

PARTHENOLIDE: SUGGESTED DRUG FOR COVID-19

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Abstract. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the 2019 novel coronavirus (2019-nCoV) that causes acute respiratory distress syndrome (ARDS) which is the main reason for patients mortality. One of the effective treatments to reduce the effects of this virus is parthenolide (PN). Parthenolide is a sesquiterpene lactone found in medicinal plants. It can inhibit several pro-inflammatory signaling pathways, in particular the ATPase activity of NLRP3. Based on its ability to suppress inflammatory signal transduction and elevated level of serum IL-1 β (a surrogate marker for NLRP3 activation) in COVID-19 patients, we suggest that PN could be potentially effective for the treatment of COVID-19.

Key words: Parthenolide, COVID-19, NF- κ B.

ПАРТЕНОЛИД: ВОЗМОЖНОЕ ЛЕКАРСТВО ОТ COVID-19

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Резюме. Новый коронавирус тяжелого острого респираторного синдрома (SARS-CoV-2) вызывает развитие респираторного дистресс-синдрома, являющегося основной причиной смерти пациентов. Одним из эффективных методов снижения воздействия этого вируса является партенолид (PN). Партенолид — сесквитерпеновый лактон, содержащийся в лекарственных растениях, способный подавлять ряд провоспалительных сигнальных каскадов, в частности АТФ-азную активность инфламмосомы NLRP3. Учитывая его способность блокировать проведение воспалительных сигналов и повышенный уровень сывороточного цитокина IL-1 β (как суррогатного маркера активации NLRP3) у пациентов с COVID-19, мы полагаем, что Партенолид мог бы быть эффективен при лечении COVID-19.

Ключевые слова: Партенолид, COVID-19, NF- κ B.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), or the 2019 novel coronavirus (2019-nCoV), is rapidly spreading from Wuhan, Hubei Province, China, to the rest of the world [11]. Respiratory failure from acute respiratory distress syndrome (ARDS) is the prominent reason for mortality [9]; so, there is a critical need for effective treatment. The P21-activated kinase (PAK1, RAC/CDC42-activated kinase 1) is the main “pathogenic” kinase. The abnormal activation of PAK1 takes place due to different diseases/disorders such as inflamma-

tion, malaria, and pandemic viral infection such as influenza and COVID-19 [8]. In the PAK1 signaling pathway, after activation of the epidermal growth factor receptor (EGFR) by epidermal growth factor (EGF), then RAS (guanosine-nucleotide-binding protein) activates; following that, PAK1 stimulates inflammatory pathways by nuclear factor kappa B (NF- κ B) activation [4]. The NF- κ B controls the expression of genes encoding the chemokines (e.g., IL-8), pro-inflammatory cytokines (e.g., IL-1, IL-2, IL-6 and TNF α), inducible enzymes (e.g., cyclooxy-

