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The effects of curcumin on the fibrous envelope surrounding silicone implants in rats

Jang Won Lee[1], Seong Heum Jeong[2], Seung Hyun Oh[3], Chung Hun Kim[2]

[1]Balance Lab Plastic Surgery, Seoul, Korea
[2]Department of Plastic and Reconstructive Surgery, CHA Bundang Medical Center, CHA University Graduate School of Medicine, Seongnam, Korea
[3]K-Plastic Surgery, Seoul, Korea

Background Capsular contracture is the most common serious breast surgery complication. The cause of capsular formation remains unknown, but chronic inflammation is commonly considered to cause excessive fibrosis. Curcumin has anti-inflammatory effects and thus can relieve the symptoms of inflammatory diseases, as demonstrated in animal studies. This study aimed to evaluate the effects of curcumin on the fibrous envelope covering silicone implants in a rat model.

Methods Two solid 1.8-cm oval-shaped silicone implants were placed beneath both sides of the back in 20 Sprague-Dawley rats. The control group included 10 rats that were fed a normal diet (group A), while the experimental group (group B) included the remaining 10 rats that were fed ground curcumin. *En bloc* excision was conducted at 8 postoperative weeks. Capsular thickness and inflammatory cell distribution were examined using a fixed tissue sample.

Results Gross findings and histologic differences between the groups were observed. The experimental group had a significantly lower mean total capsular thickness than the control group (177.4±31.4 μm vs. 145.9±32.5 μm, P=0.007). A significant decreasing tendency was found in several inflammatory cells in the experimental group (7,070±744.3/mm^2 vs. 2,640±301.7/mm^2, P=0.001).

Conclusions Curcumin significantly reduced the inflammatory reaction, and will help to lower the risk of capsular contracture. Long-term studies are required to determine whether this hypothesis can provide a basis for a viable therapeutic strategy to reduce capsular contracture.

Keywords Implant capsular contracture / Breast implants / Curcumin

INTRODUCTION

For decades, silicone breast implants have been commonly utilized for breast augmentation and reconstructive surgery. However, breast implants can cause a variety of complications, including infection and implant rupture, and capsular contracture is one of the most challenging complications to treat [1,2].

Clinically, extreme cases of capsular contracture, according to the Baker categorization, cause aesthetic and functional difficulties, such as breast stiffening followed by pain at the surgical site and twisting of the prosthesis, resulting in severe pain for patients. The specific pathophysiology of capsular contracture has yet to be established. However, capsular contracture has been linked to various causes, including foreign body reactions to silicone and the membrane that surrounds it, the anatomical position of the prosthesis, preoperative or postoperative bacterial infection, and postoperative hematoma and seroma [3]. Its pathophysiology is associated with an inflammatory reaction that results in severe fibrosis. Many researchers have proposed various experiments to overcome capsular contracture.

Curcumin, a compound found in turmeric, is known to be ac-

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Correspondence: Chung Hun Kim
Department of Plastic and Reconstructive Surgery, CHA Bundang Medical Center, CHA University Graduate School of Medicine, 59 Yatap-ro, Bundang-gu, Seongnam 13496, Korea
E-mail: chkimps@cha.ac.kr

tive in various pharmacokinetics due to its antioxidant, antitumor, and anti-inflammatory activities. Curcumin's anti-inflammatory response has previously been established in both cell culture and animal experimental models to be efficacious against ulcerative colitis, pancreatitis, arthritis, and chronic uveitis. Curcumin inhibits its cyclooxygenase-2 (COX-2) activity, lipoxygenase (LOX), and inducible nitric oxide synthase (iNOS) activity. The compound also suppresses inflammation by interfering with various inflammatory responses, such as the production of various inflammatory cytokines, tumor necrosis factor-alpha (TNF-α), interleukins (ILs), and monocyte chemoattractant proteins (MCPs) [4]. In particular, curcumin was found to reduce prostaglandin E2, which is the end product of the COX pathway that is known to activate fibroblasts involved in fibrosis, causing chronic inflammation [5].

