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Green Synthesized Silver Nanoparticles: A Promising Anti-Inflammatory and Antioxidant Compound

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Abstract

Oxidative stress and inflammation are linked pathophysiological conditions that have a major role in many chronic disease. Recently, agents with antioxidant activity have been implicated in the development of new therapeutic strategies. Therefore, it seems that management of oxidative stress by agents with antioxidant capacity may have a positive therapeutic effect on chronic diseases including disorders associated with inflammation. Based on recent researches biosynthesized silver nanoparticles (Ag-NPs) seem to have the potential to ameliorate inflammation and oxidative stress. In this regard, evidences from recent researches on the anti-inflammatory mechanism of the biosynthesized Ag-NPs are discussed here.

Keywords: Inflammation; Oxidative stress; Biosynthesized silver nanoparticle

Introduction

In recent years, nanostructured noble metals including silver nanoparticles; have gained considerable attention in the field of medicine due to their application in drug delivery, diagnosis and treatment of disease such as cancer. Among several methods which have been developed to produce nanoparticles, chemical, physical and biological approaches are the most popular [1]. Synthesis of silver nanoparticles (Ag-NPs) by physical and chemical methods requires considerable amount of energy and generates large amounts of toxic chemicals or hazardous substances. Therefore, obtaining nanoparticles using clean, non-toxic and environmental friendly procedures which follow the “green chemistry” principles had significant impact on nanotechnology. Biological methods or green chemistry approaches of nanoparticles using microorganism, enzyme and plant or plant extract have been suggested as possible ecofriendly alternatives to chemical and physical methods [2-6]. Using plants as reducing and capping agent for Ag-NPs synthesis, is advantageous over other biological processes by eliminating the elaborate process of maintaining cell cultures in addition to being cost effective [7]. Furthermore, phytochemical synthesis of

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Ag-NPs is also suitable for large-scale production of nanoparticles. Each Ag-NPs have unique mechanical and physicochemical properties due to their increased relative surface area and quantum effects, favoring their usage in various applications [1]. Several biological effects of biosynthesized Ag-NPs including antibacterial, antifungal, anti-inflammatory and anti-oxidative activities have been studied by researches [8-10]. Biological properties of nanoparticle are dependent to their size, shape and capping agent. Therefore, design and production of Ag-NPs with natural antioxidants could reduce ROS production and have significant effect on inflammation and also protect the cell proteins and lipids; thus counteract the adverse reactions [11]. So far it is clear that commercial nanoparticles; which are commonly produced by chemical methods; are not able to have the same biological properties (e.g. anti-oxidative or anti-inflammatory activity) as Ag-NPs synthesized by plants [12,13].

Oxidative stress is a major concern that can activate a variety of inflammatory pathways leading to chronic conditions including cancer, diabetes and cardiovascular, neurological and pulmonary diseases. Although, synthetic drugs have been proved to be effective for controlling inflammatory disorders, but adverse effects of these medications causes an increasing interest on the development of alternative tools that exhibit novel mechanisms of action from different origins [14]. In this regard, the phytochemical synthesis of Ag-NPs using plants or fruits offers alternative therapeutic options effective against a wide variety of diseases. Several studies demonstrated that Ag-NPs possess remarkable inhibitory effect against microorganisms as well as free radical scavenging and anti-inflammatory properties. However, a better understanding of their biological mechanisms of action and the appropriate uses as delivery systems are needed in the prevention and treatment of inflammation. Hence, evidences from recent researches on the anti-inflammatory mechanism of the biosynthesized Ag-NPs are discussed here.

Discussion

Inflammation and oxidative stress are closely related pathophysiological condition, one of which can be easily induced by another. Both of these processes are the underlying cause of many chronic conditions such as multiple sclerosis, diabetes, rheumatoid arthritis and coronary artery disease [15]. Therefore, agents with synergic antioxidants and anti-inflammatory activity are considered in treatment of these chronic diseases.

