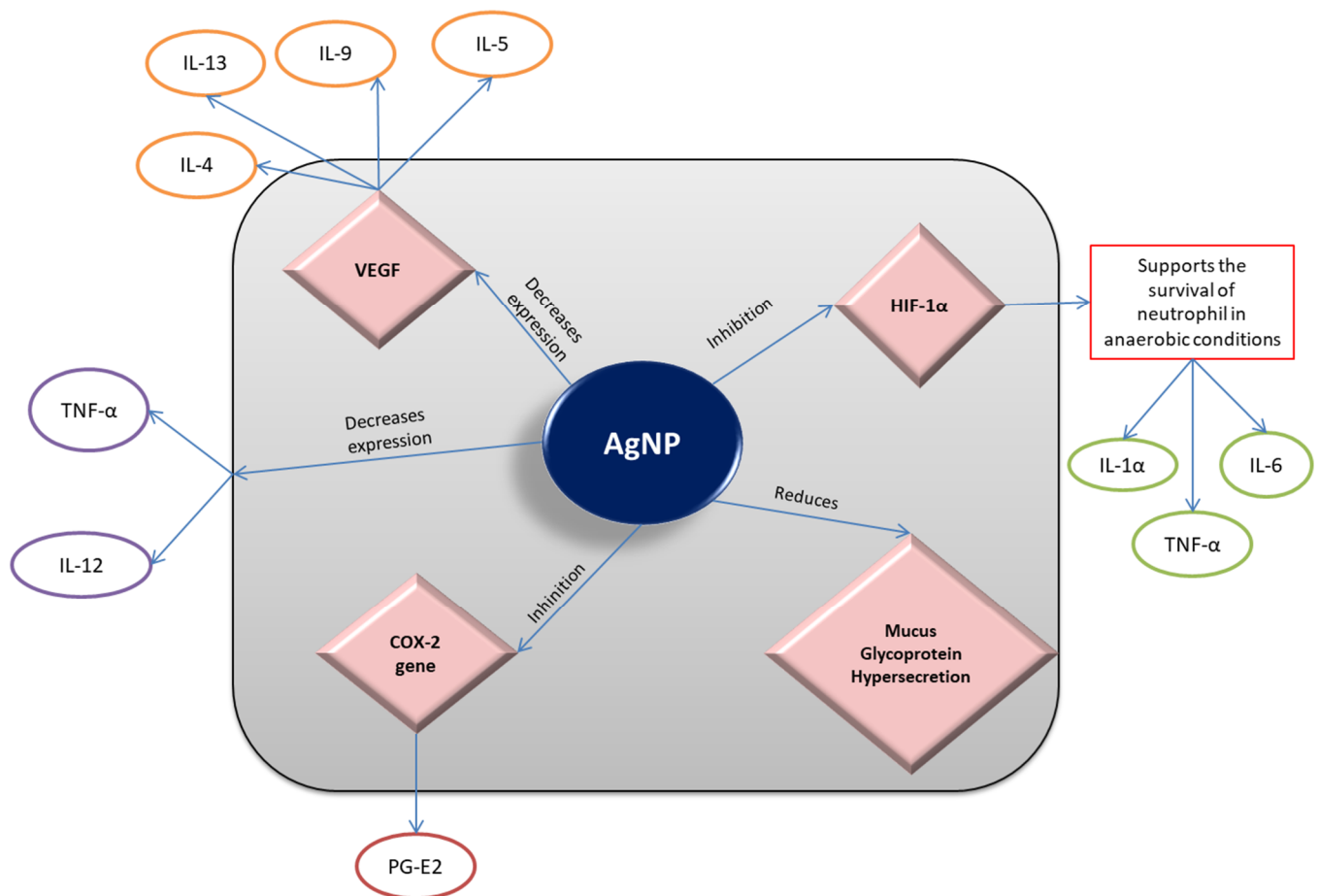


Figure 2. Mechanism of action of Silver Nanoparticles as an anti-inflammatory agent adapted from [30].

Table 2. Silver Nanoparticles having anti-inflammatory activity.

Sl No.	Biological Material Used	Characteristics of the Nanoparticles	Inflammation Model Used	Mechanism of Action	References
1	Leaves of <i>Atropa acuminata</i>	Size: 5–20 nm; Shape: Spherical	In vitro model: Albumin denaturation assay, Anti-proteinase activity	-	[31]
2	Leaves of <i>Salvia coccinea</i>	Size: 24 nm; Shape: Spherical	THP-1 cell line	Inhibition of oxidative stress transcription factor NF- κ B	[32]
3	Petals of <i>Rosa indica</i>	Size: 23.52–60.83 nm; Shape: Spherical	Rat peritoneal macrophages	Inhibition of the production of nitric oxide and superoxide	[33]
4	Seeds of <i>Acranythes aspera</i> Linn.	Size: 20–35 nm; Shape: Cuboidal, rectangular	Carrageenan-induced in albino rat	Inhibition of paw edema	[34]

5. Anti-Inflammatory Potential of Essential Oil-Mediated Silver Nanoparticles

As mentioned before, there is a high tendency of increment of the anti-inflammatory ability once metallic nanoparticles are produced with the help of plant products which already show anti-inflammatory activity. Similar can be the case with silver nanoparticles produced from essential oil as reducing agents. Table 3 shows the literature available where already such nanoparticles have been formed which has shown anti-inflammatory activity.

Table 3. Anti-inflammatory activity of essential oil-mediated silver nanoparticles.

Sl. No.	Plant Name	Characterization	Experimental Model	Reference
1	Ginger (<i>Zingiber officinale</i>)	UV-Vis spectroscopy	In vitro assay; Inhibition of albumin denaturation assay	[35]
2	Cumin	UV-Vis spectroscopy	In vitro assay; Inhibition of albumin denaturation assay	[36]

6. Conclusions

Medicinal plants have been a great source of medicine and therapy. There are similarities in between plants and animals including human beings at cellular and molecular levels due to which the molecules produced by the plants are easily accepted by the human body without any major side effects. Ayurvedic system of medicine suggests using metallic compounds during preparation to potentiate the therapeutic activity of drug.

Therapeutic application of essential oil as an anti-inflammatory, anti-microbial, insect repellent, etc. is well known. There is a high tendency of increment of the anti-inflammatory activity once metallic nanoparticles are produced from the plants showing anti-inflammatory potential.

7. Future Prospects

In the literature that is available regarding the synthesis of silver nanoparticles using essential oil is very limited. In most of the cases the characterization studies of the final product is incomplete. When it comes to assessing biological activities, animal models have not been used and the tests are limited to in vitro studies only. Also, due to the lack of animal studies, the mechanism of action is also unknown. Considering the global burden of inflammation and the deaths that occur due to chronic inflammation, there is certainly an urgency that needs to be addressed. This creates a huge scope for future scientists to explore the field and fill in the gaps.

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