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Review on pharmacological activity (inflammation) of plant extracts & green synthesized Ag nanoparticles

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Abstract
The aim of this review research was to evaluate the anti-inflammatory activity of the extract of *Tinospora cordifolia* (Guduchi), Aloe vera, *Withania somnifera* and its green nanoparticles derivatives (Ag, Au etc). Tinospora, Cordifolia (Guduchi) is a large, glabrous, perennial, deciduous, climbing shrub of weak and fleshy stem found throughout India. It is a widely used plant in ancient era and Ayurvedic systems of medicine. The chemical constituents reported from this shrub belong to different classes, such as alkaloids, diterpenoid lactones, glycosides, steroids, sesquiterpenoid, phenolics, aliphatic compounds and polysaccharides. *Withania somnifera* is commonly known as Ashwagandha. It belongs to Solanaceae family. It has anti-arthritic, anti-bacterial, anti-dote for scorpion sting, anti-stress, anti-tumour and anti-cancer activities. Potential medicinal properties of T. Cordifolia (Guduchi) and *Withania somnifera* extract reported by scientific research include anti-diabetic, antipyretic, antispasmodic, anti-inflammatory, and even in anti-arthritic, antioxidant, anti-allergic, anti-stress, antimalarial, hepato-protective. Biosynthesis of silver nanoparticles (AgNPs) from silver nitrate solution using water extract of *Myrmecodia pendans* (Sarang Semut) at room temperature was successfully carried out. The AgNPs obtained were characterized by UV-vis, XRD, FT-IR, SEM and TEM. The typical surface Plasmon resonance of the Ag NPs was observed at around 448 nm.

Keywords: Inflammation, herbal extracts, Aloe vera, *Withania somnifera* and *Tinospora cordifolia*, Ag nanoparticles

Introduction
Today, people around the globe are giving preference to alternative medicines such as ayurveda, naturopathy, homeopathy and herbal medicine. Herbal medicine is cost effective and less expensive than the medicines bought from an allopathic pharmacy. Increasing realization of the side effects of allopathic medicines, coupled with the growing awareness about the medicinal benefits as well as therapeutic effect of herbal products is pushing up the demand for herbal extracts, dietary supplements and herbal-based beauty aids worldwide. Herbal nano medicines have been widely used all over the world since ancient times and have been recognized by physicians and patients for their better therapeutic value as they have fewer adverse effects as compared with modern medicines. Herbal therapeutics can be achieved by Drug Delivery systems. This herbal treatment helps to increase the therapeutic value by reduce the toxicity and side effects of drugs at the same time it also increase the bioavailability. In this approach Nanotechnology plays a great role and the use of nanotechnology in medicine and more specifically drug delivery is set to spread rapidly. The inflammation is protective process that protects the body against harmful stimuli caused by pathogenic bacteria, virus and endogenous triggers. During inflammation, person shows signs like redness, swelling, burning sensation, pain and loss of function of their respective organ or complete breakdown of systemic body metabolic functions. Mechanism of inflammation is to work on the site of injury by increasing the blood supply by vasodilatation of vessels. Inflammation pathway is a complex pathway which involves enzyme activation, innate cell activation and tissue repair which act to repair the damage of injury. Migrated immune cells are macrophage and T lymphocyte that activates the release of pro-inflammatory cytokines. Inflammatory is an initial or primary response of the body which is not specific for any injury. Inflammation is mainly of two types Acute inflammation & Chronic inflammation [1-6].

Types of inflammation

Acute inflammation helps the body to heal after the injury. Immune cells, enzymes, reactive oxygen species all combine at the specific place to remove the injury and repair the tissue damage. Acute inflammation helps to treat at pro-inflammatory level. If the damage is repaired the pain stops, new tissue is been replaced and swelling disappears. Chronic inflammation sometimes leads to mutation and that may lead to carcinogenic and thereafter causing cancer. The chronic inflammation in inflammatory bowel diseases and prostatitis shows increase in development of cancer. Chronic inflammation creates a microenvironment that facilitates transformation, malignancy and metastasis of cells. Occurring of chronic inflammation might be due to high amount of free radical and depletion of antioxidant mechanism. Chronic inflammation accompanied by oxidative stress has been linked to various steps involved in tumour, such as cellular transformation, promotion, proliferation, invasion, angiogenesis, and metastasis. Inflammation can be treated by various ways as process is multifaceted. Inflammatory mediators, free radical activity and oxidative stress have been found to be attractive anti-inflammatory targets. The difference between the two inflammatory processes is given in table below [7-8].

