Potential Mechanism of Platelet-rich Plasma Treatment on Testicular Problems Related to Diabetes Mellitus

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Received April 14, 2023; Accepted November 15, 2023.

Key words: Platelet-rich plasma – Diabetes mellitus – Testicular problem – Growth factors

Abstract: Diabetes mellitus is a condition of continuously increased blood glucose levels that causes hyperglycemia. This condition can result in disorders of various organs including testicular problems. The use of platelet-rich plasma (PRP) which is contained in several growth factors shows its potential in overcoming testicular problems. This literature review study was conducted to identify the potential of PRP in overcoming various testicular problems due to diabetic conditions.

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https://doi.org/10.14712/23362936.2023.27

Introduction

Diabetes mellitus (DM) is a metabolic disorder characterized by a continuous increase in glucose levels known as hyperglycemia. Impaired insulin secretion and action lead to hyperglycemia, manifested in carbohydrate, fat, and protein metabolism disturbances (American Diabetes Association, 2014). The increasing prevalence of DM is a global health challenge and can affect individuals, families, and communities' well-being. International Diabetes Federation states that in 2021 as many as 537 million adults (20–79 years) have diabetes, and as many as 3 out of 4 adults with diabetes live in low- and middle-income countries (IDF, 2021). The cases of DM are predicted to increase, and it is estimated they will reach 578 million cases in 2030 and 700 million cases in 2045 (Saeedi et al., 2019). The prevalence of DM in Southeast Asia in 2021 is estimated to reach 90 million and predicted to rise to 152 million in 2045 (IDF, 2021). DM is the 3rd disease with high mortality in Indonesia, with a prevalence of around 10 million people in 2018. Its prevalence is expected to increase two to three times in the next 10 years (KEMENKES, 2018).

Reproductive system problems caused by DM have been reported in several studies. Sperm analysis in men with DM showed lower results on concentration, sperm motility, seminal fluid volume, and testosterone levels compared to healthy men (Maresch et al., 2017; Long et al., 2018). The imbalance between reactive oxygen species (ROS) production and the ability to deoxidation results in increased oxidative stress in the reproductive system of men with DM. This condition initiates the impairment of the protein and DNA structure of the cells which results in damage to cellular function. Previous studies revealed that increased oxidative stress in DM can cause testicular DNA damage, disturb the reproductive cell survival and spermatogenesis function, and further cause male infertility (Shrilatha, 2007; Shrilatha and Muralidhara, 2007).

Platelet-rich plasma (PRP) has been widely used to treat several health problems, including aesthetic dermatology as a skin rejuvenation agent, acne scar treatment, hair loss treatment, treatment for skin pigmentation problems, and several other skin problems (White et al., 2021). Several studies have been conducted to determine the therapeutic effect of PRP on male reproductive problems treatment. A previous study by Dehghani et al. (2019) showed that intratesticular injection of 80 µl of PRP in rat model of male infertility induced by Busulfan, increased the number of spermatogenic stem cells, sperm count, motility, tail length, and testosterone level. This shows that PRP has the potential to repair the testicular structure and function damage in infertility animal models (Dehghani et al., 2019). The aim of this literature review is primarily to discuss the potential mechanism of PRP to treat and improve testicular problems as a result of DM.

Molecular pathophysiology of diabetes mellitus

This condition may be due to insulin secretion disturbance resistance in responding to insulin peripheral action, or both (Zheng et al., 2018). Generally, DM is

categorized into 3 subtypes namely: type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), and gestational diabetes (GDM) (American Diabetes Association, 2009). Sedentary lifestyle, aging, and contamination of chemicals toxicity have led to an increase in the prevalence of T2DM in society with a proportion of 90% of all DM cases (Hu and Jia, 2019). DM will cause various organs disturbances such as the kidneys, heart, eyes, blood vessels, nerves, and reproductive organs. Several studies stated the adverse impact of DM on testicular function so that it can affect fertility status (Condorelli et al., 2018; Galicia-Garcia et al., 2020). Excess nutrition and obesity cause hyperglycemia and dyslipidemia which have an impact on chronic and systemic inflammation which in turn develops into complications of diabetes in various organs. Macrophages and dendritic cells will be activated as a result of chronic hyperglycemia and dyslipidemia resulting in increased release of proinflammatory cytokines such as IL-1β and TNF-α. Chronic inflammation that occurs will activate various signalling pathways including NF-κB and p38 MAPK which results in the development of several DM complications including diabetic kidney disease, diabetic retinopathy, and diabetic peripheral neuropathy (Kong et al., 2021).

