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Potential of *Moringa oleifera* extract-incorporated with folic acid-conjugated gold nanoparticles as an oral squamous cell carcinoma therapy by modulating intrinsic apoptotic pathway: A narrative review

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Abstract

Background: Oral squamous cell carcinoma (OSCC) is the most common oral cancer worldwide. Surgery, radiotherapy and chemotherapy are the most common treatments, despite their side effects including toxicity, metastasis and multidrug resistance, thus evoking the need to develop safer treatment. Moringa oleifera (Mo) acts as anticancer agent but has poor bioavailability then incorporated with folic acid-conjugated gold nanoparticles (AuNPs) as drug carriers may enhance the action of Mo in OSCC treatment.

Purpose: To describe the potential of Mo extract incorporated with folic acid-conjugated AuNPs as an OSCC therapy by modulating intrinsic apoptosis pathway.

Review: Mo-AuNPs was injected to the body and reached the target cell. Folic acid in AuNPs bound to folic acid receptors in the cell membrane thus promoting endocytosis and encapsulation of Mo. AuNPs along with irradiation using near infrared light converted light into heat thus promoting pro-apoptotic protein release. This condition was also supported by Mo's ability to downregulate Akt thus upregulating Bad. Bad induces translocation of Bax into the outer mitochondrial membrane then induces the opening of mitochondrial pores. This condition manifests in formation of apoptosomes thus activating caspase-3 and inducing formation of apoptotic bodies.

Conclusion: Mo extract-incorporated with folic acid-conjugated AuNPs may potential as an OSCC therapy by modulating intrinsic apoptosis pathway.

Keywords: Dentistry; Intrinsic apoptotic; *Moringa oleifera*; Non-communicable disease; Medicine

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1. Introduction

Oral squamous cell carcinoma (OSCC) is a malignant tumor that appears as an ulcerative and proliferative lesion between the lips and oropharynx with a 5-year survival rate of 50%. OSCC predominantly occurs in gingivobuccal sulcus, tongue and floor of the mouth whereas higher incidents are often found in male rather than women [1-3]. Alcohol consumption, betel nut chewing and tobacco smoking are considered as its etiology [2]. There are three major treatments for OSCC, such as surgery, radiotherapy, and chemotherapy[4]. Although surgery is a definitive treatment for OSCC, many complications can occur after surgery, including infection, hematoma, flap failure, wound deterioration, skin necrosis, bone resorption, osteomyelitis, and salivary fistula. Radiotherapy also has complications, including ulceration, pain, difficulty in eating, bacterial and fungal infections, loss of hair, xerostomia, dental caries, and thickening of the skin [5]. Chemotherapy is thought to have high cytotoxicity to normal cells. Since these cancer treatments are associated with lots of side effects, it is evoking the need to develop safer treatment measures [6].

Nowadays herbal drugs are gaining more attention, and one attractive plant out of thousand species is *Moringa oleifera* (Mo), which is one plant that quickly grows in tropical and subtropical regions, such as Indonesia, and is well known as miracle tree [7,8]. Mo has a fairly high micronutrient and natural bioactive compounds, including phenolic, flavonoids, tannins, alkaloids, saponins, and steroid [9]. Some studies reported that bioactive compounds from Mo may interact with OSCC cell lines and have anti-cancer action by inhibiting cell proliferation [10-12]. However, most of them are hydrophilic which is soluble in water, but have low absorption due to poor permeability to cross the lipid membranes of the cells, and have large molecular size resulting in lower bioavailability and therapeutic efficacy [7-13]. Hence, nanotechnology is found to be promising anti-cancer agents as they could reduce the required dose, enhance the action of plant extracts with minimal side effects and enhance the biological activity, and in combination might gain a better therapeutic potential of herbal medicine.