Table 1: Difference between types of inflammation (9)

Process	Acute inflammation	Chronic inflammation
Initiators	Microbial surface antigen andfragments	Non digestible microorganisms
	Injured tissue and fragments	Non-degradable foreign matter Auto-immune reactionscytokines from T-lymphocytes
Macrophage mediators	Histamine	Prostaglandins
	Prostaglandins, leukotrienes	Proteases
	Bradykinin	Reactive oxygen species
	Lysosomal contents	Complement
	Complement molecules	Plasma cells
Cell types	Neutrophils	Macrophages, fibroblasts
	Macrophages	Prolonged onset
Time course	Acute onset	Weeks to years
	Minutes to hours	Resolution
Outcome	Resolution	Tissue destruction
	Abscess formation	Fibrosis
	Chronic inflammation	Degenerative disease

Materials and Methods

Inflammatory mediators

Inflammation is mediated by chemokines that include tumour necrosis factor (TNF)-α, nuclear factor kappa beta (nfκβ), interferon (IFN)-γ, nitric oxide and interleukins. Most of the mediators synthesized in injured tissue or by migrated immune cells during an inflammatory event. Pathogenic bacteria activates nuclear factor kappa beta cells (NF-Kβ) through receptors present on the macrophages by signalling pathways.

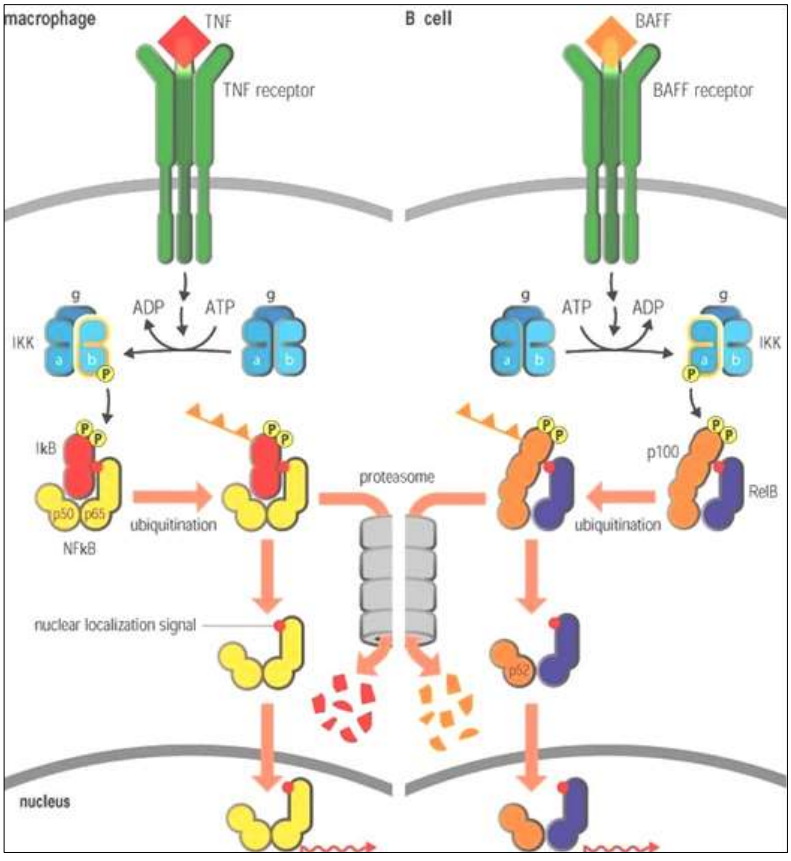

Fig 1: Nnuclear factor kappa beta pathway that activates inflammatory gene expression [9]

Tumour necrosis factor- α (TNF-α) activated by macrophagesproduces other inflammatory mediators including prostaglandin and nitric oxide. The transactivation of the gene is by liberation of nfκβ from its inhibitor molecule (Ikb-α). The Ikb entraps the nuclear locator signal that allows the nuclear factor to move into nucleus and promotes gene expression.