Diabetes progressivity and its complication development are also known to have close relation with the role of advanced glycation end products (AGEs). AGEs production is induced by uncontrolled hyperglycemia which in turn leads to the development of diabetic complications (Peppa et al., 2003; Cole and Florez, 2020). Irreversible damage caused by AGEs on structural and functional integrity through intermolecular and intramolecular cross-linking is believed to be the principal mechanism. Adjacent AGE molecules can bind to each other and to certain proteins resulting in changes in protein structure and function. The disruption caused by this binding affects in inactivation of proteins and enzymes, increased resistance to proteolytic digestion, ROS formation facilitation, increased inflammatory reactions and disrupted intracellular signalling resulting in metabolic and biochemical changes (Khalid et al., 2022). Several cell-mediated pathophysiological responses may arise as a result of interactions between AGEs and various cell surface receptors that are thought to contribute to the onset of DM. Activation of various signalling pathways is triggered by binding between AGEs and their cognate receptors that initiate changes in cellular function and metabolism through increased inflammatory reactions and oxidative stress (Asadipooya and Uy, 2019).

Diabetes mellitus and testicular problems

AGEs formation due to long-term uncontrolled hyperglycemia can indirectly cause sperm disorders in diabetes. Individuals with DM often experience increased levels of AGE in their blood. This triggers further damage processes through the general mechanisms of inflammation, oxidative stress, and apoptosis (Kong et al., 2021). Cellular damage caused by AGEs in the testes has been studied, and it is known to reduce testosterone production leading to spermatogenesis disturbances (Zhao et al., 2016b; Chen et al., 2019; Rizal et al., 2019). AGEs are able to produce ROS

through modification of macromolecular functions independently or through binding to AGEs receptors (RAGE) (Yamagishi, 2008).

Human spermatozoa have less adequate repair mechanisms; besides that, the high content of polyunsaturated fatty acids makes them vulnerable to oxidative stress (Lewis and Aitken, 2005). ROS formation causes membrane lipid peroxidation which results in an increase in malondialdehyde (MDA) levels as a biomarker of lipid peroxidation in spermatozoa (Aitken et al., 1989; Tavilani et al., 2005). Spermatozoa fertilizing ability is strongly influenced by oxidative stress conditions due to increased ROS via the production of lipid peroxides from unsaturated fatty acids which accumulate in large quantities in the sperm cell membrane phospholipids (Nakamura et al., 2002; Mahfouz et al., 2009). A study by Karimi et al. (2011) showed an increase in MDA levels of sperm and seminal plasma in diabetic men with normozoospermic that led to elevated of cell damage. This may lower the fertility capacity in diabetic men with normal semen analysis (Karimi et al., 2011). Seminal plasma has antioxidant capacity both enzymatic and non-enzymatic which can protect spermatozoa from oxidative stress (Micheli et al., 2016). Seminal total antioxidant capacity (TAC) was shown to be lower in diabetic men compare to the non-diabetic (Karimi et al., 2011). The probability of male infertility was increased regarding the reduced seminal TAC due to high levels of ROS (Mahfouz et al., 2009). The decrease in TAC level is in line with the increase in MDA level in diabetic men. Besides that, the study also revealed that AGEs negatively correlated with seminal TAC indicated the increase in stress oxidative in the semen of diabetic men (Karimi et al., 2011).

Platelet-rich plasma (PRP) in reproductive system

Definition of PRP

Platelets are part of the blood cells with the smallest density compared to other blood components. Platelet diameter is 2 μM with normal counts ranging from 150,000–400,000 platelets per μl (Daly, 2011; Williams and Sergent, 2022). The key function of platelets is in the process of aggregation and bleeding prevention through the formation of plugs in the area of damaged blood vessels. It stimulates the secretion of blood clotting factors to induce the coagulation process. The high content of growth factors in platelets also plays a role in inflammatory processes, angiogenesis, stem cell migration, and cell proliferation (Periayah et al., 2017).

