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# Fullerene: topical application for acne treatment


## ABSTRACT

Acne vulgaris is a common dermatological disease with a multifactorial etiology. There has been an increasing focus on the role of oxidative stress in the pathophysiology of acne in recent years. Research has indicated that oxygen radical scavengers have potential as therapeutic agents for acne vulgaris. Fullerene ($C_{60}$) is a collective term for spherical carbon allotropes that are potent antioxidants and reportedly react with various oxygen chemical species such as free radicals. It has been found that water-soluble fullerene inhibited the peroxidation of squalene induced by ultraviolet B. Moreover, Inui *et al.* reported that fullerene had a suppressive effect on sebum secretion.[1] Inui *et al.* also performed a clinical test using fullerene gel for the treatment of acne vulgaris; the mean number of inflammatory lesions decreased significantly after treatment for 8 weeks. Fullerene gel improved the acne vulgaris without causing any dryness of the skin or any changes in its barrier functions. The safety of fullerene material has been demonstrated by toxicity tests required for the approval of fullerene as an additive in quasi-drugs. These studies suggest that fullerene is a safe and novel skin care treatment for acne vulgaris. In this review, we report on aspects of the topical application of fullerene for the treatment of acne.


Acne vulgaris is one of the most common diseases of the skin and has increased in frequency over the last 50 years.[2] Skin diseases, such as acne, may not be life threatening but have been associated with depression, anxiety, and serious psychological damage in sufferers. Acne is characterised by the formation of non-inflammatory comedos and inflammatory papules, pustules, nodules, and cysts. Generally, the major pathogenic factors involved in acne are sebum overproduction, follicular hyperkeratinisation, and bacterial hypercolonisation, as well as immune reactions and inflammation. Androgens, microbes, and other pathogenic influences may also lead to acne, thus the disease has a complex pathogenesis.[3]

Sebum produced by sebaceous glands, altered follicular contents, and reactive oxygen species (ROS) may release from