Previous studies have observed decreased fibrous envelope formation around implants through the suppression of the inflammatory response [6,7]. For example, the injection of steroids into a capsule, the use of non-steroidal anti-inflammatory drugs, and leukotriene inhibitors insufficiently reduced fibrous envelope formation, although some studies did report a lower incidence of capsular contracture with these treatments [8-11]. Recent clinical trials have indicated that receptor antagonists play a role in the prevention of fibrous envelope formation. However, side effects can occur with each of these treatments. The injection of steroids can prolong wound healing [12]. The use of leukotriene receptor antagonists can lead to complications including liver toxicity, moderate to severe asthma, eosinophilia, pulmonary infiltrations, cardiomyopathy, and other signs of vasculitis [6,10,13,14]. In contrast, clinical trials have not reported side effects associated with curcumin, which is marketed as a dietary supplement [15,16].

This study hypothesized that the antioxidant and anti-inflammatory properties of curcumin would mitigate the chronic inflammatory responses that occur after silicone implant insertion. The researchers determined the degree of fibrous capsule formation and the number of inflammatory cells after administering curcumin in an experimental animal model using Sprague-Dawley rats.

METHODS

Experimental design

A total of 20 female Sprague-Dawley rats (weighing between 250 g and 300 g) were equally divided into group A (control group) and group B (experimental group). Group A was provided a normal diet, while group B received curcumin in its diet. Prior to the experiment, the investigation was approved by our medical institution's Animal Experimental Committee. The experimental animals were cared for in accordance with the Animal Experimental Committee's guidelines. Therefore, the temperature in the animal facility was kept at 21 ± 2 ℃, and a 12-hour on/off light cycle was maintained. Food and water were freely available to the experimental animals.

The control and experimental groups were kept under experimental conditions for a week and before being used for the procedure to increase the experimental accuracy. Additionally, miniature silicone implants were designed to resemble the shape of actual implants and inserted into the subcutaneous sac on the backs of the rats. Eight weeks after insertion, the rats were sacrificed to confirm the experimental results.

Curcumin dose

Based on prior research, after uniformly mixing general feed and curcumin samples, the mixture was pulverized into fine particles to obtain a curcumin concentration of 2% [17]. These particles were fed to the experimental group (group B).

Mammary prosthesis

Silicone lumps were fabricated by the research team using silicone implants with a smooth surface. The maximum diameter and thickness of the prosthesis were 18 mm and 7 mm, respectively (volume = ~1.19 mL). Prior to implantation, the miniature silicone implants were sterilized using ethylene oxide gas (Fig. 1).

Animal experimental model

The rats were anesthetized by administering a combination of tiletamine and zolazepam (Zoletil, Virbac Corp.; 60 mg/kg) and xylazine (Rompun, Dechra; 18.6 mg/kg) intra-abdominally, and the skin on their backs was shaved while in a prone posture. The back was then aseptically cleaned using a 10% povidone-iodine solution.

Using a strict aseptic technique, an approximately 2 cm incision was made along the midline of the spine on the imaginary line connecting the bilateral scapulae. A subcutaneous pocket was created by making a lateral dissection of approximately 2 cm in diameter to both sides of the vertebra below the panniculus carnosus muscle on each side. For quality control, two identical miniature silicone

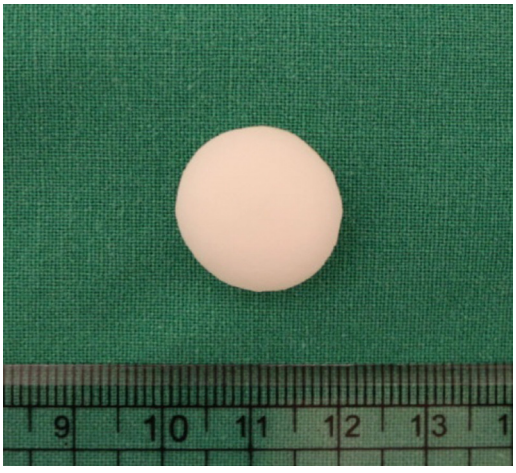

Fig. 1. Miniature silicone implant. A miniature silicone implant measuring 18 × 18 × 7 mm.

implants were placed on each side of the subcutaneous pocket (Fig. 2). A skin incision was sutured with nylon 4-0, and gentamicin (0.05 mL/kg) was injected intramuscularly as a postoperative antibiotic. The systemic condition and the wound area of the rats were monitored daily.

