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Review Article

Phytochemicals as Potential Therapeutics in Neurofibromatosis Type 1

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Abstract

Plant-derived compounds or phytochemicals are potential adjuvant or chemopreventive candidates in NF1 by regulating oxidative stress, inflammation, and dysregulated cellular signaling. One of them, the curcumin of Curcuma longa has been confirmed to have antiprolliferative, pro-apoptotic and anti-inflammatory effects in preclinical NF1 models and preliminary case studies indicate that when used with diets rich in polyphenols, tumor-volume reduction was also achieved. Likewise, catechin epigallocatechin-3-gallate (EGCG) the green tea derivative also has antioxidant and signalling modulation properties such as Nrf2 activation which is applicable to NF1 pathogenesis. Resveratrol was also reported to induce cellular differentiation inhibiting cell proliferation in NF1 patient derived cell models. Although these represent promising preclinical results, there is a dearth of clinical evidence, which is mostly small, observational studies. The ongoing trials of nutraceutical interventions are focused on the safety, the most effective dosage, and effectiveness. Potential adverse effects of the trial, including EGCG-associated hepatotoxicity at high doses and poor bioavailability of curcumin are imperative to take into consideration during trial design. All in all, although phytochemicals have promising biological agency and mechanistic applicability in the management of NF1, strong randomized clinical trials are needed to identify their potential therapeutic worth and clinical safety.

Keywords: Cafe-Au-Lait Macules (CALMs); Neurofibromatosis Type 1 (NF1)

Introduction

NF1 or neurofibromatosis type 1 is a common hereditary genetic disorder, which affects the skin and the nervous system, to the larger extent. It is a disorder that comes with the development of a number of neurofibromas and cafe-au-lait Macules (CALMs) on the skin. NF1 is an autosomal dominant condition, i.e. a mutation that occurs in one of the NF1 gene copies is sufficient to develop the condition [1,2]. NF1 gene is a tumor suppressor gene, which is found in chromosome 17q11.2 and encodes neurofibromin, a protein that regulates cell growth by the RAS/MAPK pathway. The absence or malfunction of neurofibromin results in the unregulated proliferation and malignancy.

NF1 manifests clinically in an extremely broad spectrum of mild cutaneous neurofibromas (CNs) and severe plexiform neurofibromas (PNs). The major complications linked to PNs include disfigurement, compression of nerves, blockage of the airway, and blindness in some instances. In the disease, the head and neck area is often affected but other organ systems such as the skeletal, vascular and nervous systems may be affected resulting in bone defects, vascular anomalies, and cognitive loss [3].

Besides NF1, two other clinically distinct types of neurofibromatosis have been discovered, including neurofibromatosis type 2 (NF2) and schwannomatosis which are linked with other genetic mutations and clinical features [4]. Although numerous researches were conducted, the therapeutic options of the NF1 are mostly symptomatic and surgical nowadays. Thus, it is important to comprehend the molecular pathophysiology of NF1 to devise new treatment plans, such as pharmacological and phytochemical-based ones.

Need of herbal/phytoconstituent approach

NF1 is a multi-pathway disease and various pathways can be addressed using phytochemicals.

In the absence of neurofibromin, RAS and a number of downstream pathways, including MEK/ERK, PI3K/AKT/mTOR, and JAK/STAT, are overstimulated. Even though individual-targeted therapies such as MEK inhibitors could be beneficial to some patients, these methods fail to tackle tumor heterogeneity and downstream signaling in all their manifestations. Conversely, numerous phytochemicals have pleiotropic effects, have concomitant effects on MAPK, PI3K/AKT, STAT3, NF- 0 B responses, and antioxidant activity. This polyfunctional activity theoretically renders them very appropriate to combat an illness that is motivated by various dysregulated mechanisms [5,10].

Antioxidants and anti-inflammatory agents have their effects that are directly related to the biology of NF1.

Oxidative stress and inflammation have crucial roles in the pathophysiology and pathogenesis of tumors associated with NF1. Antioxidant and anti-inflammatory antiphytic products, including polyphenols, isothiocyanates, flavonoids, among others, would alleviate tumor-promoting factors of the microenvironment and alter tumor growth signaling pathways. Such biological observations give a good reason to test certain phytochemicals in NF1 models [7].

Phytochemicals have the potential to decrease toxicity and serve as adjuvants.