Platelet-rich plasma or platelet-rich growth factor is an autologous blood product that is rich in platelets in a small volume of plasma, above baseline obtained by centrifugation (Alves and Grimalt, 2018). PRP has been used extensively in the medical field as a therapeutic option in managing various health problems. Several studies reported PRP could improve the wound-healing process by accelerating the increase in fibroblasts, macrophages, and collagen in maxillofacial surgical interventions (Menchisheva et al., 2019). In addition to the field of aesthetic dermatology, PRP is reported to have a positive effect on treating osteoarthritis by

preventing the severity of articular cartilage damage (Bansal et al., 2021). The use of PRP for the treatment of muscle injuries has been reported in several clinical studies. The PRP treatment showed a positive response to the healing process, reduced pain, and shorten the return to play in some athletes (Setayesh et al., 2018).

PRP classification

Based on the cell components and fibrin architecture, PRP is classified into four major families (Table 1) (Dohan Ehrenfest et al., 2009).

Table 1 – Platelet-rich plasma classification

Pure platelet-rich plasma (P-PRP)	1. Also known as leukocyte-poor PRP 2. Preparation without leukocyte content 3. Low-density fibrin network after activation
Leukocyte- and PRP (L-PRP)	1. Preparations with leukocytes 2. Low-density fibrin network after activation 3. The most widely used in various commercial and experimental protocols
Pure platelet-rich fibrin (PRF)	1. Also known as leukocyte-poor platelet-rich fibrin 2. Preparations without leukocytes 3. High-density fibrin network
Leukocyte- and platelet-rich fibrin (L-PRF)	1. Also known as second-generation PRP 2. Preparations with leukocytes 3. High-density fibrin network

PRP preparation

The PRP production was carried out by differential centrifugation. Sedimentation of certain cellular constituents was obtained by adjustment of acceleration force based on different specific gravity (Dhurat and Sukesh, 2014). For PRP preparation the buffy-coat method was employed, as described below:

1) PRP-method

Centrifugation was conducted two times. Separated red blood cells (RBCs) were obtained from the first centrifugation, while the second ones resulted in a concentrated platelet suspended in the small volume of the plasma.

As an initial step, the whole blood (WB) was collected in the anticoagulants-contained tube. Constant acceleration centrifugation was conducted for RBC separation. This step resulted in three layers: an upper layer contains platelets and white blood cells (WBCs), a middle thin layer namely buffy-coat that is rich-contained of WBCs, and the bottom layer consist of RBCs (Dhurat and Sukesh, 2014).

The upper layer was discarded from the tube, remaining the buffy-coat and RBCs continues to the second centrifugation. The second centrifugation was carried out

at a sufficient speed to separate the buffy coat into PRP and residual RBCs (Dhurat and Sukesh, 2014; Mijiritsky et al., 2021). The upper 2/3rd portion of the volume that mostly contained PPP (platelet-poor plasma) was discarded, and the remaining 1/3rd volume of plasma (±5 ml) was homogenized to prepare the PRP (Dhurat and Sukesh, 2014).

2) Buffy-coat method
Before the high-speed centrifugation, the WB should be stored at 20 °C to 40 °C. There are three layers produced by the high-speed centrifugation: the bottom layer consisting of RBCs, the middle layer consisting of platelets and WBCs and the top PPP layer. The supernatant plasma at the top of the tube was removed and the buffy-coat layer was then transferred to another sterile tube. The separation of WBCs was conducted by low-speed centrifugation or use Leukocyte filtration filter. In the buffy-coat method, as much as 10 ml of the whole blood can produce a very thin layer of buffy coat, making it difficult to separate WBC and platelets from the underlying RBC layer (Dhurat and Sukesh, 2014).

Growth factors component of PRP
Platelets contain three types of granules, namely alpha, delta, and lambda, which secrete various proteins and substances needed in the process of tissue repair. Granules make up about 10% of the platelet volume, with about 50–80 α-granules in each platelet. These granules consist of membrane-bound proteins (including integrin [αIIb, α6, β3], platelet endothelial cell adhesion molecule [PECAM], leucine-rich repeat family receptors [GPIb-IX-V complex], immunoglobulin family receptors [glycoprotein VI] and other receptors [CD36, Glut-3]) and soluble proteins that are released into extracellular space (Maynard et al., 2007). The majority of components of delta granules are beneficial for the clotting process such as calcium, magnesium, adenosine, and bioactive amines (serotonin and histamine) (Jedlitschky et al., 2004). Lambda granules as lysosomal-type organelles contained enzymes that have a critical role in the protein, lipid, and carbohydrate degradation process. They have also a role in the debris and infectious agents removal in the tissue damage (Boswell et al., 2012). Activated platelet-rich plasma will release several growth factors such as platelet-derived growth factor (PDGF), epidermal growth factor (EGF), transforming growth factor β (TGF-β), fibroblast growth factor (FGF), insulin-like growth factor (IGF), and vascular endothelial growth factor (VEGF) (Marck et al., 2019).