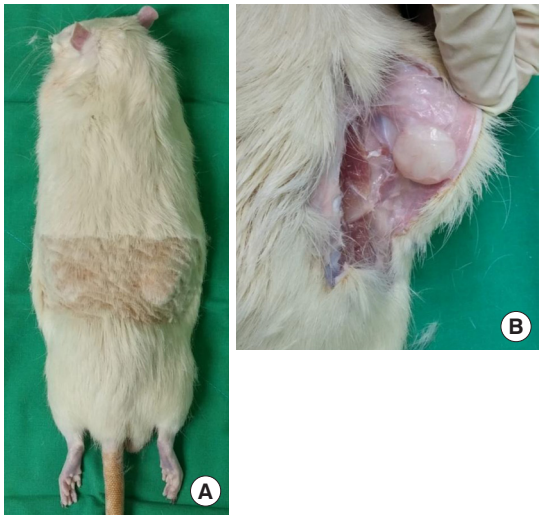

Fig. 2. Experimental procedure. (A) In a prone posture, the skin on the back was shaved. The back was then aseptically cleaned with a 10% povidone-iodine solution. Using a strict aseptic technique, an approximately 2-cm incision was made along the midline of the spine on the imaginary line joining the bilateral scapulae. (B) The subcutaneous pocket was produced by making a lateral dissection on both sides of the vertebra with a diameter of approximately 2 cm below the panniculus carnosus muscle on each side. A tiny silicone implant was then placed on each side of the subcutaneous pocket.

Histopathologic examination (morphologic examination)

Eight weeks after surgery, all of the rats were anesthetized using a lethal dose of anesthetics. After overall adjacent tissue extraction of the silicone implants, the excised tissue was fixed in a formalin solution and embedded in paraffin. The harvested tissue was sectioned at a thickness of 4 μm. It was then prepared as a sample using dyes such as hematoxylin and eosin, as well as Masson trichrome staining. The thickness of the capsule and distribution of the inflammatory cells in the capsule were investigated using QuPath (version 0.3.2) with the sectioned tissue sample at four locations (skin, visceral, and both opposite lateral sides) using a light microscope (Olympus AX80) at magnifications of ×100, ×200, and ×400. The thickness and inflammatory cell distribution at the point of maximum thickness were analyzed for each of the four locations [2].

Statistical analysis

Measurements such as capsule thickness and inflammatory cell count are given as the mean and standard deviation. SPSS (IBM Corp.) was used for statistical analysis. To determine the significance of differences in measurements between the groups, the t-test was used. The relationships between the variables were determined using Pearson correlation coefficients. For both analyses, P-values of <0.05 were considered to indicate statistical significance.

RESULTS

None of the rats appeared to experience side effects or develop infections or inflammation. Examinations of the excised tissue samples revealed differences in gross and histologic findings between the groups. Dense fibrous capsules with well-defined margins from