The traditional targeted therapies are usually associated with dose-limiting toxicity. Phytochemicals that are well tolerated could be used as adjuvants by sensitizing tumor cells to conventional therapies, decreasing effective dosage of cytotoxics drug, or by safeguarding normal tissues to side effects of treatments. Early trials are underway concerning the use of nutritional supplements in conjunction with the conventional types of treatment in cancer and NF1, including trials of curcumin and high-phenolic olive oil in NF1 patients [8,9].

There are some natural products that are active in NF1 models.

Preclinical research has shown that a number of natural compounds can prevent NF1-related signaling and tumor growth. As an example, the natural triterpenoid cucurbitacin-I has been demonstrated to inhibit STAT3 signaling, and suppress the proliferation of NF1-deficient malignant peripheral nerve sheath tumor (MPNST) in vivo. These results indicate that natural molecules have the potential to play a major role in targeting biologically important drivers of NF1 tumor biology [6].

Social and practical considerations

Existing NF1 patients are already taking dietary supplements. Potential remedies of anecdotal use would be evidence-based practice of phytochemicals into harmless and controlled treatment

modalities. The reduced price and increased availability of some phytochemicals render them especially attractive in environments with limited resources as long as the safety and effectiveness are thoroughly proven [5].

Etiology

NF-1 is regarded as an autosomal domineering disorder. NF-1 gene is situated in chromosome 17 and codes a protein named neurofibromin [11,12]. Most of the tissues have a high level of neurofibromin expression. Neurofibromin is typically a GTPase-activating protein that suppresses the signaling pathway of rat sarcoma (RAS) [13].

The mutation or deletion of the NF-1 gene that leads to the disorder causes both phenotypic and genotypic expressions. It is an autosomal dominant disorder, and therefore totally penetrant. No generations are skipped. Even within the same family, the manifestation of the disease may be different across families, not to mention individuals [14].

Pathogenesis and cellular origin of neurofibromas

NF1 gene carries two alleles both of which have been mutated to cause neurofibromas. They consist of Schwann cells, perineural cells, mast cells and fibroblasts tumors [15]. The dermal neurofibromas are source on the peripheral nerve, and the other structures around it like the neurilemmal cells. The fibroblasts of such neurofibromas as HLA-DR -positive peripheral nerves are made up of factor XIIIa -positive connective tissue cells. Large amounts of hepatocyte growth factor (HGF) and stem cell factor (SCF) are also secreted by the dermal fibroblasts and this increases the production of epidermal melanin deposition [16].

Cafe-au-lait spots in certain instances contain huge granules of pigment in the epidermal cells in addition to the melanocytes. The NF1 genotypephenotype correlation is good [13]. NFs of the skin (cutaneous neurofibromas (cNF)) show the dermal nerve endings, and those of the nerve plexuses and fascicles (plexiform neurofibromas (pNF)).

Neurofibromas grow out of the Schwann cell (SC) lineage. Neural crest stem cells (NCSC) produce.

On the motor exit point (MEP) and the dorsal root entry zone (DREZ) which express.

Krox20 transcription factor, which marks SC components of the dorsal nerve roots and ventral nerve roots, has a role in early myelination of the peripheral nervous system (PNS).

Prss56 is the nerve root constituent of the SC, the hypodermis, and dermis.

The precursors of Schwann cells, which are glial cells expressing specific glial genes and molecular markers, such as myelin protein 0 (P0) and cadherin-19, and may undergo myelination or non-myelination, are SCPs [13].

Neurofibromin represses GTP-bound Kirsten rat sarcoma virus (KRAS). This inhibition will be lost leading to activation of the following signaling pathways:

Mitogen-activated protein kinases (MAPKs) and extracellular signal regulated kinase 1 and 2 (ERK1/ERK 2).

Phosphoinositide 3- kinase (PI3K) and mammalian target of rape (mTOR) pathway that regulates transcription and cell division growth [17].

NF1 inactivation, biallelic inactivation occurs in SOX10-positive Schwann cells, leading to the development of neurofibromas [13]. Plexiform neurofibromas (pNF) develop out of the SC lineage in embryonic development and conventional (cutaneous) neurofibromas (cNF) develop out of mature Schwann cells. The degradation of contact between the SCs and axons in combination with a down-regulation of semaphorin 4F in a Ras-Raf-ERK-dependent fashion results in cellular hyperproliferation. The next phase is Schwann cell

hyperplasia, which is followed by local reinnervation, i.e. sprouting of nerve terminals into the superficial dermis, which is caused by the lack of the perineurium [13]. The mutation patterns involved in the pathogenesis of NF1 are diverse and include frameshift, nonsense, missense, and splice-site mutations, as well as large deletions.