In recent years, a great number of metallic nanoparticles have been combined with several parts of plant extracts [7]. Among the many nanoparticles being developed, studies show that gold nanoparticles (AuNPs) are stable and are useful in the treatment of rheumatoid arthritis, possess anticancer and antimicrobial properties, and have good biocompatibility. AuNPs are being used in medicine because of their non-toxicity, ease of biodegradability and decreased side effects in patients [14]. Sometimes, secondary capping molecules (such as folic acid) are attached to provide a binding surface for specific cells. This is to minimize non-specific targeting on other tissues since folic acid receptors are often found to be overexpressed in OSCC's cell surface rather than in normal cells, based on this fact, folate targeting strategy was applied in this paper [15]. Although Mo extracts have been applied in the management of cancer, there is currently no reported literature on the modulating intrinsic apoptosis pathway of Mo incorporated with folic acid-conjugated gold nanoparticles on OSCC. Thus, this study explored the apoptosis modulating action of this combination on OSCC through a narrative review.

2. Oral squamous cell carcinoma

Oral squamous cell carcinoma (OSCC) is a malignant tumor arising from the stratified squamous epithelium of the oral mucosa with a multifactorial etiology [16]. OSCC progresses through a series of events from benign hyperplasia to mild, moderate, and severe dysplasia, to carcinoma in situ, and finally to OSCC [17]. A major pathogenesis pathway in the development of oral malignancies is excessive production of reactive oxygen species (ROS) such as superoxide radicals, hydroxyl radicals and hydrogen peroxide [18]. ROS are involved in all major steps in the classical model of carcinogenesis. Initiation occurs when a critical, irreversible DNA mutation occurs in a normal cell [19]. An increase in ROS is able to induce the formation of double stranded breaks of DNA that leads to mutation of normal cells. One of the most involved protein that mutated in this process is p53, which is a protein that acts as guardian of the cell that regulates most of the cell activities. Disruption in p53 function often leads to inhibition of apoptosis. Typically, it is the intrinsic pathway that is inhibited in cancer, however, there are a wide range of means to inhibit apoptosis. One way of treating cancer is to gain control or possibly terminate the uncontrolled growth of cancer cells. Using the cell's own mechanism for death is a highly effective method. Additionally, targeting apoptosis is the most successful non-surgical treatment [20].

3. Moringa oleifera

Moringa oleifera (Mo) or 'miracle tree' is one of the world's most useful tree, with medical, nutritional, and other beneficial values.[21] *Mo* spreads in the tropical and subtropical countries around the world, and was estimated to originate from Agra and Oudh, the northwest region of India, south of the Himalayan Mountains. Globally, Mo is known under various aliases horseradish tree, drum stick tree, benzoil tree, *marango*, *mlonge, moonga, mulangay, nebeday,*

saijhan, sajna, and ben oil, whereas in Indonesia, it is known as *kelor*.[22,23] Mo's taxonomic classification is listed in Table 1.

Table 1 Taxonomic Classification of *Moringa oleifera*[21,22]

Kingdom	**Plantae**
Sub kingdom	Tracheobionta
Super Division	Spermatophyta
Division	Magnoliophyta
Class	Magnoliopsida
Subclass	Dilleniidae
Order	Capparales
Family	Moringaceae
Genus	*Moringa*
Species	*M. oleifera*

Figure 1 Flowers and leaves of M. oleifera[22]

Figure 2 Leaves of M. oleifera[22]

Every part of Mo, including the leaves, roots, seed, stem, bark, fruit, flowers, and immature pods, is a storehouse of important nutrients and antinutrients[24], shown in Table 2. Mo leaves are frequently used for research, both to determine the content of chemical compounds contained in them and to analyze their nutritional content.[25,26] Numbers of phytochemical composition can be found in the Mo, such as phenolics, tannins, sterols, terpenoids, flavonoids, saponins, anthraquinones, alkaloids and anti-cancerous agents like glucosinolates, isothiocyanates, glycoside compounds and glycerol-1-9-octadecanoate.[27]

Table 2 Phytoconstituents & Biological activity of plant *Moringa oleifera*[22]

