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Targeting Cancer Signaling Pathways by Nimbolide: A review on Chemoprevention and Therapeutic Studies

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Abstract

Neem (Azadirachta indica), has been in use as a traditional medicine since ancient time. Nimbolide, a phytochemical from neem has attracted the cancer scientists as a potential natural molecule for the effective cancer prevention and therapy. The researchers also highlight the efficiency and efficacy of nimbolide in different experimental systems. Moreover, nimbolide does not have the side effects in vivo model systems. The importance of nimbolide in cancer prevention and therapy is very high because nimbolide targets multiple signaling pathways which are involve in cell proliferation, cell cycle, apoptosis, invasion, metastasis and angiogenesis. However, more experimental proofs are needed to validate nimbolide application in cancer prevention and therapy. In this mini-review, we discuss different recent findings to target signaling molecules in different preclinical cancer. the important discoveries related to nimbolide against different preclinical cancer models. We also discuss the possibilities to use nimbolide as preventive and therapeutic molecule against the dreaded disease cancer.

Keywords: Nimbolide; Cancer; Therapy; Metastasis; Angiogenesis

Introduction

Medicinal plants have been extensively used for the treatment of various ailments including ulcers, arthritis tumors, etc. since ancient time [1]. Cancer is causing death on a large scale all over the world including developed countries. A lot of research has been done to develop anticancer drug but, its potential as a non-toxic, effective agent always remains a concern due to their side effects. Phytochemicals from various plants such as vinblastine, vincristine, paclitaxel, camptothecin, epipodophyllotoxin, combretastatin and much more as a promising anticancer agent have been elucidated with success, though their possible side effects always remain a threat to their successful application in cancer therapy [2]. Phytochemicals from Neem (Azadirachta indica), especially nimbolide has attracted the scientist all around the world as a potential natural, non-toxic molecule for the treatment of various ailments including cancer [3,4]. Nimbolide, a triterpenoid can be isolated from a various part of the neem tree such as leaves, flowers or seeds [5]. Nimbolide inhibits the cell proliferation and survival in a variety of cancerous cell lines. However, their application to preclinical and clinical models is limited and need more research to validate their possible use during various phases of chemoprevention and therapy [3,4].

Hanahan & Weinberg [6,7] described the most prominent six hallmarks and enabling characteristics of cancer. The molecules involved in these hallmarks or cancer progressions are interacted with tumor micro-environments, making the cancerous cell even more proliferative and invasive. The molecules of six hallmarks of cancer are sustenance of proliferative signals. They involve in uncontrolled cell growth, proliferation, drug resistance, angiogenesis, invasion and metastasis, reprogramming of cellular energy metabolism, evading the immune system, genome instability and mutation, tumor-promoting inflammation and tumor microenvironment modulation (that include particular cell types and regulatory interaction between them) [6,7].

Cancer Hallmarks and Nimbolide effects: a Mechanistic Insight

The multiple ways of survival by a cancer cell and possible side effects of synthetic drugs routinely used in chemotherapy possess an enigma for the targeting of cancer cell for their complete elimination [8]. Therefore, there is a need to discover an agent that target the multiple facets of cancer signaling pathways with negligible or no side effects. In recent years, nimbolide attracted the researchers all over the world for their validation of application in cancer therapy. The advantage of the use of nimbolide as an anticancer drug is due to their multi-targeting of hallmarks of cancer pathways with negligible side effects in different cancer therapy.