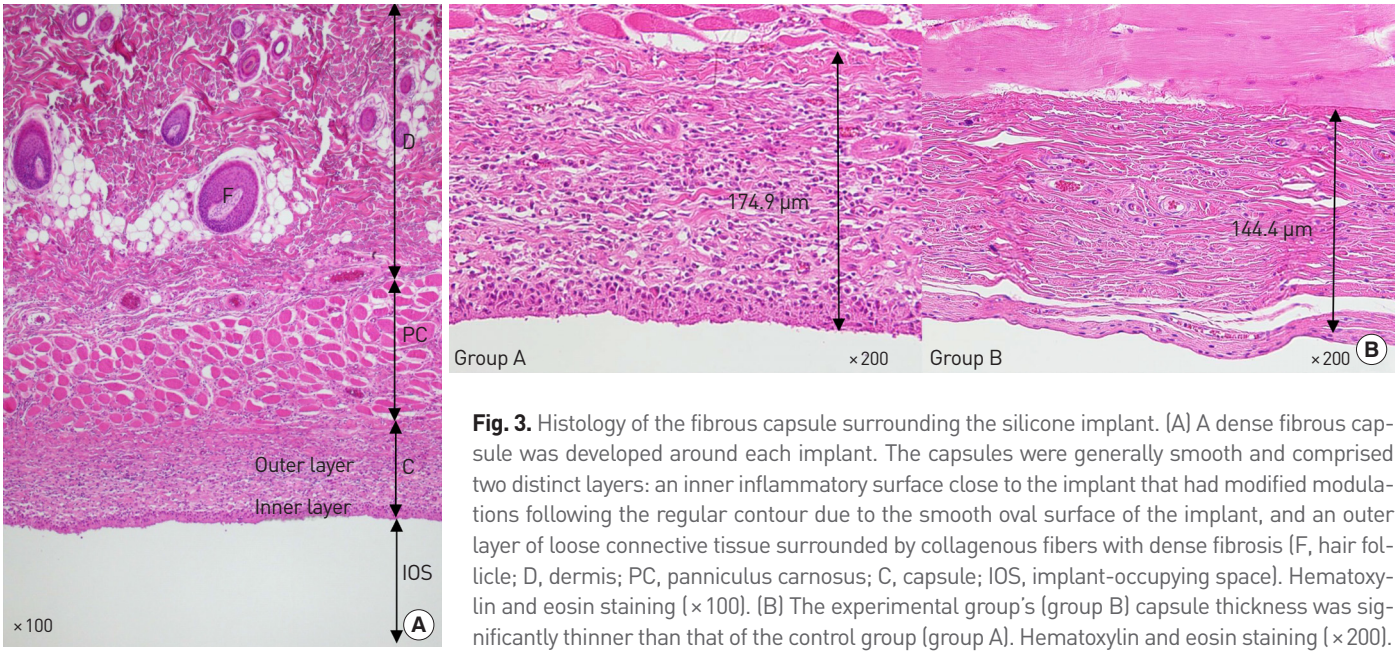

Fig. 3. Histology of the fibrous capsule surrounding the silicone implant. (A) A dense fibrous capsule was developed around each implant. The capsules were generally smooth and comprised two distinct layers: an inner inflammatory surface close to the implant that had modified modulations following the regular contour due to the smooth oval surface of the implant, and an outer layer of loose connective tissue surrounded by collagenous fibers with dense fibrosis (F, hair follicle; D, dermis; PC, panniculus carnosus; C, capsule; IOS, implant-occupying space). Hematoxylin and eosin staining (×100). (B) The experimental group's (group B) capsule thickness was significantly thinner than that of the control group (group A). Hematoxylin and eosin staining (×200).

Table 1. Mean capsule thickness and the number of inflammatory cells in each group

	Mean±SD		P-value
	Group A	Group B	
Capsule thickness (μm)	177.4±32.2	145.9±33.4	0.007
No. of inflammatory cells (/mm²)	7,070±744.3	2,640±301.7	0.001

The mean thickness of the capsule and the counts of inflammatory cells, including giant cells and eosinophils, were significantly lower in the experimental group (group B) than in the control group (group A) (P<0.05).

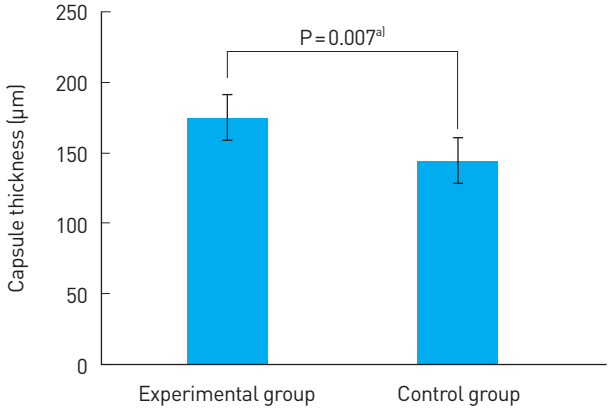

Fig. 4. Comparison of mean capsule thickness in the control group and experimental group. In control and experimental groups, the mean capsule thickness was 177.4 μm and 145.9 μm, respectively. Therefore, the mean capsule thickness was reduced by 31.5 μm. a)Statistically significant differences (P<0.05).

the adjacent tissue formed around each implant. All of the capsules were at least slightly hardened and slippery when palpated.