Parts of Plant	Phytochemical constituents	Biological activity
Leaves	Niazirin, Niazirinin, Niaziminin, Niazimicin A, Niazimicin B	Anticonvulsant, Antioxidant, Antihypertensive, antibacterial, anticancer
Seeds	Moringine, niazimicin, niazirin	Acts against asthma
Pods	Isothiocyanate, nitrites, beta- sitosterol	Act against inflammation & helmintics
Bark	Benzylgiucosinolate derivatives	Act against urolithiatic
Flowers	Present some chemical constituents like as quercetin, isoquercetin, kaemopherol, kaempferitin	Act against inflammation
Root	Some chemical constituents are extract from root are Moringine, moringinine, spirachin,also p-cymene	Antifertility
Stem	Chemical constituents are extracted from stem Vanillin , beta- sitosterone	Act against inflammation

Several studies have reported the chemopreventive properties of Mo by inhibiting the growth of human cancer cells.[28] There is report that proved the antioxidant and immunomodulatory activity of a-tocopherol and c-sitosterol found in Mo, which showed anti-tumor activity in oral squamous cell carcinoma (ORL-48) cell lines and chemopreventive activity against tobacco-induced carcinogenesis.[10] In another study, extracts of Mo and their fractions, 3-hydroxy-β-ionone inhibited cancer proliferation and progression in squamous cell carcinoma cell line (SCC15) through increased activity of caspase-3, decreased Bcl-2 and increased BAX that inducing apoptosis.[11]

4. Gold nanoparticles

AuNPs are gold-based drug carriers with diameter ranging from 50-150 nm.[29] AuNPs has high stability and functionality. This material is often used as a drug carrier, genetic material detector, and biosensing agent. AuNPs is known to be conjugated to certain ligands in order to increase their chance to be endocytosed. Previous research showed that folic acid is considered as one of the best ligan to be conjugated with AuNPs due to its ability to interact with overexpressed folic acid receptors in the surface of OSCC to promote endocytosis.[30-32]

5. Discussion

Combination of Mo and folic acid-conjugated AuNPs works by different mechanisms. Folic acid, a water-soluble vitamin, is conjugated to AuNPs in order to increase the chance of AuNPs getting endocytosed by cancer cells. Folic acid interacts with cell membrane folate receptors that are widely expressed in cancer cell membranes then Mo loaded AuNPs are endocytosed and encapsulated releasing Mo.[33-35] On the other side, the role of AuNPs as drug carriers is being enhanced by the near-infrared (NIR) light exposure. NIR light is a light with wavelength ranging from 600-1000 mm.[36] AuNPs have electrons occur on the surface thus making this material holding electric force. Light is recognized as electromagnetic waves. While injected AuNPs were irradiated to electromagnetic waves on the surface of the skin, interaction between electric force of AuNPs itself and electromagnetic force manifested in diffraction of light and excitation of electrons of AuNPs with a certain angle and disseminated parallel to the surface of AuNPs. As a consequence, electrons of AuNPs oscillate then resonate with oscillation of electric force by NIR light results in generation of plasmonic energy then producing heat, whereas this phenomenon is well-known as surface plasmon resonance (SPR), a special term in metal material especially AuNPs.[37-39] An increase in intracellular temperature manifests in Puma and Noxa expression that play a role in activating intrinsic apoptosis pathway. Puma and Noxa are considered as pro-apoptosis proteins. An increase in both proteins is known to downregulate the expression of B-cell lymphoma 2 (Bcl-2), B-cell lymphoma-extra large (Bcl-XL) and myeloid-cell leukemia 1 (MCL-1) as anti-apoptosis proteins.[40-41]

Encapsulated Mo does play a role. An increase in Puma and Noxa due to heat induction by folic acid-conjugated AuNPs has potential to work synergistically with Mo in modulating intrinsic apoptosis pathway. Mo has a lot of antioxidants due to the presence of a-tocopherol and b-sitosterol that is able to minimize the level of DNA destruction due to ROS expression. This condition slows OSCC progression by preventing further DNA mutation thus can suppress wider destruction of p53.[11]