The removal of iκβ is facilitated by IK kinase (IKK) that can be activated by TNF receptor or by the presence of large quantities of free radicals in the cell. The presence of large quantities of free radicals produces the conditions that allow the release of nfκβ from its cytosolic inhibitor Ikb. Iκβ undergoes phosphorylation by IKK which is followed by ubiquination. The ubiquination tags the inhibitor molecule for degradation by proteasomes. Nfκβ is then able to move into the nucleus to promote transcription of Cyclooxygenase (COX-2) and Inducible nitric oxide synthase (inos) genes [11-13]. The inflammatory response triggers the induction of enzymes that catalyse the production of important mediators. Cyclo-oxgenase-2 and inducible nitric oxide synthase are two examples of enzymes whose expressions are increased during inflammation. COX enzyme are membrane bound glycoprotein present in endoplasmic reticulum. Arachidonic acid is converted by cyclooxygenase enzymes to prostaglandin, the precursor molecule for all the eicosanoid molecules thatinclude prostaglandins and thromboxanes [14, 15].

Inhibition of inflammation

Inflammation can be resolved by inhibiting inflammatory mediators, quenching of radicals and by prevention of oxidative stress. Inhibition can be reversible or irreversible depending on the pathway been targeted. To inhibit the expression of mediators, NFK-β is attractive target for expression of inducible enzyme. Preventing of NFK-βtranslocation to the nucleus would result in less COX-2 and nitric oxide synthesis (Inos) expression which could reduce or eliminate the inflammatory response [15, 16]. Inhibiting the expression of enzyme by NFK-β would reduce the risk of rheumatoid arthritis and atherosclerosis. The potential of inhibiting the translocation of NFK-βfor anti-inflammatory effect would probably prevent the adverse effects associated with inhibiting constitutive forms of the enzymes. Targeting inflammatory mediators by means of therapy for inflammatory condition inhibits COX enzyme.

Results and Discussion

Current treatment for inflammation and oxidative stress using plant extracts

Analgesic relieves pain without affecting its cause. In current treatment of inflammation Narcotic, steroidal and non-steroidal (nsaids) are the options available in present scenario. However, the available drugs have reduced efficacy against inflammatory conditions due to adverse effects and relatively high potency. For example, steroidal drugs are in use as anti-inflammatory due to their specific mechanisms of action that are considered to be responsible for their adverse effects as well. Steroidal anti-inflammatory inhibit basal physiological function such as leukotriene inhibition. The side effects include hypertension due to analogy of the steroidal drugs to the steroid hormones. The non-steroidal drugs have relatively fewer and less adverse effects than the steroidal that include gastrointestinal bleeding and improper clotting of blood. Now there is a need for treatment which have effect of steroidal and nsaids drug. By selecting the inhibition and expression of COX-2 can reduce the inflammatory response. The currently available COX-2 selective inhibitors are Celecoxib and Roxecib [16]. These clinical drugs have been found to be effective selective COX-2 inhibitors. However, they also are been considered cardio, nephrotoxic and hepatotoxic effects. Two synthetic COX-2 inhibitors, Rofecoxib and Celecoxib is now been banned in the market due to its side effects. Selective inhibition of COX-2 should possess high potency to relieve inflammation and possibly prevent diseases. The inhibitors should have side role of quenching free radicals. Aspirin, diclofenac sodium has also shown potent activity for COX enzyme. Recent studies have shown that vitamin E, a known antioxidant is able to inhibit COX enzyme. Other currently available antioxidant synthetic compounds are Butylated hydroxytoluene (BHT) and Butyrate hydroxyanisole (BHA). The antioxidants are used as food additives and supplements to prevent and or remove oxidative species. But still they possess two compounds have been found have adverse effects that include carcinogenesis, liver and kidney toxicity. Inspite of adverse effect of nsaids they show activity against the numerous cancers. Now our target should be to treat inflammatory effect with the minimum adverse effect and also prevent chronic inflammation and degenerative diseases. Plants have played a remarkable role in health care since the ancient times. Traditional plant based medicines still exert a great deal of importance to people living in developing countries and also lead to discovery of new drug candidates [17-20].

Accordingly, therapeutic agents suitable for the treatment of chronic inflammatory diseases are highly desirable, which has resulted in an increased interest in complementary and alternative medicines. Large number of herbal species has been used traditionally or as folk medicines against inflammatory ailments. Many of them have been studied scientifically and proved to be beneficial anti-inflammatory agents. The success has been attained to isolate various single chemical entities responsible for anti-inflammatory activity. The core chemical classes of anti-inflammatory agents from natural sources have been usually reported to engage a vast range of compounds such as polyphenols, flavonoids, terpenoids, alkaloids, anthraquinone, lignin, polysaccharides, saponins and peptides. Still many herbal folk medicines for inflammation and rheumatism have not undergone through scientific investigations and careful assessment of their toxic effects. Hence, it is a need of time to consider all such folk use based herbal medicines for determining their pharmacological activities, isolating the single drug entity responsible for anti-inflammatory effect and developing suitable formulation, beneficial against inflammatory disorders.

