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Bioactive Molecules: Their Potential and Limitation in Tumor Therapy

MOHAMED HASSAN[1,2,3], ABDELOUAHID EL-KHATTOUITI[1], YOUSSEF HAIKEL[2,3], MOSSAD MEGAHED[4]

[1]*Cancer Institute, University of Mississippi Medical Center, Jackson, MS 39216, USA.*
[2]*Institut National de la Santé et de la Recherche Médicale, U1121.*
[3]*Department of Operative Dentistry and Endodontics, Dental Faculty, University of Strasbourg, 67000 Strasbourg, France.*
[4]*Clinic of Dermatology, University Hospital of Aachen, Pauwelsstr. 30, 52074 Aachen, Germany.*

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ABSTRACT

Cancer is one of the most common causes of death worldwide. However, the increased incidence of cancer mortality is attributed to the increased resistance of tumor to the available therapeutic modalities. Although the significant progression that has been made in tumor treatments, these available therapeutic opportunities provide only limited benefit for patients in advanced stages. In addition to their adverse effects, current anticancer agents suffer from insufficient specificity toward tumor cells because of the difficulty to target cancer cells without damaging the healthy ones. Naturally occurring bioactive molecules occupy an essential part of the available anticancer agents. These bioactive molecules are derived mainly from natural sources and have been successfully approved for tumor treatment. Although the efficiency of bioactive molecules is variable and mostly associated with threatening side effects, their clinical application in cancer treatment is indispensable. In this review, we will focus on the molecular action, potential and limitation of bioactive molecules as anticancer agent in tumor therapy.

Keywords: *BCR-ABL, VX-680, CML, Tyrosine kinase, Pharmacophore*

Introduction

Cancer continues to be one of the main causes of death worldwide. The increased resistance to available therapeutic approaches is the major cause for the increased incidence of cancer mortality. Although the visibility of available therapeutics in tumor treatment, their efficiency in the treatment of advanced tumor stages is limited [1,2]. Besides low efficiency of most available cancer therapeutics, the difficulty to target specific cancer cells without the damage of healthy ones is a challenge for clinicians and patients. Initiation and progression of cancer are a multi-step process that are associated with the alterations of signal transduction pathways that are directly linked to cell death machinery, cell survival and maintenance. These cellular alteration can be expressed in the form of genetic and/or epigenetic changes of essential key components of the aberrant signaling pathways leading to their destruction or excessive activation [3,4]. Although there is significant progression in recent years, the key problem in tumor treatments is the development of drug resistance and threatening side effects [5-7]. Apart from the expected adverse effects, current anticancer agents suffer from insufficient specificity toward tumor cells [8,9]. Naturally occurring drugs, also known as bioactive molecules occupy an essential part of the current anticancer agents. These bioactive molecules cover a wide spectrum of anticancer agents including, anthracyclines (doxorubicin, daunorubicin, epirubicin, idarubicin), camptothecan and its derivatives (topothecan, irinothecin), podophyllotoxin and its derivatives (etoposide, teniposide), taxanes (paclitaxel, docetaxel), *vinca alkaloids* (vinecristine, vinblastine, vindesine, vinorelbine) and others. Most of these

*Corresponding Author
Dr. Mohamed Hassan
Cancer Institute, University of Mississippi Medical Center, Jackson, MS, USA.
Phone: +1 601 815 8945; Fax: +1 601 984 2981
Email: dr.hassan@gmx.de

bioactive molecules and their modified forms are internationally approved for cancer treatment. Accordingly, these nature products still remain the mostly attractive source for anticancer therapeutics. Thus, the discussion of bioactive molecules based on their potential and limitation in tumor treatment may help develop a relevant therapeutic strategy for cancer treatment.

