The Effect of Curcumin in Core-Shell Nanoparticle as Therapy in Radiotherapy-Induced Hyposalivation

Nanda Rachmad Putra Gofur¹, Aisyah Rachmadani Putri Gofur², Kemal Alif Athallandi², Ayu Anggraini Broto Nagoro², Soesilaningtyas³, Rizki Nur Rachman Putra Gofur⁴, Mega Kahdina⁴, Hernalia Maritdal Putri⁴

¹Department of Health, Faculty of Vocational Studies, Universitas Airlangga, Surabaya, Indonesia
²Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia
³Department of Dental Nursing, Politekkes Kemenkes, Surabaya, Indonesia
⁴Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

Corresponding Author: Nanda Rachmad Putra Gofur
Nanda Rachmad Putra Gofur, Department of Health, Faculty of Vocational Studies, Universitas Airlangga, Surabaya, Indonesia
Email: nanda.rachmad.gofur@vokasi.unair.ac.id

Keywords: Core-shell nanoparticle, curcumin, radiotherapy-induced hyposalivation.

ABSTRACT
Background: The gold standard for treating head and neck cancer (HNC) is by radiotherapy. However, the radiation from radiotherapy affecting the salivary glands can cause hyposalivation in patients with incidence of 94-100%. This can negatively affect the function of swallowing, mastication, and vocals, decreasing the patients life quality. Pilocarpin can be used to treat hyposalivation, but it’s contradictory to various diseases. Therefore, alternative treatments are needed to treat radiotherapy-induced hyposalivation (RIH). The effect of curcumin in core-shell nanoparticle is the state-of-the-art technology that can be used to treat RIH.

Objectives: To explain the effect of curcumin in core-shell nanoparticles as RIH therapy.

Discussion: Routinely, HNC patients receive radiotherapy at a dose of 50-70 Gy, which is usually used to destroy malignant cells, but oftenly causes chronic hyposalivation. Decreased salivary levels after radiotherapy often occur in the initial period up to 3 months after radiotherapy. It occurred due to defects in major salivary glands caused by radiotherapy. Curcumin is proven to have an anti-inflammatory effects by inhibiting nuclear factor-kappaβ (NF-κB) that can trigger excessive tissue damage. This natural ingredients has low oral bioavailability that requires core-shell nanoparticles which can increase the effectiveness of biodistribution and can avoid phagocytosis process to reduce effects of RIH.

Conclusion: The effect of curcumin in core-shell nanoparticles has potential as RIH therapy.

INTRODUCTION
The salivary glands are generally exposed to radiation in radiotherapy for head and neck cancer (HNC), causing functional damage to the salivary glands. Exposure to radiation at high doses and for a long time (50-70 Gy for 5-7 weeks) can cause hyposalivation that is irreversible. The standard threshold for safe oral radiation exposure is 26 Gy.¹

The salivary glands which consist of the major salivary glands (parotid glands, submandibular glands, sublingual glands) and minor salivary glands generally produce saliva. Radiation exposure to the oral cavity causes hyposalivation or decreased saliva production. As many as 94-100% cases of hyposalivation in patients with HNC who undergo radiotherapy.¹,² In past few years, the management and treatment of hyposalivation patients after radiotherapy is by increasing the saliva rate using cholinergic drugs such as pilocarpine. Pilocarpine acts parasympathomimetic with a β-adrenergic effect which activates cholinergic receptors and requires greater attention to patients with gastritis, hypertension, and a history of heart disease.³

So that alternative treatments are needed to reduce hyposalivation caused by radiation exposure or radiotherapy-induced hyposalivation (RIH) in cases of HNC. Alternative treatments that can be used by combining natural ingredients such as curcumin. Curcumin has antioxidant and anti-inflammatory effects so that it can reduce inflammation that occurs after radiation exposure to the acinar cells of the salivary glands. Other advantage of curcumin is that curcumin has low oral bioavailability, so a core-shell nanoparticle is used which has the advantage of improved quality properties such as a much lower cytotoxicity, increased compatibility and dispersibility, and better conjunction with other bioactive molecules.⁴,⁵