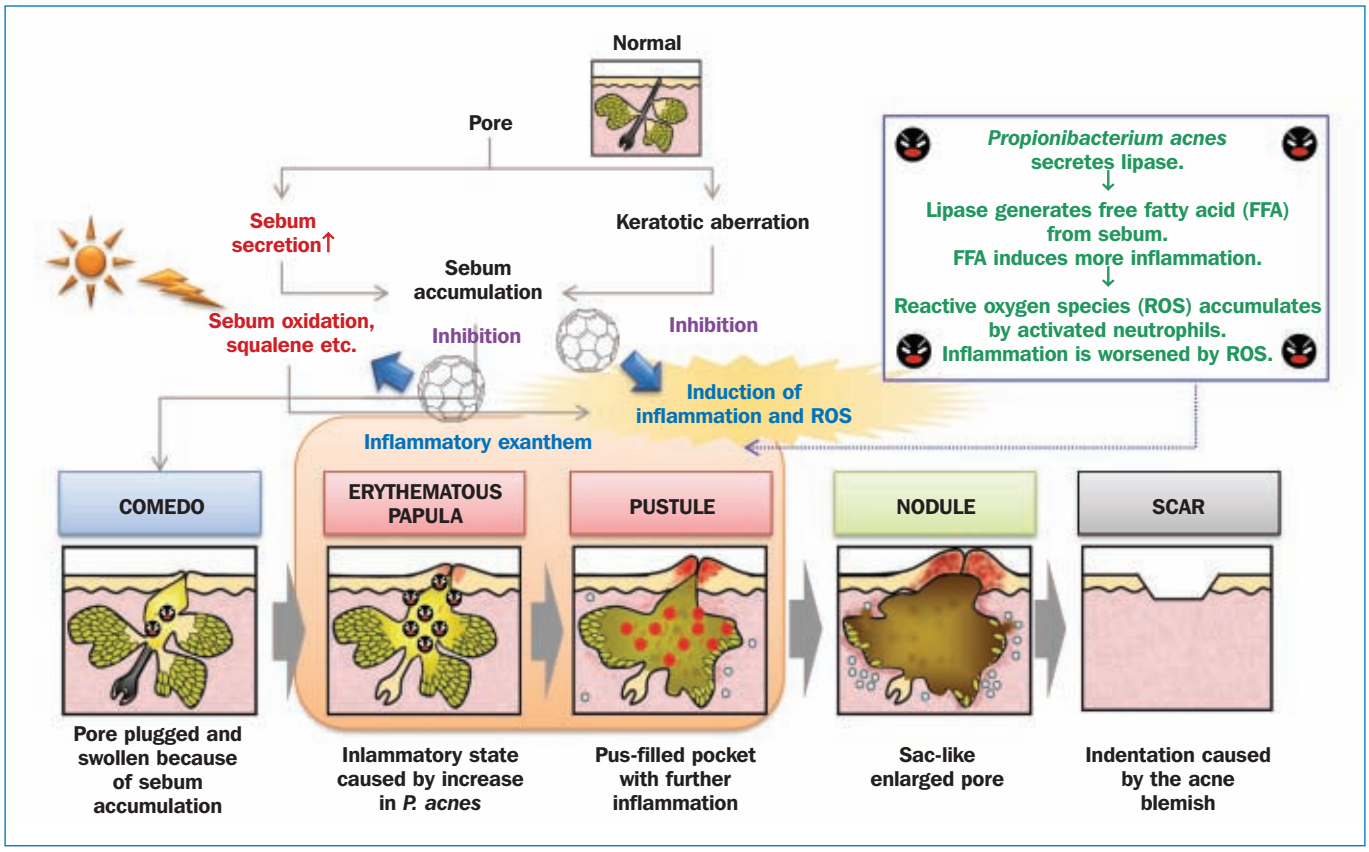


**Figure 1:** *Pathogenesis of acne and inhibition effects by fullerene.*

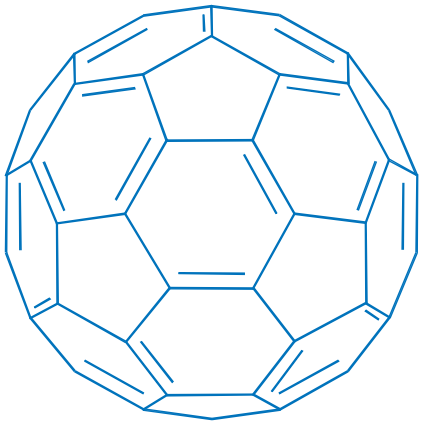

**Figure 2:** *Molecular structure of fullerene ($C_{60}$), like a soccer ball, is carbon allotrope.*

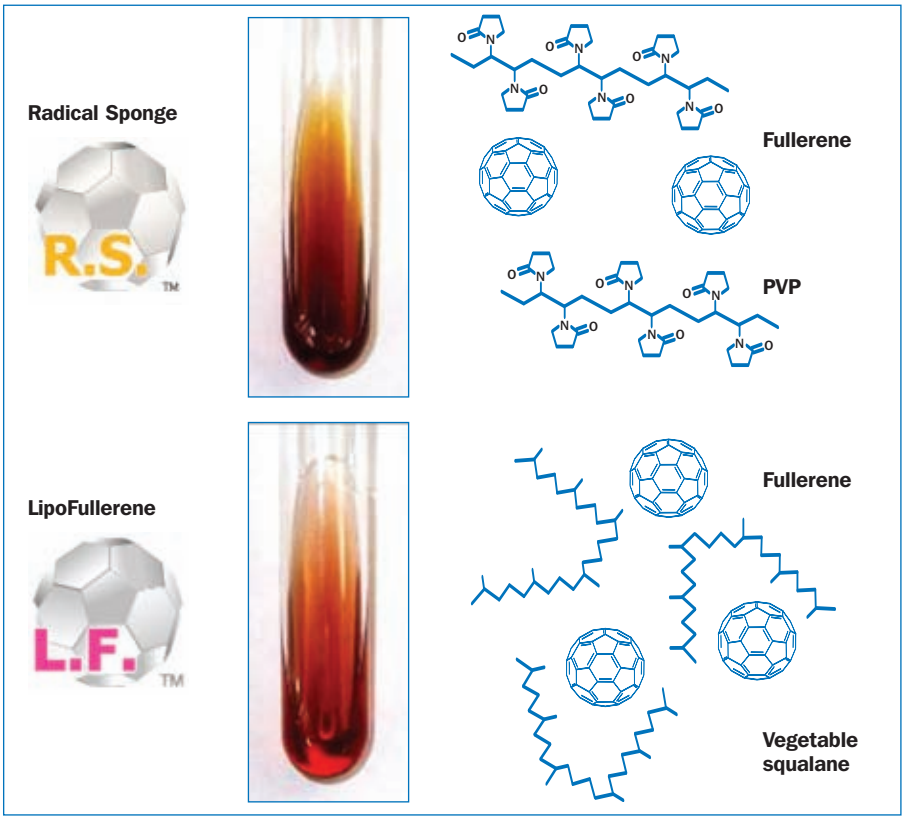


**Figure 3:** *Two types of potent antioxidant ingredients containing fullerene.*

seriously damaged follicular walls. It is thought that this process may underlie the inflammation in the pathogenesis of the disease.[4] In addition, neutrophils generate an excess of active oxygen to fight *Propionibacterium acnes*, the pathogenic bacterium responsible for causing acne vulgaris. These observations indicate that oxidative stress plays a major role in the formation of acne and antioxidants have potential as therapeutic agents for its treatment (Fig. 1).

## Applications in life science

Fullerene ($C_{60}$) is a collective term for spherical carbon allotropes, which were discovered by Kroto *et al.* in 1985.[5] Fullerene molecules have a unique cage structure consisting of twelve 5-membered rings and twenty 6-membered rings. The diameter of the carbon skeleton in a $C_{60}$ molecule is approximately 0.7 nm and that of the pi-cloud is 1.0 nm (Fig. 2). Fullerene is an electron acceptor, which can reversibly accept six electrons because its lowest unoccupied molecular orbital is at a low energy level. Due to their spherical deformation, fullerenes have a high reactivity compared with their planar state. Hence, fullerenes demonstrate antioxidative potency when they react with free radicals and ROS, such as superoxide, hydroxyl radicals, and nitric oxide, which attack lipids, proteins, DNA, and other biological macromolecules.[6] Fullerenes are expected to have applications in the field of biomedical sciences, such as in cosmetics and pharmaceuticals, because of their potent and stable antioxidant activity.

Our company focused its research on one of the bioactivities of fullerenes—their antioxidant activities. Fullerene has been marketed as an ingredient in cosmetics since 2005. Fullerene is a carbon compound that is not soluble in water; thus, it is difficult to blend with cosmetic formulations. We, therefore, developed a technique for stably dissolving fullerene in water by wrapping it in polyvinylpyrrolidone (PVP), a water-soluble polymer. Radical Sponge (a water-soluble fullerene) is the world's first fullerene-based cosmetic ingredient developed using this technique. Radical Sponge is easily formulated into water-based cosmetics, which is a very stable material. In 2009, LipoFullerene (an oil-soluble fullerene in which fullerene is dissolved in vegetable squalene) was developed as a cosmetic ingredient for

