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

Nanda Rachmad Putra Gofur[1*], Aisyah Rachmadani Putri Gofur[2], Kemal Alif Athallandi[2], Ayu Anggraini Broto Nagoro[2], Soesilaningtyas[3], Rizki Nur Rachman Putra Gofur[4], Mega Kahdina[4], Hernalia Martidal Putri[4],

[1]Department of Health, Faculty of Vocational Studies, Universitas Airlangga, Surabaya, Indonesia
[2]Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia
[3]Department of Dental Nursing, Poltekkes Kemenkes, Surabaya, Indonesia
[4]Faculty 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.

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 contradictive 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-kappaB (NF-kB 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.

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

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

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 26Gy.[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, caandidiasis 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.[7] 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-kappaβ (NF-kβ), 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 socklet 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 ^{0} C.[16]

Core-shell nanoparticles

Core-shell nanoparticle 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]

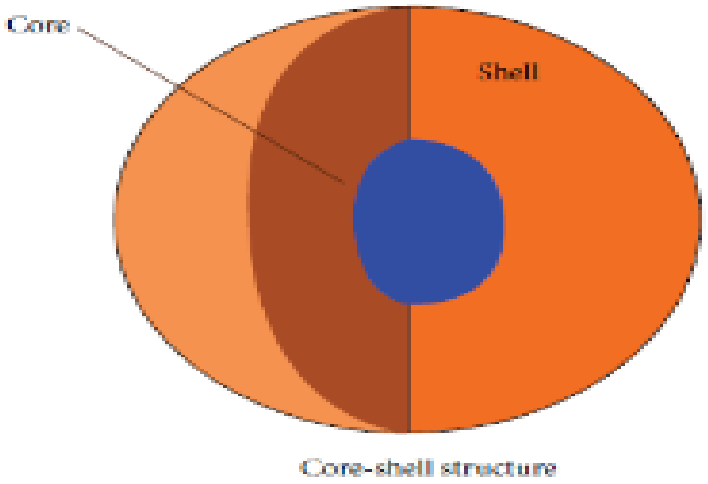

Figure 1. Schematic of the core-shell nanoparticl e.[17]

Core-shell nanoparticles have very promising potential for biological applications. The shell layer that covers the core causes decreased toxicity and increased biocompatibility of the nanoparticles inside. The coating not only acts as a non-toxic coating, but also enhances the properties of the nanoparticles. [5] When the core particles in it are hydrophobic, the hydrophilic shell layer in the form of a *core-shell nanoparticle* can cover problems in dispersibility, biocompatibility and cytocompatibility. When the core particles in it are susceptible to thermal and chemical changes during exposure to the surrounding environment, an inert material layer generally increases the stability of the core particles.[19]

Core-shell nanoparticles involve the immobilization of a particular compound in a material that is coating it or where it is dispersed. One of the methods to produce *core-shell nanoparticles* is *electrospray* . *Electrospray is* carried out based on the breaking of a liquid into finely charged droplets via an electric field . When the fluid passes through a thin metal tube such as a *nozzle* , needle or capillary, and the meniscus fluid located at the end of the tube is energized by applying a potential difference between the tube and the electrode counter. The advantage of the *electrospray* method compared to other nanoparticle manufacturing methods is that the particle size can be easily controlled and does not require a separation process to separate particles from the solvent.[20]

DISCUSSION

Radiotherapy used to treat HNC tumors often affects the structures in the salivary glands, leaving the acinar cells vulnerable to damage. When radiation is absorbed by living cells, the ionization and excitation processes on atoms produce various free radicals that can react with important macromolecules such as DNA, membrane components, or proteins. Over time, this can cause

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.[21] In normal individuals, the salivary flow rate with stimulation is generally 1.5-2.0 mL / min whereas the salivary flow rate without stimulation is about 0.3-0.4 mL / min. However, in RIH patients, the salivary flow rate with stimulation only reached ≤ 0.5-0.7 mL / min, with the salivary flow rate without stimulation ≤ 0.1 mL / min.[22]

RIH treatment is focused on increasing the salivary 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. [26] 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, uncontrolled asthma, and users of β-adrenergic-blocker drugs, and require greater attention to patients with gastritis, hypertension , and a history of heart disease.[23]

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-kβ signaling pathways, which are key mediators of inflammation by keeping the inhibitor NF-kB kinase subunit-β (IKKβ) from the phosphorylation process.[14] Inhibition of NF-kβ 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.[15,21,24]