Induction of Cell Cycle Arrest, Apoptosis, and Inhibition of Cell Proliferation

Cell growth and proliferation are coordinated with cell cycle checkpoints and apoptosis. In cancer, cell proliferates in an uncontrolled fashion and helps in tumor development and metastasis [9,10]. Cell division and proliferation requires multistep pathways with crosstalk between the multiple signaling molecules in healthy condition. However, the majority of these signaling molecules are dysregulated in almost all types of cancer. These signaling pathways include:

a. A dysregulated mitogenic stimuli such as growth factors, hormones,

b. Dysregulated expression of the molecules of cellular pathways such as PI3K/Akt/mTOR, Nuclear factor kappa B (NF-κB), protein kinases such as Protein kinase C (PKC), MAP kinases, jun, fos, c-myc etc,

c. Unregulated expression of regulatory proteins of cell cycle such as cyclins, cyclin-dependent kinases (CDKs) and its inhibitors (CKIs), cell cycle checkpoints regulatory proteins such as ATM/ATR kinases, Cdc25, Wee1,

d. Downregulation of tumor suppressor genes such as Rb, p53, p21,

e. Dysregulation of some enzymes involved in DNA replication and its repairs such as proliferating cell nuclear antigen (PCNA) and

f. Dysregulation of apoptotic gene expression (pro-apoptotic genes such as Bax, Bak, Bid, Bam, Noxa etc., and antiapoptotic genes such as Bcl-2, Bcl-xL) [9,11,12].

The DNA damage and cell cycle arrest are an interlinked process in normal condition [13]. The DNA damage initiates a cascade of signaling pathway resulting in the cell cycle arrest and if not timely repaired, leads to cell death by apoptosis [14]. Interestingly, cancer cells evade apoptosis in multiple ways [14]. Thus, cancerous drugs were designed to induce apoptosis in malignant cells. However, most of the drugs are toxic to normal cells too. The treatment of cancerous cell with nimbolide showed its potential to induce DNA damage and cell cycle arrest in various types of cancer cell lines [12]. The mechanism of cell cycle arrest relies upon the activation/deactivation (either phosphorylation or dephosphorylating) of tumor suppressor genes and cyclin-dependent kinases (CDKs).

Karkare et al. [15] showed the potential of nimbolide to arrest the cell cycle in G1/S phase and inhibit cell proliferation of glioblastoma (GBM) cell lines T98G, A172 and U87 cells. Nimbolide halt cell proliferation by directly inhibiting the activity of CDK4/CDK6 kinase leading to hypophosphorylation of the retinoblastoma (RB) protein in a variety of glioblastoma (GBM) cell lines [15]. Similarly, the treatment of human renal cell carcinoma (RCC) cell lines such as RCC-786-O and A-498 when treated with nimbolide. Nimbolide induces DNA damage and leads to G2/M phase cell cycle arrest by phosphorylating the cell cycle-related protein such as p53, cdc2, cdc25c. Further, nimbolide decreases the expression of cyclin A, cyclin B, cdc2, cdc25c with increased activity of p53 [3]

The potential of any anticancer drug relies on the induction of apoptosis of cancerous cell selectively. Hao et al. [9], in his critical review, highlights that the expression level of anti-apoptotic (Bcl-2, Bcl-xL), proapoptotic (Bax, Bak, and Bid) genes and their downstream targets such as effector caspases (caspase-3, 8 and 9) are the primary targets of most of the anticancer drugs [9]. Nimbolide treatment also showed marked decrease in the expression level of Bcl-2 in glioblastoma (GBM) and human renal cell carcinoma (RCC) cell lines, whereas increases the expression of caspase-3, 9 and ADP ribose polymerase (PARP) in 786-O and A-498 cell lines of human renal cell carcinoma [3,15]. Recently, it has been observed that both efficiency and efficacy of nimbolide to kill the cancer cell line, Waldenströms macroglobulinemia in a very selective manner by in silco, in vitro and in vivo studies [15].