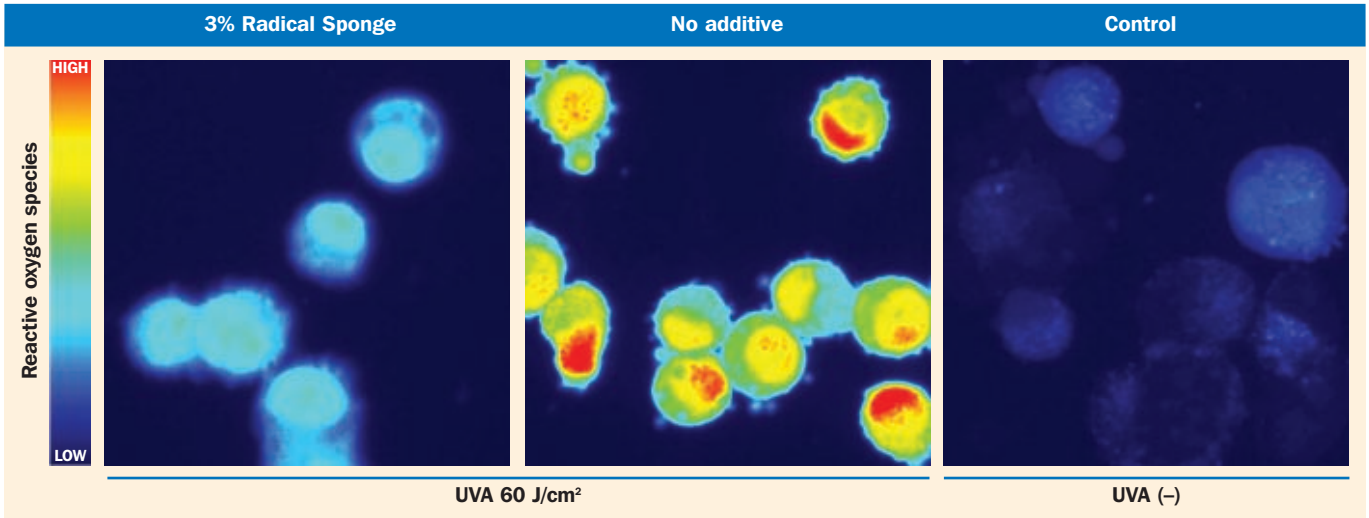


**Figure 4:** *Repressive effects of Radical Sponge on intracellular oxidative stress in UVA-irradiated HMV-II cells.*[9]

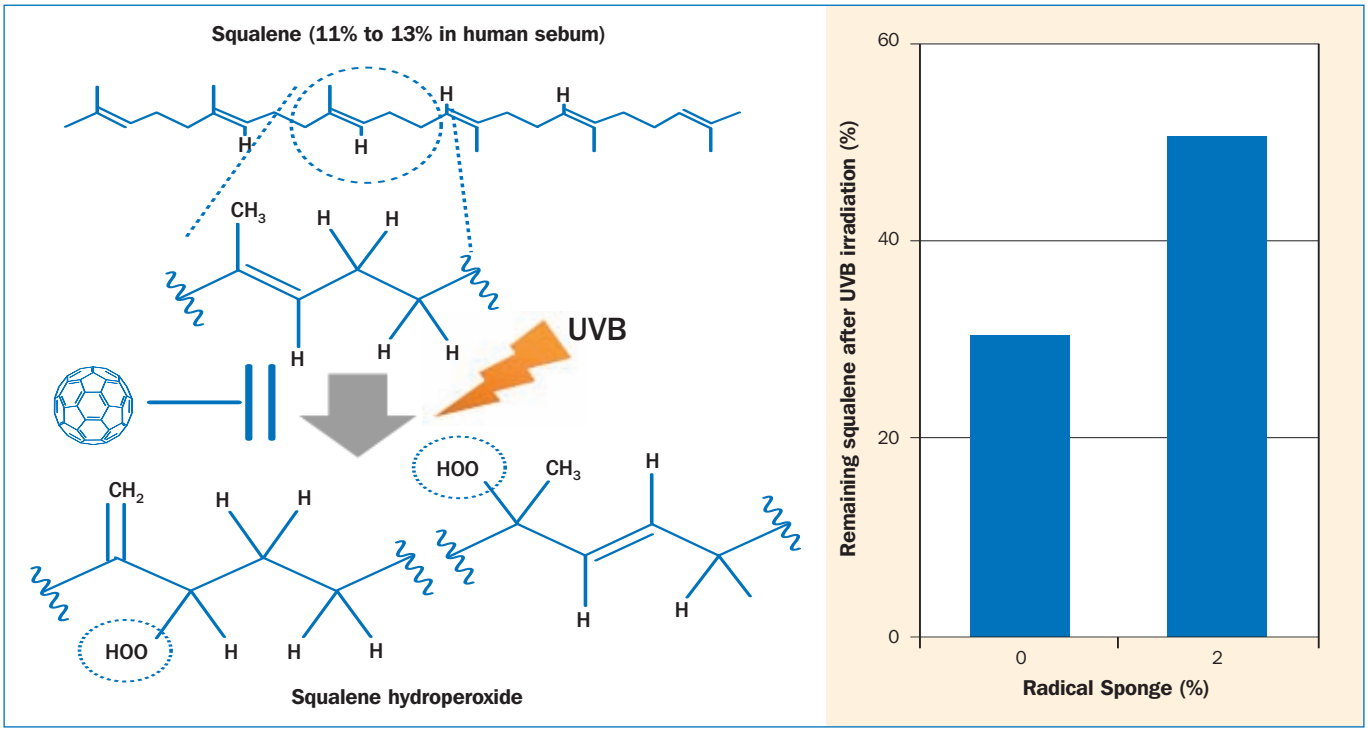


**Figure 5:** *Suppressive effect of UVB-induced squalene hydroperoxides by Radical Sponge.*

oil solutions, such as creams and serums (Fig. 3).