Anticancer Agents Derived From Plant Origin

The application of bioactive molecules derived from plant source in tumor treatment started with the discovery of the *vinca alkaloids* including, vinblastine and vincristine [10]. These *vinca alkaloids* showed a clinical visibility for the treatment of Hodgkin's disease and other forms of leukemia [11, 12]. Both vincristine and vinblastine mediate their anticancer efficiency by inhibition of microtubule assembly [13,14]. Despite the advantage of *vinca alkaloids*-derived anticancer agents as evidenced by the treatment of different tumor types including, Leukemia [15], Lymophoma [16]; Melanoma [17,18], recurrent or refractory pediatric low-grade glioma [19], refractory metastatic prostate [20], a significant resistance to *vinca alkaloids*-derived therapeutics has been reported in different tumor types including, renal cell carcinoma (RCC) [21] and hepatocellular carcinoma (HCC) [22]. Although their efficiency as anticancer agent in the treatment of melanoma [23], head and neck squamous cell carcinoma [24,25], prostate cancer [26], recurrent malignant glioma [27] as well as in the treatment of cervical, colorectal, endometrial and lung cancers [28], bioactive molecules derived from taxanes do not provide benefit for patients with metastatic papillary RCC [29]. These bioactive molecules mediate their anticancer activity *via* mechanism-mediated by the stabilization of microtubules that, in turn, leads to mitotic arrest [30,31], that ultimately results in apoptosis [32,33]. Etoposide, bioactive molecules that function as a topoisomerase II inhibitor have been reported for its killing efficiency as anticancer agents *via* mechanism mediated by stabilization of the enzyme-DNA cleavable complex leading to DNA breaks[34,35]. These etopside-derived bioactive molecules showed significant antitumor efficiency in the treatment of small-cell lung carcinoma [36,37], breast cancer [38-40], also in the treatment of pediatric cancer [41,42]. Also, bioactive molecules such as, the camptothecin derivatives including, irinotecan and topotecan have shown significant antitumor efficiency in the treatment of colorectal and ovarian cancers [43-45]. These bioactive molecules have been demonstrated to mediate their antitumor activity *via* mechanism mediated by the inhibition of topoisomerase I leading to DNA damage and subsequently cell death [46]. Moreover, flavopiridol, a further bioactive molecule that function as a cyclin-dependent kinase inhibitor has been tested for its efficiency to trigger cell cycle arrest *via* mechanism mediated by the interference with cyclin-dependent kinases (CDKs) to prevent their phosphorylation and ultimately inhibition of CDKs-dependent pathways [47].

Bioactive Molecules Derived From Marine Sources

The identification of bioactive molecules with anticancer activities among marine organisms gained more attention in the recent years. A significant number of compounds derived from marine organisms have been subjected for preclinical and early clinical evaluation. These bioactive molecules have been approved for their clinical relevance as anticancer agent [48,49]. Didemnin B, is one of the first anticancer agent that is isolated from a marine source. Didemnin B is a cyclic depsipeptide that showed therapeutic potential against non-Hodgkin's lymphoma [50-52]. These marine derived bioactive molecules can mediate their therapeutic activity through the inhibition of protein synthesis and/or cell cycle arrest [53]. Also, Aplidine, another depsipeptide has shown to be more active as anticancer agent without to produce life-threatening neuromuscular toxicity [54,55]. Accordingly, the preclinical data confirmed the antitumor efficiency of Alpidine against several tumors types. These Alpidine-induced effects are regulated by a mechanism mediated through blockade of cell-cycle progression [59]. Also, the ecteinascidins antitumor bioactive molecules isolated from marine source have showed a clinical relevance in the treatment of different tumor types [60]. One of these ecteinascidins is the selected clinical trial ET-743 that showed its antitumor efficiency in phase I studies [61]. The molecular action of the bioactive molecule, ET-743 is mediated by its ability to alkylate selectively guanine residues in the DNA minor groove [62,63], in addition to its ability to interact with nuclear proteins [64]. Further marine bioactive molecules such as dolstatins have beenapproved for their reliabiility as anticancer agents [65,66]. Dolastatines are class of peptides, which are isolated from Dolabella auricularia and showed a significant antitumor activity [67]. These bioactive molecules mediate their antitumor activity through the inhibition of microtubule assembly that, in turn, results in cell-cycle arrest [68].

Bioactive Molecules Derived From Microorganism Sources

Bioactive molecules derived from microorganisms such as, the members of anthracycline, bleomycin, actinomycin, mitomycin and aureolic acid families [69], as well as daunomycin, and its related agents (e.g. doxorubicin, idarubicin and epirubicin, the peptolides, the mitosanes and the glycosylated anthracenone and mithramycin) have been approved for their clinical relevance as anticancer agents [70-76]. Also, the screening of natural products derived from a wide range microorganisms led to the identification of many bioactive molecules with antitumor activity such as, rapamycin and its analogs [77-79], geldanamycin [80], and Wortmannin [81]. These anticancer agents have been reported for their efficiency to inhibit tumor growth and progression and to mediate their antitumor effects through inhibition of heat-shock protein HSP90[80], or the inhibition of the signal transduction pathway phosphoinositide 3 kinase (PI3K) [81].

