INTRODUCTION

Osteonecrosis of the jaw is a rare disease but it is a serious one, which can affect maxilla and mandible. It manifests as necrotic lesion and affects bone in the oral cavity and stays there for at least about eight weeks. The symptoms include pain, mucosa swelling, teeth loss, erythema and or infection. Although more than a decade this disease has been known, the pathophysiology of this disease remains unclear. Though bisphosphonate is the drug that can inhibit the formation of osteoclast and its activity, the actions of bisphosphonate on osteoblasts have not been fully understood, in which such as actions may take the forms of the decreased bone turnover and microfracture accumulation, a decrease of osteoblast collagen production, the anti-angiogenic effect triggering avascular necrosis and decreased viability of fibroblasts and keratinocytes. Although bisphosphonate is useful for the bone, but it has to do with osteonecrosis of the jaw.

Some researches have shown that VEGF may play an important role in bone improvement. Consequently, the inhibition of the physiological effect of VEGF through VEGF antagonist known as anti-VEGF agent is a predisposition to suffer from the jaw osteonecrosis. Bevacuzimab is recombinant monoclonal antibody of immunoglobulin-G specifically targeting VEGF-A, as the isoform of VEGFR receptors type 1 and 2. It has been reported that patients treated by bevacuzimab suffered from osteonecrosis of the jaw, although it is very rare occurrence.

Bunga Cempaka (Michelia champaca) or also known as Cempaka Kuning, is one of about 50 species of the genus Michelia members. Michelia champaca is a tree or shrub about 3-6 meters in height. Its flowers smell good and the colors are orange, yellow or creamy white, it is rather big in size, it has multiple petal arrangement. It has brown fruit consisting of 2-6 seeds. The oil of this flower is used as a perfume ingredient.
forests on arable land at the altitude of up to 1,500 m above sea level. This plant is used as mixture of herbs or hair fragrance or is mixed with other ingredients to produce perfumes. The flowers can be extracted to produce perfume or fragrance mixture in cosmetics. This plant is antifungal and antimicrobial,\textsuperscript{11} antifertility,\textsuperscript{12} antidiabetes,\textsuperscript{13} anticancer,\textsuperscript{13} and antileishmaniasis.\textsuperscript{14} Concerning the analogy with anti-VEGF therapy, there are no any data studying the interaction of the active components of \textit{Michelia champaca} on VEGF. Thus, the objective of this study was to analyze the effect of the active substances of \textit{Michelia champaca} on VEGF in pathomechanism of the jaw osteonecrosis.

**METHODOLOGY**

**Ligand preparation:** Three-dimensional structure of the liriodenine/macheline B, oxoxylopine/lanuginosine, beta-sitosterol, micheliolide, linalool and polyisoprenoid compounds were obtained from NCBI PubChem. ID Liriodenine/Macheline B CID10144, ID Oxoxylopine/Lanuginosine CID97622,\textsuperscript{??} ID beta-sitosterol CID222284, ID Micheliolide CID 442279 and ID linalool CID6549 and polyisoprenoid. The three-dimensional structure in.sdf file was converted to PDB format using Open Babel 2.3.1 software.\textsuperscript{15}

**Protein receptor:** The three-dimensional structure model of RCSB Vascular Endothelial Growth Factor PDB ID: PDB-2VPF was obtained from http://www.rcsb.org/pdb.

**Ligand-Protein Docking and Visualization:** Software Hex 8.0 is a rigid docking,\textsuperscript{16} used as a device to calculate the potential interactions between the liriodenine/machelineB, liriodenine/macheline B, beta-sitosterol, micheliolide, linalool, and polyisoprenoid and VEGF used to illustrate the active side of the interaction using Discovery Studio Client 3.5 software.\textsuperscript{17}

**RESULTS**
The active substances of \textit{Michelia champaca} that experienced the docking include polyisoprenoid, micheliolide, beta-sitosterol, oxoxylopine (lanuginosine), liriodenine (macheline B) and linalool.
Energies required for interaction of polyisoprenoid, micheliolide, β-sitosterol, oxoxylopine (lanuginosine), liriodenine (macheline B) and linalool were -443.16 KJ/mol; -222.73 KJ/mol; -248.16 KJ/mol; -252.41 KJ/mol; -237.78 KJ/mol; and -176.69 KJ/mol. Thus, polyisoprenoid required the smallest energy to make an interaction with VEGF.

DISCUSSION

Angiogenesis is a complex process involving growth, migration, and differentiation of endothelial cells to form new blood vessels. Angiogenesis can affect tumor growth and tumor invasion into the blood vessels, resulting in tumor cell metastasis. Angiogenesis requires the bonding of a signal molecule, ie, VEGF to a receptor in endothelial cells. This signal will support the growth of new blood vessels. Osteonecrosis is a disorder of the vascular supply or avascular necrosis, which is based on the inhibition of angiogenesis. VEGF is a positive regulator of angiogenesis and is involved in the development of vascular endothelial cells, blood vessel growth and vascular permeability progression. VEGF also plays a role in osteogenic differentiation and bone formation.

Compounds that are anti-VEGF can interfere with the integrity of microvessel. This disruption of integrity will damage bone tissue through inhibition of cell differentiation and bone function. In addition, this effect also impairs physiological bone healing. In this study, the polyisoprenoid requires the smallest energy to interact with VEGF (-443.16 KJ/mol). This shows that the polyisoprenoid represents an active compound of Michelia champaca, which is most potentially to form a complex with VEGF. Other compounds, such as micheliolide (-222.73 KJ/mol), β-sitosterol (-248.16 KJ/mol), oxoxylopine (lanuginosine) (-252.41 KJ/mol), liriodenine (macheline B) (-237.78 KJ/mol), and linalool (-176.69 KJ/mol) also interact with VEGF. Thus, the application of Michelia champaca product in the form of herbs or other preparations can become the predisposition of the jaw osteonecrosis. These findings support previous findings that lifestyles that increase the risk of osteonecrosis include smoking, alcohol
consumption, obesity, and administration of corticosteroid compounds, erythropoietin, angiogenic inhibitors, and tyrosine kinase inhibitors.26

CONCLUSION
It is concluded that the active substances of *Michelia champaka* can interact with VEGF so that this plant potentially serves as a predisposition for osteonecrosis of the jaw. The polyisoprenoid requires the smallest energy to interact with VEGF.

## REFERENCES


