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"A CURRENT REVIEW ON PHYSIOLOGY AND VARIOUS FUNCTIONS OF NUCLEAR FACTOR-KAPPA B (NF-κB) & EFFECTS OF NATURAL PLANT PRODUCTS: WITH AN INSIGHT IN CURRENT KNOWLEDGE AND FUTURE PERSPECTIVES."

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ABSTRACT

Introduction: The nuclear factor kappa B (NF-kappa B, NF-κB), a nuclear protein is a major eukaryotic transcription factor, located mainly in the brain, also in the neutrophils, mainly found in all nucleated cells. Several transcription factors are present at the synapse, and among these are the Rel-NF-kappa B pathway components. NF-kappa B is a constitutive transcription factor, found only in cells that transcribe immunoglobulin light chain genes that interact with a defined site in the κ immunoglobulin enhancer.

Role of NF-kappa B: It plays a crucial role in regulating the immune response to infection and inflammation. NF-κB plays a key role in cell protection against diverse apoptotic stimuli including chemo- and radiotherapeutic treatments through activation of the anti-apoptotic gene-program in cells. Its impairment is linked with several pathological conditions such as Acquired Immunodeficiency Syndrome (AIDS), atherosclerosis, asthma, arthritis, cancer, diabetes, Inflammatory Bowel Disease (IBD), muscular dystrophy, stroke, and viral infections. As stated by researchers, obese individuals have high circulating levels of TNF-α, IL-1β, excessive NF-κB activity has been associated with the development of type II diabetes and they also have cardiovascular risk that is directly correlated with insulin resistance.

Role of NF-kappa B in tumour cells: Nuclear factor, NF-κB, gets activated in the tumour cells; hence serves as a potential target for developing anticancer drugs. NF-κB factor activation has been associated with tumorigenesis. NF-κB is constitutively activated in human leukemias and lymphomas as well as in some solid tumors. It is also reported to be activagted in cell lines from human solid tumors which includes breast, ovarian, colon, thyroid, pancreatic, and urinary bladder carcinomas, melanomas.

Detection of NF-kappa B: Researchers have documented detection of NF-κB activation in synovial tissue of RA patients Translocation of NF-κB to nucleus can be detected immunocytochemically and measured by Laser Scanning Cytometry. Quantitative determination of human NF-κB concentrations in serum, plasma, tissue homogenates, cell lysates can be measured.

Hence, the present comprehensive review aims to emphasize the distinctive and multifactorial physiological role of nuclear factor kappa B, along with its increasing application in the field of cancer and other diseases, which affirms its current status of future research perspectives and highlights its potential therapeutic indication in various disease states.

INTRODUCTION

Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), Nuclear Factor Kappa B ("NFKB1," "NF-κB1," "nuclear factor kappa B1," "NF kappa B1," or "nuclear factor κB1"), is a nuclear protein, is a major eukaryotic inducible transcription factor, found only in cells that transcribe immunoglobulin light chain genes, that interacts with a defined site in the κ immunoglobulin enhancer [1-4]. Usually, in normal cells, NF-κB complexes are inactive, located in the cytoplasm in a complex, but when the pathway is activated, the inhibitory protein is degraded and the NF-κB complex enters the nucleus to modulate target gene expression. Hence, it is a critical regulator of many cellular processes including cell survival and inflammation as it controls transcription of DNA. Thus, NF-κB can be regarded as first responder to harmful cellular stimuli. As stated by research studies [4-6], the inducers of NF-κB activity include Reactive Oxygen Species (ROS), Tumor Necrosis Factor Alpha (TNFα), Interleukin 1-beta (IL-1β), Bacterial LipoPolysaccharides (LPS), Isoproterenol, Cocaine, and Ionizing Radiation [4, 5]. As stated by researchers, Tumor Necrosis Factor Alpha (TNF), central cytokine in inflammatory reactions, and biologics that neutralize TNF are among the most successful drugs for the treatment of chronic inflammatory and autoimmune pathologies. Nuclear factor, NF-κB gets activated in the tumour cells and hence, it serves as a potential

target for developing antineoplastic agents. Moreover, blocking of NF-κB advocates towards anticancer activity of the natural compounds [5-7].