The thicknesses of the capsules in group B were significantly lower than those in group A. The capsules were established around the implants and comprised two well-differentiated layers. The inner layer, which was attached to the implants, and the outer loose connective tissue layer were connected to the adjacent normal connective tissue and the subcutaneous layer (Fig. 3).

In groups A and B, the mean thicknesses of the capsule adjacent to the implants were 177.4 μm and 145.9 μm, respectively (Table 1, Fig. 4). This result indicates that the thickness of the capsule in group B was significantly thinner than in group A (P<0.05). A layer of epithelial-like cells lined the inner surface of the capsule with high cell density. The outer layer was thicker than the inner layer and had low cell density with loose connective tissue.

The number of inflammatory cells, including giant cells and eosinophils, was significantly lower in the experimental group. Group A had a mean inflammatory cell distribution of 7,070 cells/mm², which was much higher than the mean distribution of 2,640 cells/mm² in group B (P<0.05) (Table 1).

This study showed a significantly lower overall decreasing tendency in the mean thickness of the capsule and the number of inflammatory cells in group B than in group A. Additionally, capsule thickness and inflammatory cell count were positively correlated (P<0.01) (Fig. 5).

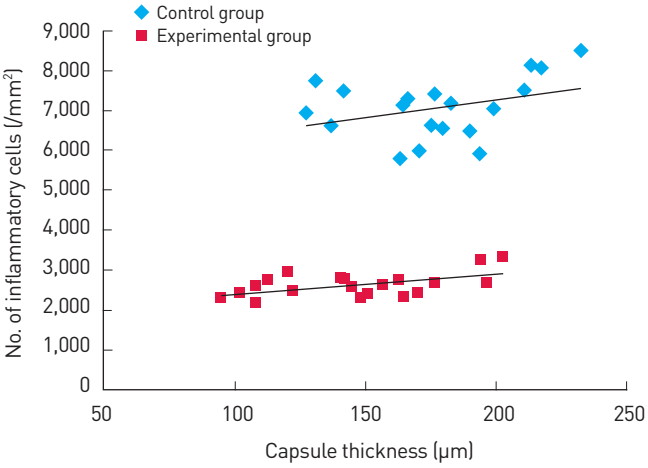

Fig. 5. Pearson correlation coefficients between capsule thickness and the number of inflammatory cells. The thickness of the capsule and the distribution of inflammatory cells were found to have a positive correlation. When compared to the control group, the frequency of inflammatory cells was lower and the capsule was thinner in the experimental group (P=0.001).

DISCUSSION

Capsular contracture after mammoplasty using implants is one of the most common and difficult-to-treat problems in the field of plastic and reconstructive surgery. However, as of this study, no definite causes and treatment methods have been established for capsular contracture. Therefore, it was hypothesized that the anti-inflammatory properties of curcumin would mitigate the chronic inflammatory response that occurred after silicone implant insertion, leading to a decrease in the rate of fibrous capsular contracture. We attempted to demonstrate this hypothesis through this experimental study.

Curcumin is a natural phytocompound found in turmeric with anti-inflammatory properties that has been used to treat chronic diseases. Its anti-inflammatory activity appears to be mediated via the suppression of COX-2, LOX, and iNOS induction, the release of cytokines such as interferon-γ and TNF-α, and the activation of transcription factors including nuclear factor kappa B (NF-κB) and activator protein 1. Toxicity studies conducted on animals have indicated no adverse effects due to prolonged use [18,19].

Many studies have shown that curcumin is a highly pleiotropic compound capable of interacting with a variety of molecular targets implicated in inflammation. However, the precise mechanism by which curcumin reduces inflammatory responses remains unknown. Curcumin inhibits inflammatory cytokines through a range

of mechanisms. Curcumin regulates inflammatory responses by inhibiting the production of inflammatory cytokines (e.g., TNF-α; IL-1, IL-2, IL-6, IL-8, and IL-12; MCP; and migration inhibitory protein) and downregulating mitogen-activated and Janus kinases [20].