NF1 pathogenesis is most affected in the Syn domain of the NF1 gene that carries about 80 percent of the mutations [18].

Calebin-A

Calebin-A might downregulate hTERT and survivin while inhibiting MPNST proliferation. The epigenetic histone modification caused by the reduced activity of HAT might be the reason for the downregulation of the two factors. Calebin A (CA) [4- (3-methoxy-4-hydroxyphenyl)-2-oxo-3-enebutanyl 3- (3-methoxy-4-hydroxyphenyl) propenoate], one of the non-curcuminoid active constituents of the rhizome of turmeric (Curcuma longa L., Zingiberaceae) [19,20] is reported to have anti-inflammatory, anti-tumor and antioxidant activities. Nevertheless, only a small number of research conducted on connective tissue cells; the majority focused on studying tumor cells [21-25].

Propolis constituents

Propolis, also referred to as bee glue, is a substance present in beehives and has been exploited since ancient Egypt as an anti-inflammatory and antibacterial substance as well as a wound-healing agent. It is an intricate chemical formulation, and the precise formulation is extremely subject to change in relation to regional plants, condition, and approach to manufacture [26]. In this way, crude propolis extracts are particularly susceptible to lot-to-lot variation of the biological activities. It has also been reported that Chinese red propolis inhibits VEGF expression and is also composed of at least a dozen components, including the phenolic ester caffeic acid phenethyl ester (CAPE) and flavonoid kaempferol. It has also been reported that Turkish propolis causes G1 arrest and apoptosis in cancer cells and the product is composed of six key components, among them caffeic acid and CAAP. Polish propolis suppresses S- phase entry and decreases cell viability and has numerous flavonoids. Bio30 is a New Zealand propolis water-soluble extract and contains various phenolic compounds, including CAPE and suppresses the proliferation of HEI-193 schwannoma and NF1-deficient S462 MPNST cells [27]. CAAP is one of the many common components of these propolis. The IC50 of HEI-193 schwannoma cells was approximately 36 10mol. We also discover that CAPE does not show any significant growth- inhibitory effect on VS and meningioma cells at 20 μM or lower [28]. Whether this high concentration of CAPE can be achieved in humans is not obvious.

Didesmethylrocaglamide, rocaglamide, and silvestrol

Several species of the mahogany family (Meliaceae), tropical trees of the genus Aglaia, synthesize rocaglates, also known as flavaglines, which is a large family of cyclopenta[b]benzofurans [29]. Because of its scarcity, rocaglamide (also known as rocaglamide A or RocA; Figure 2) was not studied further in terms of its biology several years following its initial description to have antileukemic activity [30]. Later, additional anti-proliferative rocaglates were discovered such as silvestrol which is the first flavagline derived in Aglaia foveolata with a rare dioxanyl ring ring structure resembling sugar [31]. Like camptothecin and paclitaxel, silvestrol disrupts the growth of a large number of cancer cell lines at low nanomolar concentrations [29]. As inhibitors of eukaryotic translation initiation factor 4A (eIF4A), an RNA helicase [32], silvestrol and rocaglamide bind to eIF4A, which in turn is locked to purine-rich sequences in the 5'-untranslated region (UTR) of individual mRNAs, thereby blocking translation [33,34] (Figure We have also discovered that rocaglates interact with prohibitins and inhibit Raf/ERK signaling [35]. The eIF4F components, such as eIF4A, are found to be overexpressing in MPNST, VS, and meningioma tumors [36,37]. NF2-deficient tumor cells and NF1deficient MPNSTs have their proliferation effectively suppressed by genetic depletion of eIF4A by RNA interference as well as pharmacological inhibition by silvestrol. Silvestrol is an eIF4A inhibitor that lowers the levels of a number of cyclins and oncogenic kinases, including AKT, ERK, and FAK, resulting in G2/M phase arrest and apoptosis. Furthermore, silvestrol has a significant negative effect on the growth of Nf2-/- schwannomas and NF1-/- MPNSTs. Nonetheless, a canine toxicology found out that silvestrol led to lung damage. Based on this, its additional clinical progress was abandoned [38]. Through Notably, rocaglamide had the oral bioavailability of 50 percent and multi-drug resistance-1 insensitivity. Administred orally via gavage