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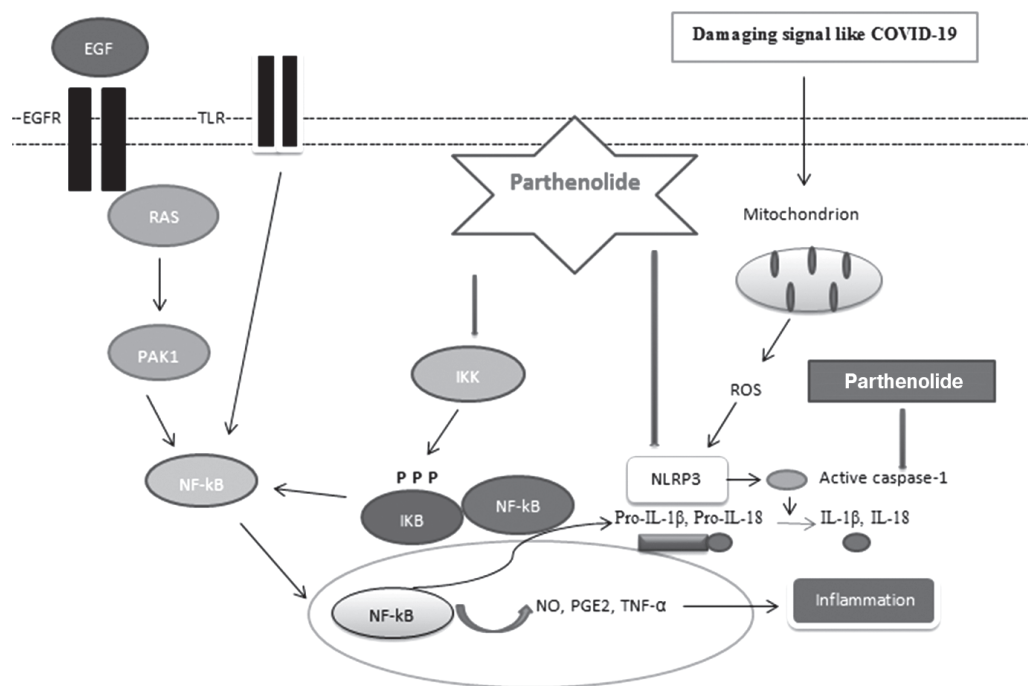


Figure. Anti-inflammatory effect of Parthenolide on COVID-19

EGF — Epidermal growth factor; EGFR — Epidermal growth factor receptor; PAK1 — P21 activated kinase 1; NF- κ B — Nuclear factor kappa B; NO — Nitric oxide; PGE2 — Prostaglandin E2; TNF α — Tumor necrosis factor-alpha; IL-1 β — Interleukin-1 β ; IL-18 — Interleukin-18; TLR — Toll-like receptor; ROS — Reactive oxygen species; IKK — I κ B kinase; I κ B — inhibitory protein of NF- κ B complex; NLRP3 — NLR family pyrin domain containing 3.

genase-2 (COX-2) and inducible nitric oxide synthase (iNOS)), adhesion molecules (e.g., intracellular adhesion molecule (ICAM) and E-selectin), growth factors, some of the acute phase proteins, and immune receptors, all of these factors play critical roles in controlling most inflammatory process [1]. One of the effective treatments to reduce the effects of this signaling pathway is parthenolide (PN). Parthenolide is a sesquiterpene lactone found in medicinal plants, particularly in feverfew (*Tanacetum parthenium*) [10]. Parthenolide has anti-inflammatory actions through the inhibition of several pro-inflammatory signaling pathways, including nitric oxide (NO), prostaglandins (PGs), leukotrienes (LTs), TNF α , and cytokines of the IL families [1]. Studies have shown that PN is capable of inhibiting the activity of the NF- κ B subunit RelA/p65 by inhibiting the I κ B (inhibitory protein of NF- κ B complex) kinase-mediated phosphorylation of I κ B [3], suggesting that PN is a novel therapeutic agent for treating COVID-19. Parthenolide also inhibits the activity of multiple

inflammasomes, which produces the active pro-inflammatory cytokines IL-1 β and IL-18 from the inactive pro-IL-1 β and pro-IL-18, in macrophages by directly inhibiting the protease activity of caspase-1 [6]. The NLR family pyrin domain containing 3 (NALP3) inflammasome [4] is an important component of the innate immune response against a broad range of microbial signals and it is activated by diverse signals such as viruses [7]. The molecular mechanism of activation of the NLRP3 inflammasome by these diverse stimuli is still unclear, but the evidence suggests that NLRP3 is transcriptionally up-regulated by NF- κ B-inducing stimuli such as ligands of the Toll-like receptors [2]. Juliana et al. have shown for the first time that PN is an inhibitor of the ATPase activity of NLRP3 [6]. On the other hand, the investigations reported that serum IL-1 β (a surrogate marker for NLRP3 activation) elevates in COVID-19 patients [5]. Therefore, we can suggest that PN, an anti-inflammatory agent that inhibits the NF- κ B, NLRP3, and caspase 1, is the potentially effective treatment for COVID-19 (fig.).

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