1) Platelet derived growth factor (PDGF)
PDGF is involved in stimulation of cell proliferation and migration in the process of embryogenesis (Andrae et al., 2008; Demoulin and Essaghir, 2014). The PDGF family consists of four polypeptide chains encoded by four different genes, namely PDGFA, PDGFB, PDGFC, and PDGFD genes that are located on chromosomes 7, 22, 4, and 11, respectively (Fredriksson et al., 2004). This protein acts via two receptors,

namely PDGFRα and PDGFRβ which have different roles in various human biological processes. PDGFRα-dependent signalling regulates the gastrulation and development of lungs, intestines, skin, testes, kidneys, and other organs. Meanwhile, the PDGFRβ is involved in the process of early hematopoiesis and blood vessel formation (Andrae et al., 2008).

2) Transforming growth factor β (TGF-β)
TGF-β consist of three isoforms, namely TGF-β, TGF-β1, TGF-β2 and TGF-β3 (Davis et al., 2014). This growth factor has a crucial role in stimulating collagen production and in protecting it from damage. In addition, TGF-β1 is also involved in the process of angiogenesis, connective tissue regeneration, and immune cell chemotaxis (Gurtner et al., 2008).

3) Vascular endothelial growth factor (VEGF)
VEGF is involved in the process of angiogenesis, nutrient transport, and increases blood flow to the place of injury. The increase in VEGF secretion is interrelated with other growth factors such as PDGF, TGF-β and EGF (Barrientos et al., 2008; Dhillon et al., 2012).

4) Epidermal growth factor (EGF)
EGF is reported to have a close correlation to the action of mesenchymal and epithelial cells in secreting cytokines. The presence of EGF can stimulate mesenchymal cells to undergo mitotic division. The processes of angiogenesis and chemotaxis in endothelial cells are also known to be stimulated by EGF secretion. Other studies also state that EGF can accelerate the epithelialization and healing process (Barrientos et al., 2008; Berlanga-Acosta et al., 2009; Knezevic et al., 2016).

5) Insulin-like growth factor (IGF)
During platelet activation, IGF was released and has a role in the stimulation of differentiation and mitogenesis of mesenchymal cells (Marques et al., 2015). IGF is known to have critical roles in cell growth, differentiation, and together with PDGF it stimulates the collagen synthesis (Pavlovic et al., 2016).

6) Fibroblast growth factor (FGF)
FGF as the most potent mitogen, is involved in various actions in various cell types, especially mesenchymal cells, chondrocytes, and osteoblasts. FGF has a crucial role in the growth and differentiation of chondrocytes and osteoblasts and supports the process of angiogenesis along with VEGF (Barrientos et al., 2008; Oliveira Filho et al., 2010).

PRP treatment in reproductive system
PRP administration in the management of human reproductive problems has been reported in several studies. A previous study reported that PRP has been used

to manage poor ovarian response (POR) (Dawood and Salem, 2018). PRP is also used in assisted reproductive technology, especially for the treatment of premature ovarian failure (POF), which is a condition where the ovary fails to respond to stimulation for follicle production. Based on the study conducted by Pantos et al. (2019), an increase in folliculogenesis and improvement in ovarian function is reported from 8 perimenopausal women/POF after PRP administration.

A study by Bader et al. (2020) showed that the use of autologous PRP in male infertility management showed an improvement in vitality and motility, and a significant reduction in vacuolization, DNA fragmentation, and ROS levels. As much as 2% PRP treatment was reported to improve sperm parameters and prevented cell death in H_2O_2-exposed spermatozoa compared to a fresh-collected semen sample (Bader et al., 2020). Another study conducted by Samy et al. (2020) showed that PRP has an essential role in preventing testicular degeneration in testicular-detorsion-induced rats as indicated by increasing antioxidant markers (TAC, GSH, GST), increasing Bcl2 expression, and decreasing IL-1β, TNF-α, and caspase-3.