Radiotherapy-induced hyposalivation
Decreased salivary rate, or hyposalivation is one of the predisposing factors for caries, candidiasis and sialadenitis in the oral cavity. In addition, hyposalivation is also a common complication that persists in HNC patients treated with radiotherapy. In general, conventional radiotherapy treatment is used to treat HNC patients using a daily fraction of 1.8-2.0 Gy, for a total dose of 50-70 Gy over a period of 5-7 weeks. However, the study found that the average dose at 20-40 Gy of the major salivary glands, namely the parotid glands, submandibular glands, and sublingual glands can produce a significant decrease in the salivary rate, making it almost undetectable. The decrease in salivary rate can occur as much as 50-60% in the period from the beginning to the 3rd month after radiotherapy.⁶,⁷

Hyposalivation caused by radiotherapy (RIH) can be followed by compositional changes in salivary characteristics such as immunoglobulin (Ig) levels, protein and electrolyte concentrations, pH, viscosity, and color.⁸ This can cause dry mouth syndrome, dysphagia, trismus and changes in the sense of taste. Moreover, RIH can increase susceptibility to infection of the oral cavity and oropharynx by Candida albicans.⁹ Some patients find...
improvement in RIH within 12-18 months after radiotherapy, but most patients do not find any significant changes over time, causing RIH to be a lifelong morbidity that has a major effect on reducing the patient’s quality of life.6,9

**Curcumin**

Curcumin is a yellow active phenol component that can be extracted from the rhizomes of the *Curcuma longa* or *turmeric* plant in high concentrations, with a chemical structure in the form of 1,6-heptadiene-3,5-dione-1,7-bis (4-hydroxy-3-methoxyphenyl)-(1E, 6E).10 Curcumin is commonly used as a cooking spice and a major component in traditional medicine.11 The best known molecular structure of curcumin is phenolic hydroxyl which can mediate antioxidant activity, α, β-unsaturated enone which mediates protein bonding, and β-dicarbonyl which mediates metal ion chelation.12 Studies in vitro and in vivo, particularly in clinical trials showed that curcumin has enormous potential as therapeutic agents in a variety of chronic diseases such as inflammatory bowel disease, arthritis, pancreatitis, chronic anterior uveitis, and cancer.13 Curcumin has been shown to be a pleiotropic molecule that interacts with various proinflammatory molecular targets, exhibiting strong antioxidant and anti-inflammatory activity.14 At the molecular level, curcumin can modulate several proinflammatory factors such as interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-12 (IL-12), tumor necrosis factor-α (TNF-α), and interferon (INF), as well as signaling pathways such as nuclear factor-kappaB (NF-kB), tumor necrosis factor-α (TNF-α) and nuclear factor-E2-related factor 2 (Nrf2).11,14,15 Curcumin can be obtained by extracting the rhizomes of the turmeric plant. Rhizoma turmeric is boiled in boiling water for 30 minutes and dried under the sun, then the rhizomes are filtered using a net to become a coarse powder. The resulting turmeric rhizome powder is then extracted using ethyl acetate in the socket assembly so that it becomes a brown semi-solid crude extract. After that, every 1 gram of crude extract was added to 25 mL of hexane and kept for 12 hours. Next, the solution was stirred using a magnetic stir at 600 rpm for 3 hours. In stirring, the coarse powder chunks will break into small fragments and become a fine powder. The fine powder was separated by centrifugation and oven-dried at 40°C.16

**Core-shell nanoparticles**

Core-shell *nanoparticles* is a nanomaterial composed of core particles (central material) with a shell (coating material) that can cover in whole or in part, and can be identified separately.17 These nanoparticles have increased interest in research as they exhibit unique properties derived from the combination of core and shell material, geometry, and design.18