or intraperitoneally, rocaglamide had a significant role in inhibiting tumor growth in an orthotropic MPNST model. Above all, rocaglamide had good tolerance of mice and did not cause pulmonary toxicity in dogs. In addition, the two rocaglamides were powerful anti-tumor agents against other sarcomas such as osteosarcoma, Ewing sarcoma and rhabdomyosarcoma. Such data should be used to conduct a clinical trial to establish the effectiveness of such rocaglamides in patients with sarcomas and in those with NF. Even more to the point, synthetic rocaglates have been made which keep the scaffold required to inhibit eIF4A intact, but to add modifications to the side chains to enhance pharmacokinetic and pharmacodynamic characteristics. A single one of these compounds (-)-CR-1-31B has been shown to enhance the survival of mice that have pancreatic adenocarcinoma allografts [39]. More recently another rocaglate-like compound, eFT226 (zotatifin) has been shown to be anti-tumorigenic against various cancers whose growth is mediated by fibroblast growth factor receptors and ErbB2 [40] and recently entered a phase 1/2 trial in patients with advanced solid tumors in which K-Ras or RTK mediate growth.

Honokiol

An ingredient of herbal tea preparations against anxiety, honokiol, a biphenolic lignan obtained as a byproduct of Magnolia tree bark also has anti-tumor activity [41] and its approximate IC50 is 26 μM against HEI-193 schwannoma cells [42]. However, this compound has never been tested on any other models of NF2- or NF1-related. Even though honokiol exhibits low bioavailability orally and a plasma half-life, it can cross the blood-brain barrier [41] Some strategies are also being pursued to improve these characteristics, such as encapsulating honokiol into liposomes or nanoparticles.

Curcumin

Curcumin has also been reported to stimulate the pro-inflammatory oxidative injury which, in turn, triggers the apoptosis process. Curcumin suppresses colony growth at concentrations of approximately 10 -1 by inhibiting the ERK, AKT, and NF- -KB pathways and promoting the occurrence of apoptosis induced by free radicals using HEI-193, a human papillomavirus oncogene transformed NF2-associated VS cell line [43,44,48]. All these findings imply that the action of curcumin is contextdependent. Curcumin too activates a molecular protector that is related to drug resistance, named heat shock protein 70 (HSP70). In synergy with the pan-HSP inhibitor KNK437, curcumin inhibits the HEI-193 cell growth. As it was noted earlier, IC50 of curcumin in primary VS cells was about 20 μM [45] and about 7 μM in NF2-deficient Ben-Men-1 meningioma cells. Moreover, the growth of NF1 deficient MPNST cells is inhibited by curcumin at IC50 at 25-100M [46]. Calebin-A is another curcuminoid which was found to inhibit cell growth at IC50 of 12.5 to 25M, as well as, decrease phospho-AKT and survivin levels in the same MPNST cell lines. Calebin-A showed a comparatively low anti-tumor effect in an NF1-deficient MPNST xenograft model when used at the 100mg/kg dosage rate [43,48]. A dietary study of a small cohort of NF1 patients who were fed a Mediterranean diet that was supplemented with curcumin suggested that the number of CNFs was reduced by 30-51% but a Western diet supplemented with the same did not show tumor inhibition [47]. A bigger study having clearly outlined objective outcomes is required to provide conclusive findings about the efficacy of curcumin in NF1 patients.

Conclusion

Neurofibromatosis type 1 (NF1) is a complex genetic disorder due to the lack of neurofibromin, characterized by the hyperactivation of various signaling pathways like RAS/MAPK, PI3K/AKT, and mTOR, which contribute to tumor formation. Treatment options are very limited at present, and most of the available therapies are only partially effective and associated with significant side effects. Thus, the exploration of herbal and phytoconstituent-based approaches serves as a good alternative/complementary strategy. Phytochemicals like curcumin, calebin-A, EGCG, resveratrol, propolis components (CAPE), rocaglamides, honokiol, and cucurbitacins possess anti-proliferative, antioxidant, anti-inflammatory, and pro-apoptotic properties relevant to NF1 tumor biology. They target multiple molecular pathways simultaneously, which also aligns with the complex pathogenesis of NF1. Preliminary and limited clinical evidence shows promise regarding tumor suppression and symptom improvement, but there are bioavailability, optimization

of dosage, and safety issues that need to be resolved. Herbal and phytochemical therapies thus hold significant therapeutic promise for NF1 due to their multi-targeting action and favorable safety profiles. However, well-designed clinical trials are absolutely necessary in order to establish their efficacy, determine safety dosing, and translate preclinical findings into effective, evidence-based treatments for NF1 patients.

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Conflict of Interest

The author(s) do not have any conflict of interest.

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