There are evidences demonstrating that carrageenan-induced inflammatory response is linked with the production of ROS [16,17]. In this regard, recent studies demonstrated that biosynthesized Ag-NPs are able to inhibit the inflammation induced by carrageenan. Moreover, Ag-NPs inhibit UVB irradiation-induced skin inflammatory edema, cytokine production, myeloperoxidase activity and oxidative stress. During an inflammatory response, several pro-inflammatory mediators are released, including interleukin-1 beta (IL-1β), IL-6, tumor necrosis factor alpha (TNF-α) and Interferon gamma (IFN-γ). These mediators have important functions in the initiation and amplification of inflammatory processes. The same happens during inflammation caused by carrageenan in mice paw. Inflammation induced by carrageenan is a biphasic event and the release of the neutrophil-derived free radicals, nitric oxide (NO) and pro-inflammatory cytokines such as TNF-α, IL-6 and IL-1β occurs during the delayed phase [18]. As mentioned in introduction, several studies have confirmed the antioxidant and anti-inflammatory properties of Ag-NPs. Moldovan et al. demonstrated that Ag-NPs synthesized by black elderberry fruit extract exhibit promising antioxidant activity and hence have a great potential in the development of therapeutic agents against oxidative tissue injuries [11]. Moreover, David et al. reported that Ag-NPs synthesized by black elderberry possess remarkable anti-inflammatory properties. It was shown that Ag-NPs are able to decrease cytokines production in HaCaT cells exposed to UVB radiation and reduces psoriasis lesions in human. Furthermore, it is reported that pre-administration of Ag-NPs is responsible for the reduction of edema via ameliorating cytokines levels in the paw tissues [19]. El-Rafie and Hamed reported that the synthesized nanoparticles by *Terminalia* species have antioxidant activity due to the capped phenolic and flavonoid compounds and can be used against deleterious effects of free radicals and have powerfully anti-inflammatory activity [20]. Mani et al. evaluated the *in vitro* anti-Inflammatory activity of Ag-NPs synthesized by *Piper nigrum* extract in carrageenan induced paw edema. It was shown that the synthesized Ag-NPs exert a greater inhibition of all three cytokines (IL-1β, IL-6 and TNF-α) in comparison to the commercial silver nanoparticles [12].

Another cytokine that also plays a crucial role in inflammation is IFN-γ. A recent study by Wong et al. has shown that IFN-γ induces cyclooxygenase (COX)-2 pathways and when COX is inhibited by indomethacin, IFN-γ will increase [18]. In our recent study, an optimum condition to synthesize Ag-NPs using *Chamaemelum nobile* (*C. nobile*) was developed [21]. The anti-inflammatory and antioxidant activity of the Ag-NPs against carrageenan-induced paw inflammation was also evaluated in mice. In carrageenan-induced inflammation, it was also demonstrated that IFN-γ is significantly increased by indomethacin, but is decreased by Ag-NPs synthesized by *C. nobile* compared to the control. In addition, it was also found that these synthesized Ag-NPs are able to reduce IL-1β, IL-6 and TNF-α during inflammation. On the other hand, the synthesized Ag-NPs by *C. nobile* had the potential antioxidant activity which caused a reduction in ROS level while the commercial Ag-NPs didn’t show significant anti-inflammatory and antioxidant activity [22]. Therefore, it can be concluded that the anti-inflammatory mechanism of Ag-NPs is different from that of indomethacin. Although it has been reported that high doses of Nano-materials produce ROS and can cause cytotoxicity, the results of recent studies indicate that equitable quantities of Ag-NPs will not only decrease ROS production, but also ameliorates the inflammation. Both of these reports emphasize the role of oxidative stress in the suppression of inflammation (FIG. 1). Consequently, it is suggested that the synthesis of Ag-NPs by plant extracts with antioxidant activity (e.g., C. Nobile) may improve inflammation towards ameliorating ROS production [23]. This is well-supported by the reports showing the presence of biologically active capping agents with high antioxidant capacity in these biosynthesized Ag-NPs. Since the phytochemical composition of plants are different from each other the capping agent for biosynthesized nanoparticle are different. However, studies on this issue shows that plants having high content of flavonoids and polyphenols have significant anti-inflammatory and anti-oxidative activity. Hence, it is assumed that Ag-NPs may facilitate the local accumulation and persistence of natural extracts in the inflammation zone and, consequently, an enhanced permeability and retention effect of Ag-NPs in the edema region and also Ag-NPs uptake by the lymphatic system from the inflammation site may occur [19]. In addition to the capping agent; the shape and size of silver nanoparticles is another important factor to be considered in the biological activity of Ag-NPs. By reviewing the articles which have evaluated the anti-inflammatory and anti-oxidant activity of Ag-NPs synthesized by plants we have found that all of the biosynthesized nanoparticles were spherical in shape and their size were ranging from 7 to 26 nm as revealed by transmission electron microscopy (TEM) analysis. Although, different sizes of nanoparticle had desirable results on inflammation and oxidative stress but, further studies are needed to elucidate the effect of shape and size of silver nanoparticles on their anti-inflammatory and antioxidant activity.