Plants at present have become a focus study in new therapeutic agent to have treatment for anti-inflammation and chronic disease. To reduce the chemotherapeutic toxicity in cancer patients an alternative and complementary treatment regimen is the need of the hour**.** Natural products have proved to be reliable source of new therapeutic agent. Medicinal plants have become important in the health of individuals and their value lies in their ability to produce compounds that could have a therapeutic effect in the body. Secondary metabolites are complex substances that are synthesized from relatively simple molecules such as

glucose and water. Photochemical could serve as proto types for development of more effective and less toxic medicine. The low toxicity of the plant derived anti-inflammatories has been attributed to the compounds being biological in nature and, therefore, metabolism by the body would be easier. Several phytoconstituents from *Tinospora cordifolia* Aloe, and *Withania somnifera* have been found to have COX-2 inhibitory activity [21, 22].

Tinospora cordifolia

Various properties of T. Cordifolia, described in ancient texts of Ayurveda, like Rasayana, Sangrahi, Balya, Agnideepana, Tridoshshamaka, Dahnashaka, Mehnashaka, Kasa-swasahara, Pandunashaka, Kamla-Kushta-Vataraktanashaka, Jwarhara, Krimihara, Prameha, Arshnashaka, Kricch-Hridroganashak, etc., are acquiring scientific validity through modern research adopting "reverse pharmacological" approach. *Tinospora cordifolia* (Willd.) Hook. F. And Thoms. (Guduchi) is a large, glabrous, deciduous climbing shrub, belonging to the family Menispermaceae. It is distributed throughout the tropical Indian subcontinent and China, ascending to an altitude of 300 m. In Hindi, the plant is commonly known as Giloe, which is a Hindu mythological term that refers to the heavenly elixir that has saved celestial beings from old age and kept them eternally young. In Ayurveda, T. Cordifolia is regarded high for its medicinal values. The entire plant is used for medicinal benefits. However, higher activities are attributed to its stem. The phyto-constituents present in the plant belong to different classes of compounds such as alkaloids, diterpenoids, lactones, glycosides, steroids, phenols, aliphatic compounds and polysaccharides [5].

Aloe barbadensis (Aloevera)

Aloe barbadensis commonly known as aloe vera belongs to liliaceae family. In Ayurveda it is called *kathalai*. Matured leaves are present on the outward region of rosette. 98.5% water is present in the leaf. The residual solid material approximately 0.5 to 1% consists of a range of compounds which include vitamins which are water-soluble and fat soluble, minerals, enzymes, polysaccharides, phenolic compounds and organic acids. The structural components of leaf portions of the *Aloe vera* plant, the rind was found to compose 20-30% and the pulp 70-80% of the whole leaf weight. On a dry-weight basis, the rind and pulp contain 2.7% and 4.2% lipids, and 6.3% and 7.3% proteins, respectively. The percentages of soluble sugars is around 11.2% and 16.5%, primarily as glucose, and the percentages of ash is 13.5% and 15.4%, in particular calcium, were relatively high in the rind and pulp, respectively. Non-starch polysaccharides and lignin represented the bulk of each leaf fraction and were found to be 62.3% and 57.6% of the dry weight of the rind and pulp, respectively. Its Medicinal use is one of the best medicinal plant used since long periods in skin burns, cuts, eczema, etc. It is not only useful in the inflammatory responses but also used in treating stomach alignments, gastrointestinal problems, skin diseases, constipation, anti-ulcer, diabetes and radiation injury. Now days this plant is mainly used in cosmetic field and nutraceutical. Aloe vera leaves contain phytochemical like mannans, polymannans, anthraquinone like emodin and various lectins. Aloin is the main component of aloe vera. Aloin if present in higher amount in aloe vera causes toxic effect and also possess side effect [7, 17, 18].