In silico study showed the exquisite binding of nimbolide to antiapoptotic BCL-2 protein most strongly followed by HSP90 and PI3K [16]. They support their result by other in vitro study that gave an ample evidence for the nimbolide induced down regulation of PI3K signaling pathways, most notable inhibition of NF-κB expression [16-18]. Further, they observed that nimbolide selectively kill the cancer cells in a BCL2-dependent manner [16]. They tested the apoptotic activity of nimbolide in a variety of Waldenströms macroglobulinemia cell line and found a marked reduction in cell viability in a dose-dependent manner through inhibition of expression of BCL2, Akt, pAkt, NF-κB, and induction of expression of effector caspases of apoptotic pathways [16]. Interestingly, they also showed the apoptotic activity of nimbolide even in ibrutinib-resistant (BC/IR) Waldenströms macroglobulinemia cells. Furthermore, they showed that BCL2-dependent cell line (RS4;11) undergone maximal cell death (82%) as compared to BCL2-independent cell line (Jurkat BCL2Ser70-Ala) with only 28% cell death [16]. The marked reduction in tumor size after nimbolide treatment in vivo also supports the anti-apoptotic activity of nimbolide [16]. Similarly, Chien et al. [19] also reported that nimbolide induces down regulation of anti-apoptotic gene (Bcl-2 and Bcl-xL) and up regulation of pro-apoptotic genes (Bax, Bid, Bik) and their effector caspases (Caspase-3, 8, 9 and PARP) in human nasopharyngeal cancer cells [19]. The similar evidence of nimbolide targeting anti-apoptotic gene (Bcl-2 and Bcl-xL) and induction of the expression of proapoptotic genes (Bax and Bak) and effector caspases (Caspase-3, -9, Apaf-1, and PARP) have been reported in various types of cancer such as prostate, cervical, choriocarcinoma, hepatocarcinoma, colon, lymphoma, leukemia and others [20-24].

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The extrinsic pathway of cell death in cancer cells involve the expression of death receptor (DR5) or TRAIL receptor 2 for TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) [25]. TNF-α ligand therapy for induction of cell death in cancer is limited due to its side effects such as hypotension and other systemic side effects [26]. Chantana et al. [27] recently reported for the first time that nimbolide sensitize the TNF-α induced JNK pathway with upregulation of DR5 in human colon adenocarcinoma (HT-29) cells. The combinatorial dose of nimbolide and TNF-α showed enhanced phosphorylation of JNK and expression of Bid with significant cell death as compared to TNF-α ligand-induced cell death alone [27]. The nimbolide induced induction of cell cycle arrest and apoptosis in cancer cells is well supported by the inhibition of cell proliferation. Cell proliferation is marked by the increased expression of PCNA, Cyclin D1, c-Myc, Survivin, NFκB, PI3K, Akt, IGF and IGF-R [4,28,29] and decrease expression of PTEN that control the activation Akt [30].

The treatment of nimbolide showed marked a reduction in the expression of PCNA and inhibition of cell proliferation in human choriocarcinoma (BeWo) cells [23]. The central signaling pathway to cell survival and cell proliferation is the activation of NF-κB. However, the NF-κB is remained in an inactive state by IκB proteins in healthy cells [31]. However, in cancer cells, IκB (heterodimer of IκBα, IκBβ, and IκBε) get phosphorylated by IκB kinase (IKK) at 32 and 36 serine residues and ubiquitinated at 21 and 22 lysine residues, thereby activating the NF-κB [31]. Nimbolide inhibits the activation of NF-κB through inhibition of IκB kinase, thereby suppress the phosphorylation and ubiquitylation of IκB [32]. NF-κB inhibition results in the inhibition of its downstream target involve in cell survival and cell proliferation [32]. Interestingly, Harish et al. [4] also showed the anti-proliferative activity of nimbolide by a marked reduction in the expression of PCNA and Cyclin D1 in an animal model of oral carcinogenesis. Raja et al. [29] showed the active role of nimbolide on inhibition of cell survival and proliferation through both in silico and in vitro study in human androgen-independent prostate cancer (PC-3) cells.