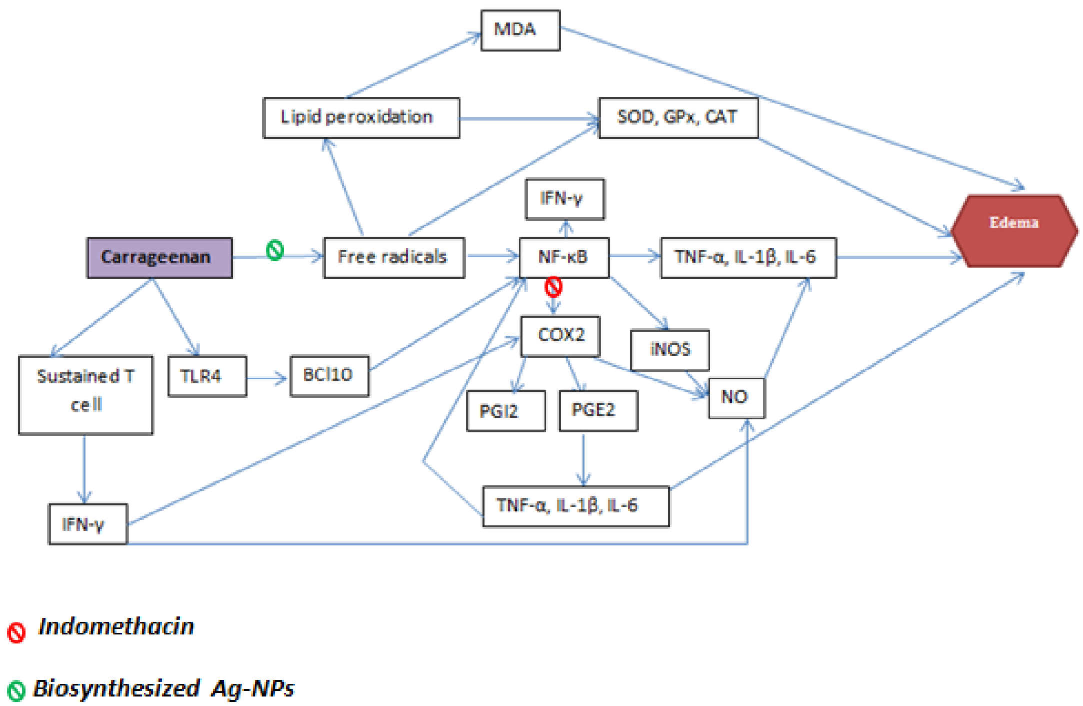

FIG. 1. **Anti-inflammatory activity of Ag-NPs and indomethacin.**

Conclusion

It is well known that ROS plays an important role in modulating the extent of inflammatory response and cell injury. Recently, the development of new therapeutic strategy against many diseases has been based on agents with antioxidant activity. Thus, it seems that management of the oxidative stress status by agents with antioxidant capacity may have a positive therapeutic impact against inflammation. In general, from different evidence it is suggested that biosynthesized Ag-NPs can provide novel, effective and safe approaches to create future anti-inflammatory therapies by their antioxidant capacity. Although these compounds are promising, but further preclinical and clinical investigation is required in this respect.

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