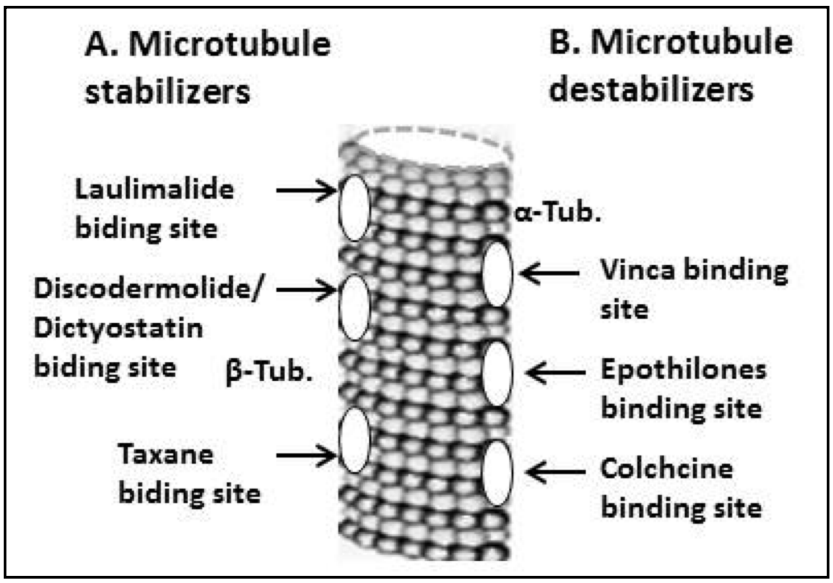

Figure 1: α and β tubulin binding sites of bioactive molecules leading to either stabilization or destabilization of microtubules up binding to. **A)** Microtubule stabilizers include laulimalide and Peloruside A that bind to laulimalide binding site, Discodermolide and Dictyostatin binding to the corresponding binding site, *Cyclostreptin*, *Eleutherobin*, *Sarcodictyins A+B* and *Taxanes* (*Paclitaxel*, *Docataxel*, *ABI-007* and *CT-2103*) binding to taxane binding site, *Epothilone B* (*Ixabepilone*, *Patupilone*, *BMS-310705*, *ABJ-879*, *ZK-EPO*) and *Epothilone* (*KOS-862*, *KPS-1584*). **B)** Microtubule destablizers include *Vinca* alkaloids (*vincristine*, *vinblastine*, *vinorelbine*, *vinflunine*, *halichondrin B*, *eribulin*, *mesylates*, *crypophycins* and *dolastatins*) binding to *vinca* binding site, Colchicine, *2-Methoxyestradiol*, *Sulphonamides* and *Aspergillus* derivatives binding to colchicine.