ROLE OF NUCLEAR FACTOR-*κ*B IN HEALTH AND DISEASE:

The transcription factor NF-κB is a critical regulator of many cellular processes including cell survival and inflammation. The dysregulation of NF-kappaB is associated with many disease states such as AIDS, atherosclerosis, asthma, arthritis, cancer, diabetes, inflammatory bowel disease, muscular dystrophy, stroke, and viral infections. Moreover, researchers have suggested that the dysfunction of NF-kappaB is a major mediator of some human genetic disorders [4-6].

Moreover, as documented by researchers [3-5], NF-κB is largely responsible for cytokine gene expression in adipocytes. Excessive NF-κB activity has been associated with the development of type 2 diabetes as obese individuals have high circulating levels of TNF-α, IL-1β and IL-6 that, like cardiovascular risk, directly correlate with insulin resistance. NF-κB factor activation has been associated with tumorigenesis. NF-κB is constitutively activated in human leukemias and lymphomas as well as in some solid tumors and in cell lines from human solid tumors including breast, ovarian, colon, thyroid, pancreatic, and urinary bladder carcinomas, melanomas, and others. NF-κB plays a key role in cell protection against diverse apoptotic stimuli including chemo- and radiotherapeutic treatments through activation of the antiapoptotic gene program in cells. Nuclear factor, NF-κB, is a transcription factor (TF) that gets activated in the tumour cells. Thus, it serves as a potential target for developing anticancer drugs. [3, 4, 5]. NF-κB is important in regulating cellular responses because it belongs to the category of "rapid-acting" primary transcription factors, i.e., transcription factors that are present in cells in an inactive state and do not require new protein synthesis in order to become activated (other members of this family include transcription factors such as c-Jun, STATs, and nuclear hormone receptors) [5-6].

LOCATION OF NUCLEAR FACTOR-*κ*B

Nuclear factor-*κ*B (NF-*κ*B) was initially identified in 1986, as a transcription factor. As stated by researchers [1-3], several transcription factors are present at the synapse, and among these are the Rel-NF-kappa B pathway components. The NF-kappa B is a constitutive transcription factor, and its family consists of p50 (NF-*κ*B1), p52 (NF-*κ*B2), p65 (RelA), c-Rel (Rel), and RelB. The nuclear factor kappa B (NF-kappa B), is mainly located in the brain of which a considerable part is located in the neutrophils, mainly found in cell nuclei, also, NF-kappa B

translocates from cytosol to nucleus as a result of transduction by tumor necrosis factor alpha (TNF alpha), phorbol ester, and other polyclonal signals [7-9]. It is found only in cells that transcribe immunoglobulin light chain genes, that interacts with a defined site in the κ immunoglobulin enhancer [5,6].

REGULATION & ROLE OF NUCLEAR FACTOR-*κ*B

As stated by researchers [7-9], growth factors, cytokines such as interleukin-1 (IL-1) and tumour-necrosis factor (TNF), hormones and other signals activate NF-κB by the phosphorylation of IκB. A new pathway for NF-κB activation that is strictly dependent on IKKα was described by Senftleben, U. et al. (2001) [9]. This pathway [9], now known as the alternative pathway, is activated by certain members of the TNF cytokine family [10].

Nuclear factor-*κ*B is associated with the pathogenesis of numerous malignancies, and the functional polymorphism. As stated by Researchers Meier-Soelch, J; et al (2021) [6], "NF-κB-activating stimuli includes more general adverse signals such as DNA damage, lipid peroxidation, free DNA or RNA, and UV radiation. Moreover, NF-κB-activating stimuli also include specific signals that functions through plasma membrane receptors such as proinflammatory cytokines (IL-1α or IL-1β, TNFα), lipopolysaccharide (LPS), and T-cell co-stimulation" [6]. NF-κB plays a key role in cell protection against diverse apoptotic stimuli including chemo- and radiotherapeutic treatments through activation of the antiapoptotic gene program in cells [11].

Role in Cancer Cells:

As stated by researchers [5-7], Tumor Necrosis Factor Alpha (TNF), central cytokine in inflammatory reactions, and biologics that neutralize TNF are among the most successful drugs for the treatment of chronic inflammatory and autoimmune pathologies. Nuclear factor, NF-κB gets activated in the tumour cells and hence, it serves as a potential target for developing antineoplastic agents. Moreover, blocking of NF-κB advocates towards anticancer activity of the natural compounds. NF-κB serves important functions in pathogenetic regulation and influences cancer development and aggressiveness by enhancing tumour angiogenesis, antiapoptosis, and proliferation and by repressing immune response [7, 11, 12]. Several investigators reported the constitutive activation of NF-κB in various malignancies [11], including nonsmall cell lung carcinoma and colon, prostate, breast, bone, and brain cancers.