---

**Figure 1. Schematic of the core-shell nanoparticle.**17
primary damage that can change the structure and damage important components of progenitor and stem cells, including DNA, causing acinar cells to malfunction, decreasing saliva-secreting performance, resulting in RIH. In normal individuals, the saliva flow rate with stimulation is generally 1.5-2.0 mL/min whereas the saliva flow rate without stimulation is about 0.3-0.4 mL/min. However, in RIH patients, the saliva flow rate with stimulation only reached <0.5-0.7 mL/min, with the saliva flow rate without stimulation ≤0.1 mL/min.

RIH treatment is focused on increasing the saliva rate for an adequate period of time. Until now, the treatment has been using cholinergic drugs such as pilocarpine. Pilocarpine is a broad-spectrum parasympathomimetic drug with a β-adrenergic effect that activates cholinergic receptors, stimulating a rapid increase in salivary secretion over an adequate period of time. This stimulating effect does not only occur in the salivary glands, but also on other exocrine glands such as the lacrimal and sweat glands, as well as goblet cells in respiration and digestion. In general, pilocarpine is given at a dose of 5 mg three times daily for 3 months. However, pilocarpine has side effects such as vomiting, headache, increased urine frequency, wheezing, diarrhea, and visual disturbances. In addition, pilocarpine is relatively contradictory to patients who have chronic respiratory disease, uncontrollable asthma, and users of β-adrenergic-blocker drugs, and require greater attention to patients with gastritis, hypertension, and a history of heart disease.

One of the materials that could potentially be used in RIH therapy is curcumin, where curcumin can protect cells from unwanted radiotherapy effects. This is because curcumin has anti-inflammatory properties through suppression of the TNF-α, Nrf2, and NF-κB signaling pathways, which are key mediators of inflammation by keeping the inhibitor NF-κB kinase subunit-β (IKKβ) from the phosphorylation process. Inhibition of NF-κB can effectively block the production of pro-inflammatory cytokines such as IL-1β, IL-6, IL-12, and chemokines, as well as the production of proinflammatory enzymes such as cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS) and other molecules such as cyclin D1, which can overall reduce oxidative stress in cells.

Curcumin has an effect which is known as protective effect of curcumin against free radicals. Curcumin as a pro-oxidant molecule against cancer cells can stimulate the formation of reactive oxygen species (ROS). ROS triggers depolarization of the mitochondrial membrane potential (MMP) causing release of cytochrome-c, activates caspasas, and induces apoptosis. However, the curcumin itself has a low oral bioavailability, reaching only 1%, thus negatively affecting biological efficiency as it requires very high doses to have a beneficial effect. Core-shell nanoparticles show great potential as carriers for bioactive substances because their sub-cellar size allows for relatively higher intracellular uptake as well as improved stability and protection against degradation. In addition, applicatively, core-shell nanoparticles have advantages over other nanoparticles due to enhancements in properties such as much lower cytotoxicity, increased compatibility and dispersibility, and better conjugation with other bioactive molecules.

Curcumin has a radioprotective effect on acinar cells in the salivary glands with antioxidant and anti-inflammatory properties that can reduce free radicals generated by radiation rays in radiotherapy. Implantation of curcumin in a core-shell nanoparticle media can increase intracellular absorption as well as stability and protection of substances against degradation from the environment, thereby increasing its effectiveness as an RIH therapy.

CONCLUSION
Curcumin in the core-shell nanoparticle has a radioprotective effect with antioxidant and anti-inflammatory properties that can inhibit free radicals, so it has potential as RIH therapy.

REFERENCES
1. Lin CY, Ju SS, Chia JS, Chang CH, Chang CW, Chen MH. Effects of radiotherapy on salivary gland function in patients with head and neck cancers. Journal of Dental Sciences. 10 (3), pp 253-262