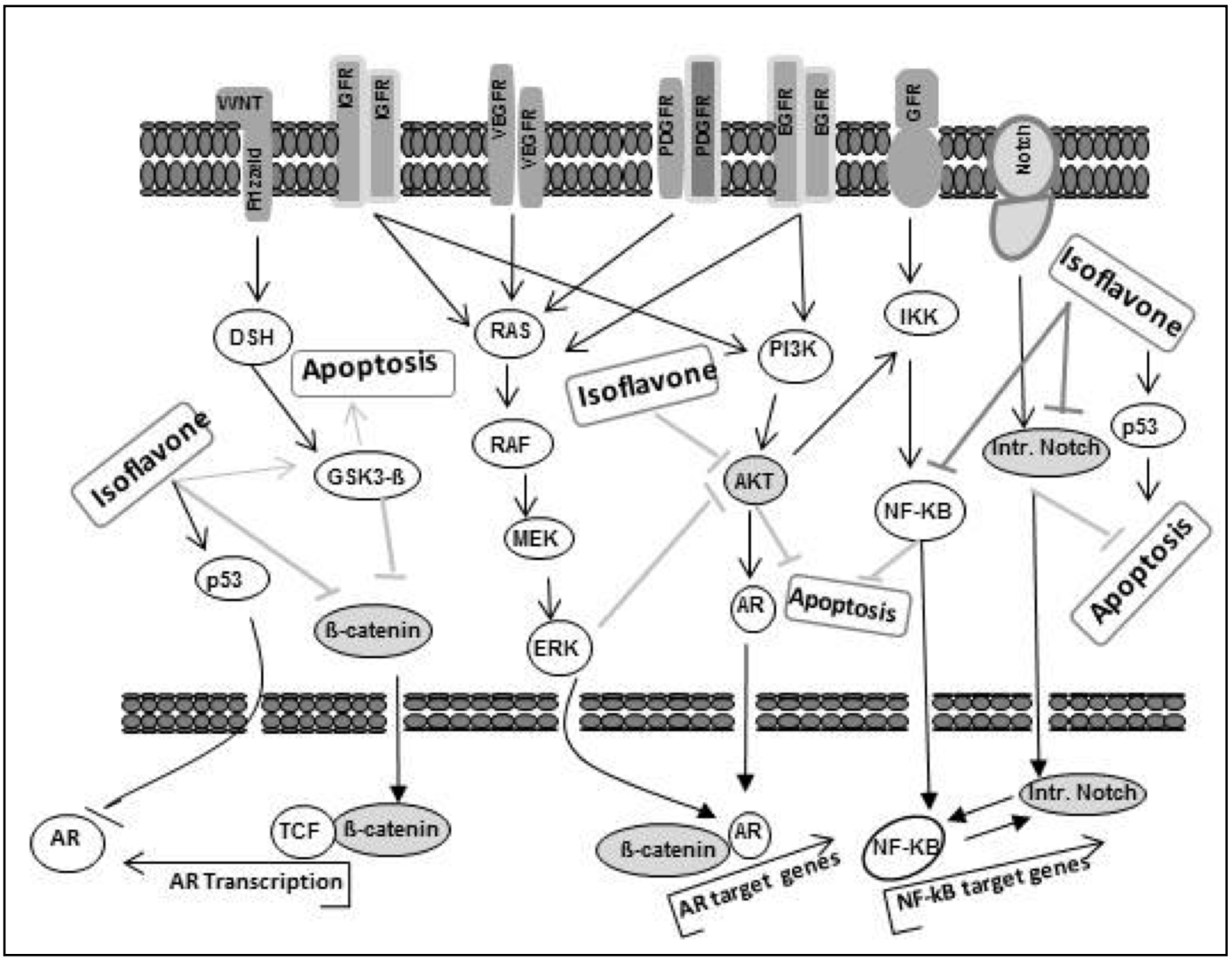

Figure 2: Schematic representation of the bioactive molecule isoflavone- mediated apoptosis in tumor cells, an example for the molecular action of bioactive molecules as anticancer agent in tumor cells. The exposure of tumor cells to isoflavone results in the modulation of intracellular signaling pathways that are essential for the regulation of cell fate.

Mechanistic Action of Bioactive Molecules in Tumor Cells

The match of bioactive molecules with their biological targets is essential key to understand the impact of the bioactive molecules as anticancer agent on the deregulation of cellular function with the aim to kill tumor cell without to damage healthy cells.