Role in Neuronal Plasticity and Memory: [14]

It is well documented about numerous transcription factors located in the brain, at the synapse, and among these are the Rel-NF-kappa B pathway components. NF-kappa B is a constitutive transcription factor, with a strong presence in the brain of which a considerable part is located

in the neuropiles [1-5]. Evidence from researchers Salles A; et al (2014) [14], indicates two general hypotheses for synaptic NF-kappa B. Firstly, the role of NF-kappa B in the synapse to nucleus communication, and it is retrogradely transported from polarized localizations to regulate gene expression. Second hypothesis states that the transcription factor modulates the synaptic function locally. Evidence from researchers Salles A; et al (2014) indicates that both mechanisms can operate simultaneously [14].

Role in Asthma: [15]

Glucocorticoids are the most clinically effective treatment available for bronchial asthma. Asthma is characterized mainly by inflammation in the lung, besides bronchoconstriction. NF-kappa B has its role in inflammation. As stated by Umland SP; et al (2002) [15] the success of chronic Glucocorticoid therapy for asthma is based on the ability of the Glucocorticoid to alter transcription of a wide array of molecules involved in the inflammatory process. Glucocorticoids produce their pharmacological actions by binding to the wild-type GR, GR (alpha) [15], and this complex can directly or indirectly alter gene transcription by binding to specific DNA sites or by activating transcription factors. In the pharmacotherapy of bronchial asthma, the GR (alpha) down-regulates proinflammatory mediators such as interleukin-(IL)-1, 3, and 5, and up-regulates anti-inflammatory mediators such as IkappaB [inhibitory molecule for nuclear factor kappaB1 IL-10, and 12. Newer GCs are being designed to increase potency and topical activity [15].

Role in Parkinson's Disease (PD): [16]

There are numerous literatures stating that oxidative stress and apoptosis play a role in neurodegeneration in Parkinson's disease (PD). Reactive oxygen species may be directly involved in apoptosis or via upregulation of toxic cytokines, i.e. tumor necrosis factor alpha (TNF alpha). Researchers Wintermeyer P,; et al (2002) [16], demonstrated that the TNF alpha pathway contributes to the pathogenesis of sporadic PD using a genetic approach. As stated by researchers Wintermeyer P,; et al (2002) [16], “these signalling pathways converge to the transcription factor nuclear factor kappaB (NF-kappaB), which has been found activated in affected neurons in PD”.

EFFECTS OF NATURAL PLANT PRODUCTS ON NF-κB: [17-20]

Role of Curcumin and Resveratrol in Obesity:

Curcumin and resveratrol are able to inhibit TNFα-activated NF-κB signaling in adipocytes and as a result significantly reduce cytokine expression as stated by the researchers [17]. These data suggest that curcumin and resveratrol may provide a novel and safe approach to reduce or inhibit the chronic inflammatory properties of adipose tissue. The natural products, curcumin

and resveratrol, are established anti-inflammatory compounds that mediate their effects by inhibiting activation of NF-κB signaling [17, 21, 22].

Obesity is now known to play a causal role in the complex disease state of metabolic syndrome, as well as being a significant risk factor for cardiovascular disorders and diabetes [3-6]. In addition to these mechanisms of metabolic regulation, adipose tissue is also capable of producing proteins that are classical mediators of the inflammatory response. NF-κB itself is a heterodimeric transcription factor that is retained in the cytosol in its inactive state by complexing with a set of inhibitory proteins designated IκB [7-10]. Upon receptor activation of NF-κB signaling the IκB complex is phosphorylated by IκB kinase (IKK) [9]. This in turn leads to its dissociation from NF-κB and rapid degradation by the proteosome. Free NF-κB is then able to translocate to the nucleus where it binds to specific promoter elements resulting in the activation of a battery of genes, including those encoding for inflammatory proteins [7-10]. Excessive NF-κB activity has been associated with the development of type 2 diabetes as obese individuals have high circulating levels of TNF-α, IL-1β and IL-6 that, like cardiovascular risk, directly correlate with insulin resistance [9]. Studies indicates that the natural products can be used to inhibit the chronic inflammatory response of adipose tissue which might provide a new approach to reduce systemic cytokine levels which in turn is expected to improve cardiovascular health and insulin sensitivity [21-22].