Activation of p53 as tumor suppressor leads to inactivation of protein kinase B (Akt).[42,43] Akt is inactivated by disrupting phosphorylation process of T308 and S473 which causes a decrease in the catalytic process and inactivation manifests in decreased expression of Bcl-2 as an anti-apoptotic protein.[44,45] A decrease of Bcl-2 accompanied by downregulation of Bcl-XL and MCL-1 leads to activation of Bcl-2 homologous antagonist killer (Bak) by BH3 on the mitochondrial outer membrane.[46] The activation of Bak may also be caused by an increase of BH3-interacting-domain death agonist (Bid) and p53 upregulated modulator of apoptosis (Puma). This results in the autoactivation and translocation of Bcl-2-associated X protein (Bax) to the mitochondria and sustained stability of Bcl-2-related ovarian killer (Bok) so that mitochondrial outer membrane fusion is performed.[47,48] This condition induces pore opening on the mitochondrial membrane, and interferes with the lowering of mitochondrial outer membrane permeability so that cytochrome c is released.[47,49]

Cytochrome c is a protein that makes up the apoptosome and acts on the nucleus by inhibiting the activity of histone chaperones in the DNA damage process.[50] The apoptosome is composed of cytochrome c, apoptotic protease activating factor-1 (Apaf-1), pro-caspase-9, and adenosine triphosphate (ATP). The presence of cytochrome c results in fixation with Apaf-1 through the caspase recruitment domain so that the formation of bonds with pro-caspase-9 and ATP is performed so that the apoptosome is completely formed.[51,52] The opening of the pore in the mitochondria causes the release of cytochrome c and SMAC/Diablo from the inner mitochondrial membrane into the cytoplasm. This condition is supported by the expression of E2F which induces the synthesis of Apaf-1, resulting in oligomerization of cytochrome c with Apaf-1 through the caspase recruitment domain of Apaf-1. This structure will then bind to pro-caspase-9 and ATP which manifests in the formation of a heterodimer structure as an apoptosome that induces proteolytic activity so that an active site is formed on caspase-3.[53-54]

On the other hand, the activation of caspase-3 and caspase-9 is also assisted by Smac/Diablo and Htr2/Omi which are released when the pores of the mitochondria are opened. This condition resulted in the inhibition of the binding process of XIAP as a caspase inhibitor with caspase-3/9 because Smac/Diablo and Htr2/Omi would induce the degradation of XIAP. This causes the subdomain of XIAP, namely BIR3 to be unable to bind to pro-caspase-9 and BIR2 not to bind to pro-caspase-3 so that the caspase-3/9 could be activated.[55,56] Activation of caspase-3 will cause an increase in hydrostatic pressure in the cell which is accompanied by cell contraction by actomyosin, resulting in membrane blebbing. This process occurs repeatedly and causes retraction of cells undergoing apoptosis, resulting in the formation of apoptotic bodies that are covered with organelles and cellular material. Apoptotic bodies that have been formed are easily recognized by immune cells and can then be phagocytosed by macrophages.[57]

6. Conclusion

According to this narrative review, Mo extract-incorporated with folic acid-conjugated AuNPs may potential as an OSCC therapy by modulating intrinsic apoptosis pathway. More researches need to be carried out to determine the prospective uses of this combination as a therapeutic agent because of their unique properties. Its ligand targeted mechanism makes it promising anti-cancer candidates to transport drugs for a targeted treatment. However, several tests should be done to determine its toxicity, duration, dosage, and excretion precisely before being given to patients safely, and in vivo studies also should begin so that the potential of Mo extract-incorporated with folic acid-conjugated AuNPs as an OSCC therapy can be achieved in the future.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare there is no conflict of interest in this study.

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