Potential mechanism of PRP in treated the testicular problems related to DM

Anti-inflammation

PRP is known to contain high concentrations of growth factors which play an important role in anti-inflammatory activity through inhibition of the nuclear factor-kB (NFκB) cascade. In line with these, there is a decrease in the expression of inflammatory mediators accompanied by a decrease in COX-2 expression (Thursina et al., 2022). The growth factors contained in PRP also facilitate cellular anabolism, increasing the release of inflammatory mediators and modulators resulting in anti-inflammatory and analgesic effects (Xie et al., 2014). This is also supported by research results which show that PRP can counteract the inflammatory cascade by increasing various anti-inflammatory factors such as hepatocyte growth factor (HGF) (Wu et al., 2011; Thu, 2022). The HGF content in PRP is known to inhibit the translocation of the NF-κB-p65 subunit into the nucleus resulting in downregulation of the transcription of several proinflammatory factors such as MMPs, ADAMTs, and IL-1β (Camargo Garbin and Olver, 2019). Apart from HGF, several growth factors contained in PRP are involved in inhibiting the inflammatory process, including PDGF, TGF-β, and IGF (Andia and Maffulli, 2013). The schematic of growth factors contained in PRP in regulating the inflammatory process is depicted in Figure 1.

Anti-apoptosis

PRP is known to have an anti-apoptotic effect, this was shown through a study conducted by Samy et al. (2020) using a rat model of testicular torsion. Testicular torsion is known to reduce Bcl-2 expression as an anti-apoptotic factor. Administration of PRP is known to significantly increase Bcl-2 expression and decrease Caspase-3 expression which indicates PRP's ability to ameliorate the tissue

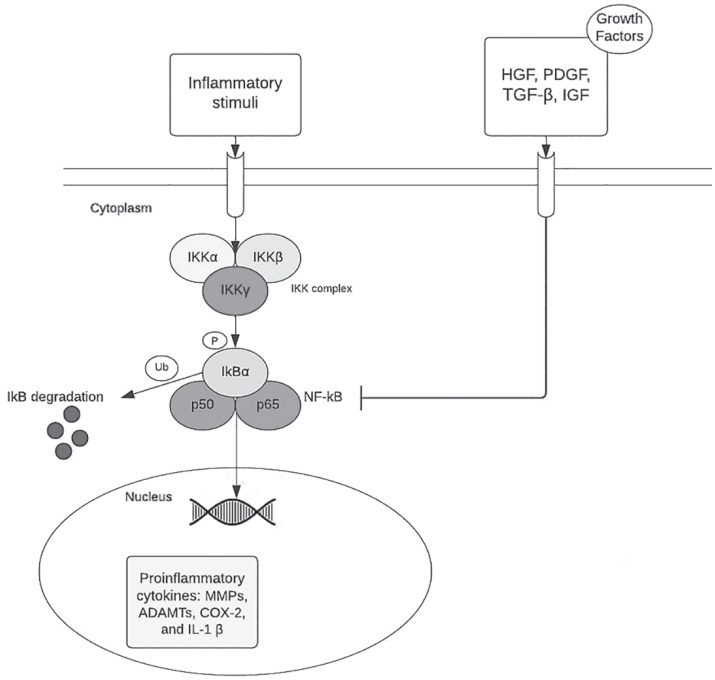

Figure 1 – Platelet-rich plasma (PRP) involvement in inhibitory of inflammation process. Extracellular inflammatory stimulus activates the IκB kinase (IKK) enzyme through binding to integral membrane receptors. This activation causes the IκBα protein to be phosphorylated, resulting in ubiquitination and dissociation of NF-κB which will then be degraded by the proteosome. An activated NF-κB will enter the nucleus for binding to specific DNA sequences and affect several cell functions. Administration of PRP containing growth factors can inhibit the translocation of activated NF-κB into the nucleus resulting in downregulation of various pro-inflammatory factors (Brasier, 2006; Gilmore, 2006; Perkins, 2007; Camargo Garbin and Olver, 2019).

repair ability of testis regarding the ischemia/reperfusion effects due to testicular torsion (Samy et al., 2020) (Figure 2). PRP contains VEGF which has a critical role in cell proliferation, cell cycle maintenance, and germ cells apoptosis prevention (Tunçkiran et al., 2005; Caires et al., 2012; Tao et al., 2017). The overproduction of ROS will be suppressed by PRP administration through the activation PI3K/Akt signalling pathway, resulting in the downregulation of NFκB (Salem et al., 2018).