Essential Oils: [23]

There is vast literature during the last decade, regarding the use of essential oils in cancer therapy. In a review study [23], Gautam N,; et al, (2014), reported the activity of the natural compounds. α-terpineol have been reported to target NF-κB and downregulates its related genes. Linalyl acetate and α-terpineol monoterpenes act synergistically and inhibit the expression of NF-κB leading to cell death of colon cancer cells [24]. Human leukaemia cell line (HL-60) treated with EO of Cymbopogon flexuosus and its major constituent isointermedeol has been reported to lower NF-κB which is one of the contributing multiple pathways resulting in apoptosis [25].

Effects of Probiotics: [26]

As stated by researchers Petrof EO; et al;, (2004) [26] probiotics may provide clinical benefit by ameliorating colitis. Proteasome inhibition is an early event that begins almost immediately after exposure of the epithelial cells to the probiotic-conditioned media. In addition, these bacteria inhibit the proinflammatory nuclear factor-kappaB pathway through a mechanism different from the type III secretory mechanisms described for other nonpathogenic enteric flora. As stated by them [26] through animal studies, it was shown to induce the expression of

cytoprotective heat shock proteins in intestinal epithelial cells. The resulting inhibition of nuclear factor-kappaB and increased expression of heat shock proteins may account for the anti-inflammatory and cytoprotective effects reported for probiotics and may be a novel mechanism of microbial-epithelial interaction. These effects seem to be mediated through the common unifying mechanism of proteasome inhibition [26].**Detection of NF-kappa B: [6]**

As stated by Researchers Meier-Soelch, J; et al (2021) [6], they have documented detection of NF-κB activation in synovial tissue of RA patients Translocation of NF-κB to nucleus can be detected immunocytochemically and measured by Laser Scanning Cytometry. Quantitative determination of human NF-κB concentrations in serum, plasma, tissue homogenates, cell lysates can be measured.

Numerous researchers have studied over the last two decades, regarding nuclear factor kappa B. It is known that they play a crucial role in the immune and metabolic systems in physiology and the pathology of cancer, autoimmunity, chronic inflammation, and others. Hence, the present comprehensive review was aimed to emphasize the distinctive and multifactorial physiological role of nuclear factor kappa B, along with its increasing application in the field of cancer and other diseases, which affirms its current status of future research perspectives and how enhanced information highlights its potential to lead to better diagnostics and therapeutics for widespread human diseases.

BIBLIOGRAPHY:

[1] Sen R, Baltimore D. Inducibility of κ immunoglobulin enhancer-binding protein NF-κB by a posttranslational mechanism. Cell. 1986 Dec 26;47(6):921-8.

[2] Van Waes C. Nuclear factor-κB in development, prevention, and therapy of cancer. Clinical Cancer Research. 2007 Feb 15;13(4):1076-82.

[3] Hayden MS, Ghosh S. Shared principles in NF-κB signaling. Cell. 2008 Feb 8;132(3):344-62.

[4] Rothwarf DM, Karin M. The NF-κB activation pathway: a paradigm in information transfer from membrane to nucleus. Sci. STKE. 1999 Oct 26;1999(5):re1-.

[5] Mankan AK, Lawless MW, Gray SG, Kelleher D, McManus R. NF-κB regulation: the nuclear response. Journal of cellular and molecular medicine. 2009 Apr;13(4):631-43.

[6] Meier-Soelch, J., Mayr-Buro, C., Juli, J., Leib, L., Linne, U., Dreute, J., Papantonis, A., Schmitz, M. L., & Kracht, M. (2021). Monitoring the Levels of Cellular NF-κB Activation States. Cancers, 13(21), 5351. https://doi.org/10.3390/cancers13215351

[7] Bonizzi, G. & Karin, M. The two NF-κB activation pathways and their role in innate and adaptive immunity. Trends Immunol. 25, 280–288 (2004).

[8] Jobin, C. & Sartor, R. B. The IκB/NF-κB system: a key determinant of mucosa inflammation and protection. Am. J. Physiol. Cell Physiol. 278, C451–C562 (2000).