The treatment of PC-3 cells with nimbolide inhibits the expression of PI3K, Akt, and mTOR along with the down regulation of PCNA, cyclin D1, cMyc and Survivin [28]. They supported their result by in silico study and showed the strong interaction of nimbolide with Cyclin D1, PCNA and Akt [29]. The inhibition of PI3K-Akt is mostly due to upregulation of PTEN that dephosphorylate the PIP3 thereby repressing the activation of Akt through phosphorylation [33]. At the same time, Elumalai et al. [33] also reported the inhibitory effect of nimbolide on IGF-1 mediated MAPK signaling pathway and cell proliferation in human breast cancer cell lines MCF-7 and MDA-MB-231.Thus, in totality nimbolide exerts its potential as an anticancer drug through induction of cell cycle arrest, apoptosis, and inhibition of cell proliferation.

Inhibition of cell invasion, metastasis, and angiogenesis

Invasion and metastasis of cancer cells followed by angiogenesis are one of the most dreaded parts of cancer development and the prime cause of cancer patient death [34]. The cancer invasion and metastasis are promoted by up regulation of different pathways such as NFκB pathway that modified the extracellular matrix (ECM) of the invading microenvironment. ECM molecules are matrix metalloproteinase's (MMPs), intracellular adhesion molecule-1 (ICAM-1), urokinase plasminogen activator (uPA) and its receptor (uPAR), chemokines such as CCL2, CXCL12, and CXCL8 and their receptors CCR2, CXCR1, CXCR2, and CXCR4, followed by down regulation of the tissue inhibitors of MMP (TIMPs) [35,36]. However, the potential of nimbolide again came to rescue the invasion and metastasis of cancer by regulating the expression of the molecules mentioned above. Babykutty et al. [1] reported that nimbolide inhibit the expression of MMP-2/9 and restrict the cancer cell invasion and cell migration in colon cancer cells (WiDr) [1].

Similarly, nimbolide also restrict the cancer cell invasion and metastasis through inhibition of MMP-9, ICAM-1and CXCR4 expression in a colorectal cancer xenografts and various tumor cell lines such as myeloid leukemia (KBM-5, HL-60, U-937, and K-562), T-cell lymphoma (Jurkat), and myeloma (U266, MM.1S, and RPMI-8226) [18,32]. In an another study, nimbolide also showed its efficiency to inhibit the expression of MMP-2, MMP-9, uPA, uPAR, and chemokines and up regulate the expression TIMPs, thereby, retard the invasion and metastasis of breast cancer cells MCF-7 and MDA-MB-231 [36]. The nimbolode also showed its potential to inhibit the invasion and cell migration by inhibiting the expression of Integrins (αvβ5) RNA and protein in osteosarcoma cell lines MG63 [37].

Along with invasion and metastasis, nimbolide also showed its potential to inhibit the angiogenesis through down regulation of vascular endothelial growth factor (VEGF). Babykutty et al. [1] showed the potential of nimolide to retard the angiogenesis process via inhibition of the promoter activity and expression of VEGF in colon cancer cells (WiDr) [1]. Similarly, Gupta et al. [18] and Elumalai et al. [36] also reported the anti-angiogenesis properties of nimbolide via suppression of expression of VEGF in colorectal cancer xenografts and breast cancer cells such as MCF-7 and MDA-MB-231, respectively [18,36].

Conclusion

Natural phytochemicals have always shown their potential for the treatment of various forms of the diseases since ancient time. The growing incidence of cancer patients and the limitations of synthetic chemotherapy due to their side effects has always been a major concern to the cancer scientists. Nimbolide is a phytochemical from neem plant has also shown its potential to combat cancer. The initial experimental evidence

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of nimbolide in cancer treatment both in vitro and in vivo model has shown much promise for their successful application in cancer prevention and treatment strategies. Researchers showed the potential of nimbolide as a useful natural molecule due to its multifaceted targeting of cancer progression strategies without any side effect to other organs of the body. However, there is always a scope for improvement for the proper management and implication of any drug for the disease treatment. In this context, our laboratory is working in this direction to further explore the pros and cons of nimbolide as preventive and therapeutic molecule against cancers.

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Conflict of Interest

The authors have declared no conflict of interest.

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