## Evaluation of safety as a cosmetic ingredient

Governments and research institutions worldwide are investigating the potential applications of fullerenes and their safety. We have also performed safety tests on Biofullerene, which is a major ingredient of Radical Sponge (now referred to as 'the water-soluble fullerene') and LipoFullerene.[7,8] All safety studies meeting the standards for application as an external-use quasi drug demonstrated that Biofullerene did not induce any toxicity to human skin.[9,10] In addition, it has been more than five years since fullerene-based cosmetics arrived on the market and no adverse reactions have been reported to date. On the basis of the above finding and previously published data, we are certain of the safety of our product as a cosmetic ingredient for application to human skin.

## Potent antioxidant capacity

Oxidative stress, caused by active oxygen or free radicals, is known to be harmful to healthy skin. The main factor contributing to oxidative stress in skin tissue is ultraviolet (UV) radiation. When skin is exposed to UV radiation, active oxygen or free radicals are produced, which cause flecks and freckles, wrinkles, and irritation. The addition of antioxidative ingredients to cosmetic products is effective for protecting the skin from oxidative stress.

UV radiation generates ROS or free radicals, which can cause a series of biological effects in human skin cells, resulting in cell damage or cell death. Xiao *et al*.[11] found that the scavenging effect of fullerenes eliminated free radicals and active oxygen from cells. They evaluated the UVA-induced elevation of intracellular ROS in human melanocyte HMV-II cells by using the CDCFH method. They monitored the antioxidative effect of the water-soluble fullerene against the UVA-induced generation of ROS. The water-soluble fullerene was found to prevent the UVA-induced increase in intracellular ROS and cell degeneration.

From these findings of its potent antioxidative properties, fullerene is expected to reduce oxidative stress thereby helping to sustain healthy skin.

## Preventive effect against squalene peroxides

Squalene is one of the components of human sebaceous lipid and easily undergoes photo-oxidation, giving rise to squalene monohydroperoxide.[12] Squalene peroxides have been demonstrated to be causally involved in certain skin conditions[13] and induce comedogenesis with a higher reactivity than that of other peroxides.[14]

Miwa *et al.* investigated the suppressive effect of fullerene on squalene peroxides. Squalene oxidation products were produced by UV radiation of squalene. The authors added 2% the water-soluble fullerene solution and a non-fullerene solution (as a control) to the squalene. After UV B (35 J/cm$^2$) irradiation, the samples were extracted with acetone. The amount of squalene remaining in each extract was monitored by high-performance liquid chromatography. The percentage of residual squalene in the water-soluble fullerene solution was higher than that in the control (Fig. 5). This finding indicated that fullerene suppressed the UVB-induced formation of squalene peroxides.

## Availability as a treatment for acne vulgaris

Results published in 2010 showed that fullerene improves acne vulgaris.[1] Inui *et al*. evaluated the clinical efficacy of fullerene in treating acne vulgaris. Their study was conducted on 11 subjects (5 men and 6 women) aged from 23 to 39 years with a mild or moderate form of physiological acne. The subjects applied 1% LipoFullerene-containing gel (4 mL) to the entire face twice daily, once in the morning and once in the evening, for a period of 8 weeks. The response of the subjects was evaluated according to certain clinical features (acneiform comedos, erythematous papules, pustules, and nodules) by using facial photographs. The skin moisture level and sebum value were measured using a corneometer and a sebumeter. The LipoFullerene gel significantly reduced the number of inflammatory lesions by 23% and 38% after 4 and 8 weeks, respectively (Fig. 6). The total number of comedos was decreased by 16% and 28% after 4 and 8 weeks of use, respectively. The general active ingredients for the treatment of acne decrease the barrier function and moisture level of the skin dramatically by reducing its

sebum content. However, the fullerene gel did not cause any decrease in the skin's barrier function or moisture level. Therefore, the results demonstrated that fullerene is a suitable agent for treating acne vulgaris while maintaining skin barrier functions.

