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Novel Chalcones as Promising Vascular Endothelial Growth Factor Receptor-2 (VEGFR-2) Inhibitors

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ABSTRACT

The current study focuses on the emerging idea of naturally occurring, chalcone-based inhibitors that will prevent angiogenic switching (fibroblast growth factor angiogenin, TGF- β), which is prevented by directly inhibiting vascular endothelial growth factor receptor-2 (VEGFR-2), which prevents neovascularization, vascular formation, and network formation. The presented papers will encourage future researchers, pharmaceutical scientists, aspirant investigators, and related specialists to develop or look at potential angiogenic inhibitors.

Keywords: Angiogenesis, Cancer, Chalcone, Inhibition, Vascular endothelial growth factor, Vascular Endothelial Growth Factor Receptor-2

INTRODUCTION

Several natural products such as chalcones, aurones, flavonoids, flavones, flavonols, flavanones, isoflavones, anthocyanidine, flavan-3-ols, proanthocyanidins, etc. are regarded as potential anti-angiogenic compounds [1]. Chalcones (prop-2-ene-1-one) are the class of natural products having a composition of two aromatic rings bound by α , β unsaturated carbonyl bridge [2]. They are the chromophoric compounds first synthesized in the 19th century by Tambor and Kostanecki [3]. It is regarded as an open chain intermediates in the flavonoid synthesis in the aurones pathway [4]. The chalcone scaffold bearing compounds are known to have anti-bacterial, anti-inflammatory, anti-cancer, anti-fungal, hypnotic, anti-viral, sedative, anti-convulsant, anti-malarial, anti-leishmanial, anti-trypanosomal, anti-retroviral, anti-platelet, antihypertensive, anti-hyperlipidemic, anti-arrhythmic, anti-gout, analgesic, anti-diabetic, anti-obesity, etc [5-7]. The present article highlights the anti-angiogenic perspectives of natural chalcones.

VEGF-1 and VEGF-2 continued to be the major targets for the pharmacotherapeutics despite logically finding several possible angiogenic inhibitors [8]. It is solitarily formed in the cells and promotes neovascularization. During the embryonic stages, it is vastly expressed and plays a critical role in the fetal vasculogenesis [9]. In adults, it plays a central

role in the formation of blood vessels under injury conditions and cardiac blockade. Under tumor conditions, it is largely over-expressed and leads to swift growth in tumor and it's spreading across the body due to the enormous availability of nutrients and oxygen in the metabolizing cells [10].

The family of VEGF genes comprises of 7 members which include VEGF-E, a viral genome-derived component. VEGF plays an essential role in the cardiovascular system, atherosclerosis, cardiac myofibroblasts, central nervous system, non-endothelial cells, bones, hematopoietic cells, hematological malignancies, autocrine signaling, tumor cells, etc [11]. VEGF-A, VEGF-B, VEGF-C, and VEGF-D have been glimpsed to regulate the process of angiogenesis at early embryogenesis, show vascular permeability activity, have pro-angiogenic activity, stimulates cell migration in macrophage, and are considered as significant regulators of lymphangiogenesis [12]. VEGFs of diverse origin have proangiogenic characteristics for the development and maintenance of blood vessels physiological levels to overcome ischemic diseases. Based on the conditions, inhibitors of angiogenesis have been developed and pre-clinically evaluated to determine but none of them proved very promising for a complete cure [13]. Multi-kinase inhibitors and Anti-VEGF-A neutralizing antibody have been produced as an alternative way of treatment; keeping

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possible side effects aside, however, the clinical efficacy is under question [14]. Chalcone based compounds have been reported very recently as promising inhibitors of VEGF and may be applied in the near future as angiogenesis inhibitor with several advantageous pharmacodynamics and pharmacokinetics attributes.

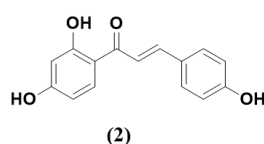
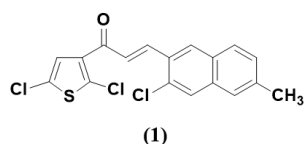
INHIBITION OF VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR-2

Depending on the type of vertebrate species, the genes of VEGFR comprises of 3 to 4 members. It comprises of 3 loops produced by the intramolecular disulfide bonding and loop-1 cooperates with the loop-3 to exhibit necessary binding and activation cascade for angiogenic switching [15]. VEGFR-1 (VEGF receptor 1 also known as Flt-1, fms-like tyrosine kinase) and VEGFR-2 (KDR/Flk-1, Fetal liver kinase 1 is the murine homolog of human Kinase insert Domain-containing Receptor) are the most prominent receptors involved in vasculogenesis, neovascularization, and pro-angiogenesis processes [16]. VEGFR-2 is a receptor of VEGF-A and mostly mediates endothelial growth and signaling. The angiogenic promoters are foremost expressed by VEGF-E (Orf-virus derived VEGF) [17]. Inhibition of VEGFR-2 may be regarded as the most fitting biological target for the suppression of solid tumor [18]. Researchers working on chalcone scaffold have put forward some recently tested VEGFR-2 inhibitors as perspective anti-angiogenic agents.

Based on the structure-based virtual screening, quinolyl-thienyl chalcone series was *in silico* screened for their ability to inhibit VEGFR-2 kinase. Further, *in vitro* research on human umbilical vein endothelial cells (HUVEC) produced noteworthy inhibition by the chalcone hybrids. The highest activity was recognized by inhibitor (1) [19].

Isoliquiritigenin (2), a natural product has been identified as anti-angiogenic candidate that mediates the activity inhibiting the VEGF expression. The natural chalcone exhibits HIF-1 α (Hypoxia inducible factor-1 α) proteasome degradation in breast cancer cells and blocking the kinase activity via interaction with VEGFR-2 [20].

The strong VEGFR-2 inhibitory activity of 2,4-dihydroxy-6-methoxy-3,5-dimethylchalcone (2) remained the key highlights of Patent CN1454895A which further depicts its utility in chemoprevention due to anti-angiogenesis activity [21].



CONCLUSION

The current study focuses on the emerging perspective of chalcone-based natural inhibitors that will prevent angiogenic switching (fibroblast growth factor angiogenin, TGF- α), which is prevented by directly inhibiting vascular endothelial growth factor receptor-2 (VEGFR-2), which prevents neovascularization, vascular formation, and network formation. Aspiring intellects, pharmaceutical scientists, aspiring investigators, and associated experts will be favourably inspired by the featured studies to create or investigate possible angiogenic inhibitors.

Conflict of Interest

Declared none.

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