Antioxidant (ROS)

Vascular endothelial growth factor (VEGF) as one of the growth factors contained in PRP exhibits antioxidant capabilities via activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway *in vitro* (Kweider et al., 2011; Tohidnezhad et al., 2014) as depicted in Figure 3. During the processes of spermatogenesis and fertilization, the Nrf2/antioxidant response element (ARE) signalling pathway and its regulatory antioxidants, play an important role in countering cellular oxidative stress (Kensler et al., 2007; Nakamura et al., 2010). The antioxidant enzymes Zn/

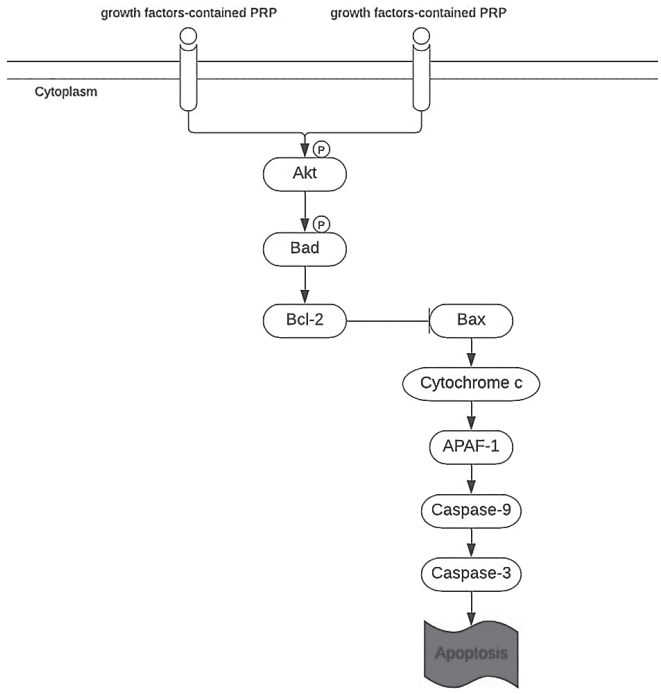

Figure 2 – Schematic inhibition pathway of apoptosis by platelet-rich plasma (PRP). PRP administration has an anti-apoptotic potential by means of activation of the Akt/Bad/Bcl-2 signalling pathway (Tao et al., 2017).

Cu SOD (superoxide dismutase) contained in PRP play a crucial role in protecting sperm motility by increasing the integrity of the sperm membrane. As an important role holder in the ROS scavenger system, this enzyme works by reducing DNA fragmentation due to exposure to H_2O_2 through inhibition of lipid hydroperoxide (LPO) of spermatozoa (Perumal, 2014; Lee et al., 2016; Zhao et al., 2016a).

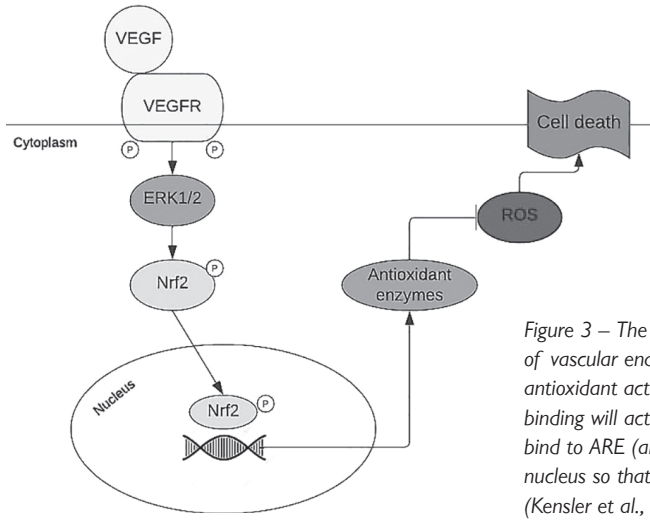

Figure 3 – The potential of signal transduction of vascular endothelial growth factor (VEGF) in the antioxidant activity regulation. VEGF-VEGF receptors binding will activate the Nrf2 pathway which can bind to ARE (antioxidant response element) in the nucleus so that it can regulate antioxidant enzymes (Kensler et al., 2007; Nakamura et al., 2010).

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