Curcumin's suppression of NF-κB activation is most likely responsible for COX-2 and iNOS inhibition. NF-κB is a widespread eukaryotic transcription factor that regulates inflammation, cellular proliferation, and transformation. Curcumin has been hypothesized to reduce NF-κB activation and pro-inflammatory gene expression by inhibiting the phosphorylation of the inhibitory factor I-kappa B kinase [21]. The suppression of NF-κB activation inhibits the inflammatory process by downregulating COX-2 and iNOS. Curcumin also suppresses arachidonic acid metabolism and inflammation in the epidermis of animal models by downregulating the COX and LOX pathways [22].

In this experiment, the hypothesis that the curcumin might contribute to eventually reducing the thickness of the fibrous capsule surrounding the silicone implant in an animal model was demonstrated. Inflammation is considered to lead to increased capsule thickness, and this study verified the positive relationship between the number of inflammatory cells and capsule thickness. Therefore, the effects of anti-inflammatory and antioxidation activities of curcumin could help decrease inflammation and capsule formation.

However, the capsule was not as thick in rats as in humans, and capsule contracture did not occur in our experiment. Therefore, although the results indicate that curcumin might help to reduce the thickness of the capsule, it could not be determined whether it could prevent or relieve the formation of the capsule.

The study design had multiple limitations. First, the mammoplasty procedure is more complicated than merely placing silicone implants into patients' backs. Furthermore, the dose of curcumin was not equivalent for each rat since the rats were allowed to eat unrestricted amounts of feed. Curcumin is also poorly absorbed due to limited systemic bioavailability. To compensate for these limitations, future research should involve rats that are fed the same doses of curcumin with saline. Analysis of curcumin serum levels and major metabolites via liquid chromatography-tandem spectrometry would help determine whether the doses are equivalent [5,23]. Since a variety of silicone implants are used in current clinical practice, it would also be beneficial to conduct an experiment to compare the effect of curcumin on capsule formation according to the type of implant.

The clinical applicability of experimental results seen in animal models has yet to be determined since rats and humans differ in terms of immune response and wound healing. Humans are more vulnerable to infections than rats. Capsules in rats are not hard and thick; therefore, to determine the degree of fibrotic change in capsules, not only does the capsule thickness need to be measured and analyzed, but a quantitative analysis must also be performed, including immunohistochemical staining such as Masson trichrome staining and picrosirius staining [24].

In conclusion, curcumin could significantly reduce inflammatory reactions, resulting in less fibrosis formation, as well as lower the incidence of capsular contracture. Long-term studies are needed to determine if curcumin can be used to develop safe and reasonable therapeutic strategies to reduce capsular formation, which frequently causes pain in patients with breast implants.

NOTES

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Ethical approval

Animal care and experimental procedures in this study were approved by the Animal Care and Use Committee of CHA University (IACUC140052).

ORCID

Jang Won Lee https://orcid.org/0009-0004-6692-6321
Seong Heum Jeong https://orcid.org/0000-0003-4407-2914
Seung Hyun Oh https://orcid.org/0009-0007-9878-1069
Chung Hun Kim https://orcid.org/0009-0000-4054-2929

REFERENCES

1. Handel N, Cordray T, Gutierrez J, et al. A long-term study of outcomes, complications, and patient satisfaction with breast implants. Plast Reconstr Surg 2006;117:757-72.
2. Humphries MP, Maxwell P, Salto-Tellez M. QuPath: the global impact of an open source digital pathology system. Comput Struct Biotechnol J 2021;19:852-9.
3. Henriksen TF, Fryzek JP, Hölmich LR, et al. Surgical intervention and capsular contracture after breast augmentation: a prospective study of risk factors. Ann Plast Surg 2005;54:343-51.
4. White CM, Pasupuleti V, Roman YM, et al. Oral turmeric/curcumin effects on inflammatory markers in chronic inflammatory diseases: a systematic review and meta-analysis of randomized controlled trials. Pharmacol Res 2019;146:104280.
5. Jurenka JS. Anti-inflammatory properties of curcumin, a major constituent of Curcuma longa: a review of preclinical and clinical research. Altern Med Rev 2009;14:141-53.
6. Safran T, Nepon H, Chu CK, et al. Current concepts in capsular contracture: pathophysiology, prevention, and management. Semin Plast Surg 2021;35:189-97.
7. Kim CH, Kim DH, Oh SH, et al. Human embryonic stem cell-derived endothelial precursor cell conditioned medium reduces the thickness of the capsule around silicone implants in rats. Ann Plast Surg 2015;75:348-52.