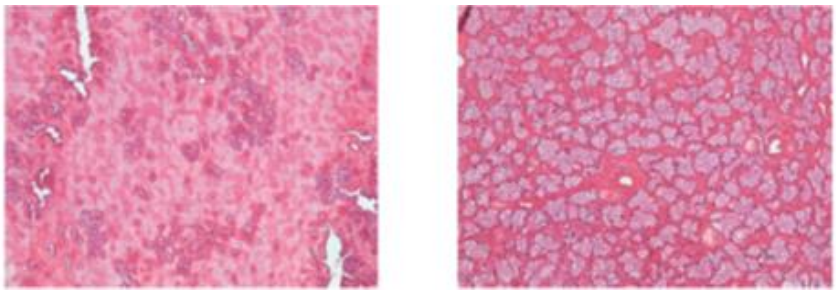

Figure 2. Histopathological studies in parotid gland control after radiotherapy (left) and in the parotid gland after curcumin and radiotherapy (right).[21]

Curcumin has an effect which is known as protective effect of curcumin against free radicals.[25] 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 caspases, and induces apoptosis.[26]

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.[15,27] Core-shell nanoparticles show great potential as carriers for bioactive substances because their sub-cellular size allows for relatively higher intracellular uptake as well as improved stability and protection against degradation.[28] 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.[5,29]

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[30]. 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
2. Cheng SCH, Wu, VWC, Kwong DLW, Ying MTC. Assessment of post-radiotherapy salivary glands. International Journal of Radiology, Radiation Oncology and All Related Science. 2011. pp. 393-402.
3. Pinna R, Campus G. Cumbo E, Mura I, Milia E. Xerostomia induced by radiotherapy: an overview of the physiopathology, clinical evidence, and management of the oral damage. Ther Clin Risk Manag. 2015. 11. pp. 171-188.
4. Farhood B, Mortezaee K, Goradel NH, Salehi E, Nashtaei MS, Najafi M, Sahebkar A. Curcumin as an anti-inflammatory agent: Implications to Radiotherapy and Chemotherapy. Journal of Cellular Physiology. 2018. pp. 1-13.
5. Chatterjee K, Sarkar S, Jagajjanani Rao K, Paria S.Core / shell nanoparticles in biomedical applications. Adv