[9] Senftleben, U. et al. Activation by IKKα of a second, evolutionary conserved, NF-κB signaling pathway. Science 293, 1495–1499 (2001).

[10] Hayden, M, S. & Ghosh, S. Signaling to NF-κB. Gene. Dev. 18, 2195–2224 (2004).

[11] Tergaonkar, V., Bottero, V., Ikawa, M., Li, Q. & Verma, I. M. IκB kinase-independent IκBα degradation pathway: functional NF-κB activity and implications for cancer therapy. Mol. Cell. Biol. 23, 8070–8083 (2003).

[12] Van Loo, G., Bertrand, M.J.M. Death by TNF: a road to inflammation. Nat Rev Immunol 23, 289–303 (2023). https://doi.org/10.1038/s41577-022-00792-3

[13] Hayden M.S., Ghosh S. Shared principles in NF-kappaB signaling. Cell. 2008;132:344–362. doi: 10.1016/j.cell.2008.01.020.

[14] Salles A, Romano A, Freudenthal R. Synaptic NF-kappa B pathway in neuronal plasticity and memory. J Physiol Paris. 2014 Sep-Dec;108(4-6):256-62. doi: 10.1016/j.jphysparis.2014.05.002. Epub 2014 May 20. PMID: 24854662.

[15] Umland SP, Schleimer RP, Johnston SL. Review of the molecular and cellular mechanisms of action of glucocorticoids for use in asthma. Pulmonary pharmacology & therapeutics. 2002 Jan 1;15(1):35-50.

[16] Wintermeyer P, Riess O, Schöls L, Przuntek H, Miterski B, Epplen JT, Krüger R. Mutation analysis and association studies of nuclear factor-kappaB1 in sporadic Parkinson's disease patients. J Neural Transm (Vienna). 2002 Sep;109(9):1181-8. doi: 10.1007/s00702-001-0688-x. PMID: 12203044.

[17] Kumar H, Kim IS, More SV, Kim BW, Choi DK. Natural product-derived pharmacological modulators of Nrf2/ARE pathway for chronic diseases. Natural product reports. 2014;31(1):109-39.

[18] Saxena RS, Gupta B, Saxena KK, Singh R, Prasad DN. Study of Anti-inflammatory Activity of the leaves of Nyctanthes arbor-tristis Linn.: An Indian Medicinal Plant. J Ethnopharmacol 1987;11:319-30.

[19] Nadkarni AK. Indian Materia Medica. Bombay: Popular Prakashan PVP; 1954.

[20] Leung A. Encyclopedia of common natural ingredients used in food, drugs & cosmetics. John Weily 198;31: 314.

[21] Tohda C, Nakayama N, Hatanaka F, Komatsu K. 2006. Comparison of anti inflammatory activities of six curcuma rhizomes: a possible curcuminoid-independent pathway mediated by curcuma phaeocaulis extract. eCAM 3(2): 255-60.

[22] Mukhopadhyay A, Basu N, Ghatak N, Gujral PK. 1982. Anti-inflammatory and irritant activities of curcumin analogues in rats. Agents and Actions 12(4): 508-15.

[23] Gautam N, Mantha AK, Mittal S. Essential oils and their constituents as anticancer agents: a mechanistic view. Biomed Res Int. 2014; 2014:154106. doi: 10.1155/2014/154106. Epub 2014 Jun 9.

[24] Deeb SJ. Enhancement of Cell Death by Linalyl Acetate and α-terpineol through Targeting the Nuclear factor-κb Activation Pathway in Human Colon Cancer Cells. American University of Beirut; 2009.

[25] Kumar A, Malik F, Bhushan S, et al. An essential oil and its major constituent isointermedeol induce apoptosis by increased expression of mitochondrial cytochrome c and apical death receptors in human leukaemia HL-60 cells. Chemico-Biological Interactions. 2008;171(3):332–347.

[26] Petrof EO, Kojima K, Ropeleski MJ, Musch MW, Tao Y, De Simone C, Chang EB. Probiotics inhibit nuclear factor-kappaB and induce heat shock proteins in colonic epithelial cells through proteasome inhibition. Gastroenterology. 2004 Nov;127(5):1474-87. doi: 10.1053/j.gastro.2004.09.001.