8. Caffee HH. Capsule injection for the prevention of contracture. Plast Reconstr Surg 2002;110:1325-8.
9. Lemperle G, Exner K. Effect of cortisone on capsular contracture in double-lumen breast implants: ten years' experience. Aesthetic Plast Surg 1993;17:317-23.
10. Graf R, Ascenco AS, Freitas RD, et al. Prevention of capsular contracture using leukotriene antagonists. Plast Reconstr Surg 2015;136:592e-596e.
11. Schlesinger SL, Ellenbogen R, Desvigne MN, et al. Zafirlukast (Accolate): a new treatment for capsular contracture. Aesthet Surg J 2002;22:329-36.
12. Eder H, Lejour M, Smahel J. Steroid related complications of double-lumen prostheses with cortisone. Chir Plast 1981;6:95-103.
13. Reinus JF, Persky S, Burkiewicz JS, et al. Severe liver injury after treatment with the leukotriene receptor antagonist zafirlukast. Ann Intern Med 2000;133:964-8.
14. Guilpain P, Pagnoux C, Lhote F, et al. Antileukotrienes and Churg-Strauss syndrome. Presse Med 2007;36(5 Pt 2):890-4.
15. Belcaro G, Cesarone MR, Dugall M, et al. Efficacy and safety of Meriva®, a curcumin-phosphatidylcholine complex, during extended administration in osteoarthritis patients. Altern Med Rev 2010;15:337-44.
16. Chainani-Wu N. Safety and anti-inflammatory activity of curcumin: a component of tumeric (Curcuma longa). J Altern Complement Med 2003;9:161-8.
17. Huang MT, Lou YR, Xie JG, et al. Effect of dietary curcumin and dibenzoylmethane on formation of 7,12-dimethylbenz[a]anthracene-induced mammary tumors and lymphomas/leukemias in Sencar mice. Carcinogenesis 1998;19:1697-700.
18. Aggarwal S, Ichikawa H, Takada Y, et al. Curcumin (diferuloylmethane) down-regulates expression of cell proliferation and antiapoptotic and metastatic gene products through suppression of IkappaBalpha kinase and Akt activation. Mol Pharmacol 2006;69:195-206.
19. Adapala N, Chan MM. Long-term use of an antiinflammatory, curcumin, suppressed type 1 immunity and exacerbated visceral leishmaniasis in a chronic experimental model. Lab Invest 2008;88:1329-39.
20. Avasarala S, Zhang F, Liu G, et al. Curcumin modulates the inflammatory response and inhibits subsequent fibrosis in a mouse model of viral-induced acute respiratory distress syndrome. PLoS One 2013;8:e57285.
21. Li N, Liu TH, Yu JZ, et al. Curcumin and curcumol inhibit NF-kB and TGF-b1/Smads signaling pathways in CSE-treated RAW246.7 cells. Evid Based Complement Alternat Med 2019;2019:3035125.
22. Kahkhaie KR, Mirhosseini A, Aliabadi A, et al. Curcumin: a modulator of inflammatory signaling pathways in the immune system. Inflammopharmacology 2019;27:885-900.
23. Bangphumi K, Kittiviriyakul C, Towiwat P, et al. Pharmacokinetics of curcumin diethyl disuccinate, a prodrug of curcumin, in Wistar rats. Eur J Drug Metab Pharmacokinet 2016;41:777-85.
24. Silva EN, Ribas-Filho JM, Czeczko NG, et al. Histological evaluation of capsules formed by silicon implants coated with polyurethane foam and with a textured surface in rats. Acta Cir Bras 2016;31:774-82.