Colloid Interface Sci . 2014 ; 209: 8 -39. doi: 10.1016 / j.cis.2013.12.008
6. Lovelace TL, Fox NF, Sood AJ, Nguyen SA, Day TA. Management of radiotherapy-induced salivary hypofunction and consequent xerostomia in patients with oral or head and neck cancer: Meta-analysis and literature review. Oral Surg Oral Med Oral Pathol Oral Radiol . 2014 ; 117 (5): 595-607. doi: 10.1016 / j.oooo.2014.01.229.
7. Surjadi N, Amtha R. Radiotherapy Reduced Salivary Flow Rate and Might Induced C. albicans Infection. J Dent Indones . 2013 ; 19 (1): 1-6. doi: 10.14693 / jdi.v19i1.124
8. Palma LF, Gonnelli FAS, Marcucci M, et al. Impact of low-level laser therapy on hyposalivation, salivary pH, and quality of life in head and neck cancer patients post-radiotherapy. Lasers Med Sci . 2017 ; 32 (4): 827-832. doi: 10.1007 / s10103-017-2180-3
9. Almståhl A, Skoogh Andersson J, Alstad T, Fagerberg-Mohlin B, Finizia C. Explorative study on quality of life in relation to salivary secretion rate in head and neck cancer patients treated with radiotherapy up to 2 years post treatment. Int J Dent Hyg . 2019 ; 17 (1): 46-54. doi: 10.1111 / idh.12363
10. Gupta SC, Patchva S, Koh W, Aggarwal BB. Discovery of curcumin, a component of golden spice, and its miraculous biological activities. Clin Exp Pharmacol Physiol . 2012 ; 39 (3): 283-299. doi: 10.1111 / j.1440-1681.2011.05648.x
11. Naksuriya O, Okonogi S, Schiffelers RM, Hennink WE. Curcumin nanoformulations: A review of pharmaceutical properties and preclinical studies and clinical data related to cancer treatment. Biomaterials . 2014 ; 35 (10): 3365-3383. doi: 10.1016 / j.biomaterials.2013.12.090
12. Edwards RL, Luis PB, Varuzza P V., et al. The anti-inflammatory activity of curcumin is mediated by its oxidative metabolites. J Biol Chem . 2017 ; 292 (52): 21243-21252. doi: 10.1074 / jbc.RA117.000123
13. Boroumand N, Samarghandian S, Hashemy SI. Immunomodulatory, anti-inflammatory, and antioxidant effects of curcumin. J HerbMed Pharmacol . 2018 ; 7 (4): 211-219. doi: 10.15171 / jhp.2018.33
14. He Y, Yue Y, Zheng X, Zhang K, Chen S, Du Z. Curcumin, inflammation, and chronic diseases: How are they linked? Molecules . 2015 ; 20 (5): 9183-9213. doi: 10.3390 / molecules20059183
15. Pulido-Moran M, Moreno-Fernandez J, Ramirez-Tortosa C, Ramirez-Tortosa MC. Curcumin and health. Molecules . 2016 ; 21 (3): 1-22. doi: 10.3390 / molecules21030264
16. Pawar HA, Gavasane AJ, Choudhary PD. A Novel and Simple Approach for Extraction and Isolation of Curcuminoids from Turmeric Rhizomes. Adv Recycl Waste Manag . 2018 ; 06 (01): 1-4. doi: 10.4172 / 2475-7675.1000300
17. Kumar KS, Kumar VB, Paik P. Recent Advancement in Functional Core-Shell Nanoparticles of Polymers: Synthesis, Physical Properties, and Applications in Medical Biotechnology. J Nanoparticles . 2013 ; 2013: 1 -24. doi: 10.1155 / 2013/672059
18. Nomoev A V., Bardakhanov SP, Schreiber M, et al. Structure and mechanism of the formation of core-shell nanoparticles obtained through a one-step gas-phase synthesis by electron beam evaporation. Beilstein J Nanotechnol . 2015 ; 6 (1): 874-880. doi: 10.3762 / bjnano.6.89
19. Gawande MB, Goswami A, Asefa T, et al. Core-shell nanoparticles: synthesis and applications in catalysis and electrocatalysis. Chem Soc Rev . 2015 ; 44 (21): 7540-7590. doi: 10.1039 / c5cs00343a
20. Cao L, Luo J, Tu K, Wang LQ, Jiang H. Generation of nano-sized core-shell particles using a coaxial tri-capillary electrospray-template removal method. Colloids Surfaces B Biointerfaces . 2014 ; 115: 212-218. doi: 10.1016 / j.colsurfb.2013.11.046
21. Lopez-Jornet P, Gómez-García F, García Carrillo N, Valle-Rodríguez E, Xerafin A, Vicente-Ortega V.Radioprotective effects of lycopene and curcumin during local irradiation of parotid glands in Sprague Dawley rats. Br J Oral Maxillofac Surg . 2016 ; 54 (3): 275-279. doi: 10.1016 / j.bjoms.2016.01.013
22. Villa A, Connell CL, Abati S. Diagnosis and management of xerostomia and hyposalivation. Ther Clin Risk Manag . 2014 ; 11: 45-51. doi: 10.2147 / TCRM.S76282
23. Farag AM, Holliday C, Cimmino J, Roomian T, Papas A. Comparing the effectiveness and adverse effects of pilocarpine and cevimeline in patients with hyposalivation. Oral Dis . 2019 ; 25 (8): 1937-1944. doi: 10.1111 / odi.13192
24. Xu XY, Meng X, Li S, Gan RY, Li Y, Li H Bin. Bioactivity, health benefits, and related molecular mechanisms of curcumin: Current progress, challenges, and perspectives. Nutrients . 2018 ; 10 (10). doi: 10.3390 / nu10101553
25. Ghelishli N, Ghasemi A, Hosseinimehr SJ. The influence of piperine on the radioprotective effect of curcumin in irradiated human lymphocytes. Turkish J Pharm Sci . 2019 ; 16 (3): 366-370. doi: 10.4274 / tjps.galenos.2018.50103
26. Rather RA, Bhagat M.Cancer Chemoprevention and Piperine: Molecular Mechanism and Therapeutic Opportunities. Front Cell Dev Biol. 2918. p.10. (Rather and baghat: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5818432/).
27. Hu K, Huang X, Gao Y, Huang X, Xiao H, McClements DJ. Core-shell biopolymer nanoparticle delivery systems: Synthesis and characterization of curcumin fortified zein-pectin nanoparticles. Food Chem . 2015 ; 182: 275 -281. doi: 10.1016 / j.foodchem.2015.03.009
28. Baspinar Y, Üstündas M, Bayraktar O, Sezgin C. Curcumin and piperine loaded zein-chitosan nanoparticles: Development and in-vitro characterization. Saudi Pharm J . 2018 ; 26 (3): 323-334. doi: 10.1016 / j.jsps.2018.01.010
29. Gofur NRP, Handono K, Nurdiana N, Kalim H, Wahono CS, Poeranto S, et al. Association of Th – Tc protein CD28+ and periodontal inflammation among Indonesian women with SLE disease. Sys Rev Pharm 2020;11:580-6.
30. Gofur NRP, Handono K, Nurdiana N, Kalim H, Barlianto W. Oral hygiene and dental caries status on systemic lupus erythematosus patients: A cross-sectional study. Pesqui Bras Odontopediatria Clín Integr 2020;20:e0013. doi:10.1590/pboci.2020.116