The hypersecretion of sebum from sebaceous follicles is one of the most important factors relating to acne. This process leads to the formation of microcomedos, and the follicular hyperproliferation of microcomedos causes inflammation. It was revealed that fullerene had a suppressive effect on sebum secretion by Inui *et al*.[1] Sebum production in hamster sebocytes was quantified based on Oil Red O staining. The cells were administered with or without the water-soluble fullerene, and then the sebum production was measured. Sebum production was significantly decreased in the water-soluble fullerene-pretreated cells compared with the non-pretreated cells (Fig. 7).

Yudoh *et al*. reported that fullerene had a suppressive effect on proinflammatory cytokines.[15] We also confirmed that fullerene had an anti-inflammatory effect on COX-2 and IL-8 (unpublished data). In addition to its antioxidant effects and the suppression of sebum production, fullerene's anti-inflammatory activity might have contributed to the improvement of acne vulgaris.

## Conclusion

Previous studies and our investigation reported here revealed fullerene to be an excellent antioxidant and a safe material for the suppression of acne vulgaris. This occurred by the inhibition of lipid peroxidation as a result of fullerene's antioxidant activity and the suppression of sebum production without the production of any side effects. We believe that fullerene is potentially useful as a multi-functional active ingredient for the treatment of acne.

McEwen *et al.*, researchers at the company, Dupont, described fullerene as a 'radical sponge'.[16] This radical scavenging property is due to a large number of conjugated double bonds in the fullerene structure and the lowest unoccupied molecular orbital having a low energy level. Thus, fullerene can easily take up electrons thereby attacking ROS. Due to this feature, fullerene is considered the most efficient radical scavenger in medical and cosmetic applications worldwide. On the basis of the above findings, we are convinced of the possibility of increasing the utilisation of fullerene in the field of life sciences. PC

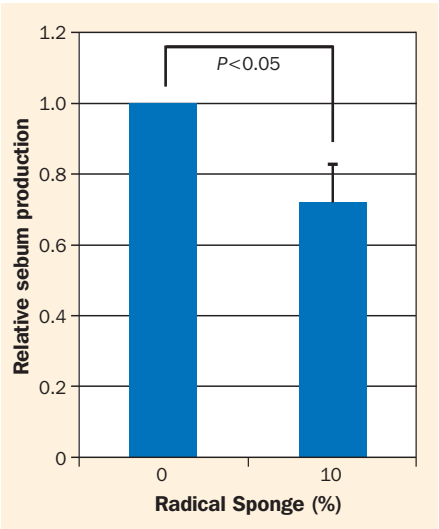


**Figure 7:** *Suppressive effect of sebum production in hamster sebocytes by Radical Sponge.*[1]

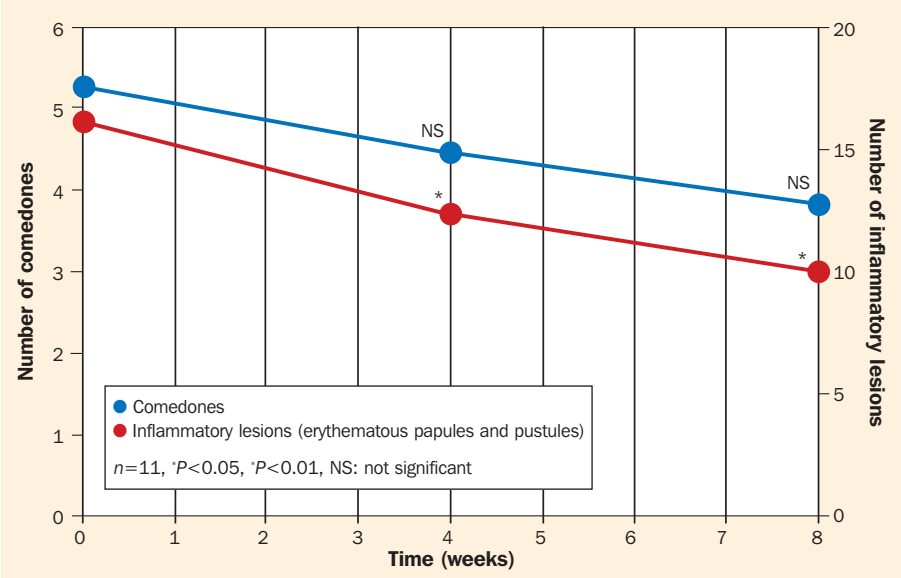


**Figure 6:** *Effect of fullerene gel on the number of acne lesions.*[1]

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