The mechanistic action of bioactive molecules in tumor cells, based on experimental studies, is expected to be mediated *via* signaling pathways, whose excessive activation or destruction mediate cell cycle arrest, growth inhibition or cell death [82,83]. These signal transduction pathways including, mitogen-activated protein kinases (MAPK), protein kinase C (PKC), phosphoinositide 3- kinase (PI3K), glycogen synthase kinase (GSK), activator protein-1 (AP-1) and NF-κB pathway have been shown to be involved in the modulation of the anticancer activity of bioactive molecules under preclinical and clinical investigation, even those approved for tumor treatment [84-86].Thus, the antitumor efficiency of bioactive molecules reflects their ability to counteract the function of signaling pathways that are implicated in cell proliferation, tumor initiation, and progression [85,86]. Bioactive molecules such as, taxol and vinblastine have been shown to target malfunctioning components along the disrupted signal transduction pathway in cancer represents a rational strategy in tumor treatment. For example, NF-κB and AP-1 provide a mechanistic link between cancer and inflammation, and are important targets of several bioactive molecules in tumor treatment [87-90]. Also, epigenetic mechanisms, which are essential for the development of carcinogenesis are considered potential targets of bioactive molecules [91,92]. Thus, epigenetic alteration such as, DNA methylation, histone modifications and posttranscriptional gene regulation by non-coding microRNAs (miRNA) are potential targets of bioactive molecules [93,94]. Although epigenetic alterations are heritable in somatic cells, these modifications can be reversed and thereby provide a promising strategy for cancer prevention and treatment. In contrast to genetic changes such as, mutations and gene deletion, epigenetic modifications offer a very promising and attractive condition for tumor prevention and treatment. Accordingly, several bioactive molecules have been approved for their potential to reverse the methylation status of methylation silenced genes [95,96]. Other bioactive molecules such as, trichosanthin [97], triterpene [98,99], lupeol gained more attention based on their antioxidant, apoptosis-inducing and antiproliferative properties, as evidenced by their antitumor efficiency *in vivo* and *in vitro* [100].

The mechanistic action of many bioactive molecules such as, lupeol has been characterized. These bioactive molecule seems to be a multi-target agents with immense anti-inflammatory potential targeting key molecular pathways, which involve NF-κB, cFLIP, Fas, Kras, phosphatidylinositol-3 Kinase (PI3), AKT and Wnt/β-catenin in a variety of cells [83,85]. NF-κB, a transcription factor that is known to be closely involved in the regulation of the multi-step process of tumorigenesis [101-103]. Whereas, the transcription factor AP-1 is implicated in the regulation of genes that are essential for cellular adaption, differentiation and proliferation [104,105].Therefore, the activation of AP-1 is associated with malignant transformation, tumor development and progression [106, 107]. Taken together, most of the bioactive molecules with antitumor activity mediate their activity by either stabilization or destabilization of microtubulines. The binding sites of bioactive molecules that function either as microtubule stabilizers or destabilizers are outlined in figure 1. The binding of these bioactive molecules to α and β microtubules mediates molecular action that, in turn, triggers signaling pathways, whose excessive activation or destruction lead to cell arrest or apoptosis. Figure 2 outlines an example for bioactive molecules-mediated tumor cell death-dependent pathways.

Conclusion

Bioactive molecules are an important source for anticancer agents that are currently applied for the treatment of different tumor types. Although these bioactive molecules are established as an effective treatment for many types of cancer, like other cancer therapeutics often cause threatening side effects. Bioactive molecules- associated side effects vary from patient to patient as well as tumor type and location; therapeutic dose and the overall health of the patients can also take place. Despite their limitation in the treatment of some tumor types, bioactive molecules provide significant therapeutic benefit for cancer patients. Thus, the shift from monotherapy to combination therapy may increase the therapeutic efficiency of bioactive molecules in tumor treatment. Also, the continuous improvement of already approved bioactive molecules in tumor treatment by the modification of their chemical structures as well as their bioavailability may provide more benefit to cancer patients. More importantly, the reduction or elimination of the undesired adverse effects thats result during the course of the treatment is a great advantage for patients. Thus, the functional analysis of the molecular action of the bioactive molecules that are approved for tumor treatment may help improve their therapeutic efficiency and reduce expected and unexpected side effects.

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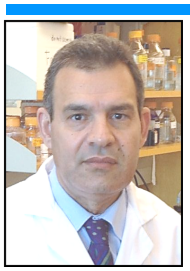

Dr. Mohamed Hassan. Is the leader of the Molecular Tumor Therapy at "Institut National de la Santé et de la Recherche Médicale (INSERM), and Dental Faculty, University of Strasbourg, Strasbourg, France, and Cancer Institute, University of Mississippi Medical Center, Jackson, Mississippi, USA. Dr. Hassan specialized in Cancer Research/ Molecular Tumor Therapies. He is the recipient of Robert Frank award 2007, and Japanese society of internal medicine award, 2011. Dr. Hassan published more than 40 publications in the field of Cancer Research and Infectious Diseases. Dr. Hassan is editorial board member of many international journals and invited Reviewer by many international journals.