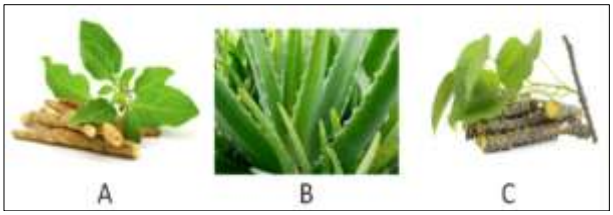

Fig 2: *Withania somnifera*n, Aloe vera and Tinospora cardiofolia plant images

***Withania somnifera*n (Ashwagandha)**

Withania somnifera is commonly known as Ashwagandha. It belongs to Solanaceae family. It has anti-arthritic, anti-bacterial, anti-dote for scorpion sting, anti-stress, anti-tumour and anti-cancer activities. It is used in toning of uterus, consumption, dropsy, leucoderma, impotence, rheumatism, debility from old age, ulcer, sexual and genital weakness, assumption, rheumatic swelling, loss of memory, loss of muscular energy, spermatorrhoea, syphilis, sterility of women, blood discharge, leucorrhoea, anaemia with emaciation, nervous exhaustion, multiple sclerosis, neoplasia, cancer and fatigue. Fruits and seeds are diuretic and used in coagulation of milk.

Green synthesized Ag nanoparticles

Silver nanoparticles have a special role in modern anti inflammation and anticancer therapy, being explored for detection and diagnosis of malignant tumors, controlled and externally triggered drug delivery systems. In a similar way with the antimicrobial activity of agnps, their efficiency against cancer cells require the cellular uptake of nanosilver, which can be acquired by diffusion, phagocytosis, pinocytosis and receptor-mediated endocytosis. The size, morphology and surface properties of agnps are favorable for internalization by cancer cells, which results in local release of silver ions and oxidative stress. Such events further cause the death of cancer cells, either by (i) apoptosis, which occurs due to alteration of mitochondria and generation of imbalance between antiapoptotic proteins and proapoptotic kinases, and (ii) structural and functional impairment of cellular substructures, which occurs due to specific interactions with silver nanoparticles and ions. A novel burn wound ointment consisting of sheep's tail ointment loaded with plant extract capped silver nanoparticles. The silver nanocrystals in the ointment serves as an anti-inflammatory agent. The silver nanoparticles was developed *via* the biological method with the assistance of the medicinal plant *Rhodiola rosea*. The characterization of silver nanoparticles was assessed using XRD, SEM, UV-PL spectroscopy and EDX techniques. The formation of silver nanoparticles was confirmed by UV-Vis spectrum at the absorbance of430 nm, [26] and the biomolecules responsible for reducing and capping the silver nanoparticles were characterized by Fourier transformation infrared spectroscopy. The as synthesized silver nanoparticles regulated both pro-inflammatory and anti-inflammatory gene expression, thereby promoting burn wound closure on BALB/c mice. The developed silver nanoparticles -loaded ointment has the potential to be applied in the medicines [27-30].

Conclusion

It appears that the *withania somnifera* was more efficant than the *Tinospora cordifolia* & Aloe vera, in any case the

over preclinical tests as it were allow us an thought approximatelythe anti-inflammatory action, of *withania somnifera* and Tinosopra cordifolia but huge scalec linical trials are vital for last appraisal. The present review findings give directions for economically feasible and eco-friendly method for green synthesis of silver nanoparticles. Since this method does not involve the use of any hazardous chemicals, the strategy for synthesis is called 'green synthesis of silver nanoparticles' also. In this study, to understand the acting mechanism of plant phytochemicals on silver nitrate deeply, we identified the biomolecules of stem extracts and studied the interaction between plant phytochemicals and silver nitrate through UV. Studies have revealed that water-soluble phytochemicals such as flavonoids and phenols are responsible for the immediate reduction and stabilization of silver nanoparticles. T obtain small size silver nanoparticles with higher stability, synthesized method was carried out at different conditions such as concentration of silver nitrate solution, ratio of extract to silver nitrate solution, reaction temperature and time. The effect of these conditions on the synthesis of plant extract capped nano-silver was monitored by UV-Visible spectrophotometer at a resolution of 1 nm from 300 to 700 nm. Further confirmation of the size and phase of synthesized silver nanoparticles at optimized conditions were determined by diffraction method or XRD. According to the review of inflammation, the expression of IKK was inhibited by CGlcN. Furthermore, the level of the cytoplasmic phospho-IκBα protein was also decreased, in a dose-dependent manner, after treatment with CGlcN. This indicates that IκB binds to NF-κB to make an inhibitory complex.

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