

Review

Nutraceutical Preventative and Therapeutic Potential in Neuroblastoma: From Pregnancy to Early Childhood

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Abstract: Neuroblastoma (NB) is a highly malignant embryonic extracranial solid tumor that arises from sympathoadrenal neuroblasts of neural crest origin. In addition to genetic factors, NB has been linked to maternal exposure to a variety of substances during pregnancy. Recent interest in the potential of nutrients to prevent cancer and reduce malignancy has resulted in the identification of several nutraceuticals including resveratrol, curcumin, and molecular components of garlic, which together with certain vitamins may help to prevent NB development. As NBs arise during fetal development and progress during early childhood, specific NB inhibiting nutraceuticals and vitamins could enhance the preventative influence of maternal nutrition and breast feeding on the development and early progression of NB. In this article, we review NB inhibitory nutraceuticals and vitamins, their mechanisms of action and expound their potential as maternal nutritional supplements to reduce NB development and progression during fetal growth and early childhood, whilst at the same time enhancing maternal, fetal, and infant health.

Keywords: nutraceuticals; neuroblastoma; pregnancy; therapy; prevention



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1. Introduction

Neuroblastoma (NB) is the most common pediatric extracranial solid tumor and accounts for approximately 8% of all pediatric cancers. NBs are diagnosed in approximately 1400 children per year in Europe, 140 children per year in Italy, and 800 children per year in the USA [1–3] and are responsible for approximately 15% of all pediatric cancer-related deaths [2]. These highly aggressive heterogeneous tumors are more frequently diagnosed in advanced stage and despite aggressive multimodal therapeutic approaches, they exhibit frequent post-therapeutic relapse associated with low survival rates, making an effective cure for advanced stage NB highly challenging [4].

NBs arise from immature sympathoadrenal cells of neural crest origin [5,6] and exhibit a high degree of heterogeneity and variable clinical courses ranging from spontaneous regression to therapy-resistant metastatic disease. Overall survival rates range from 85–90% in low- and intermediate-risk NBs to less than 50% in high-risk NBs [5]. Current multimodal NB therapy consists of surgery, chemotherapy, radiotherapy, and autologous stem cell transplant, which are associated with significant side effects including reversible myelosuppression, kidney and cardiotoxicity, genetic damage, and hearing impairment [7]. Considering the difficulty in treating advanced stage NBs, recent interest has also focused on the cancer therapeutic and preventative properties of natural dietary compounds. This has resulted in the identification of several nutraceuticals and vitamins with potent tumor inhibitory activity [8], suggesting that dietary supplementation with anticancer nutraceuticals and vitamins may not only improve cancer prevention, but also hamper progression. In this article, we review nutraceuticals and vitamins that exhibit NB inhibitory activity, their mechanisms of action (pro-apoptosis, proliferation inhibiting, pro-differentiation, and chemotherapy efficacy promoting) and their potential use as maternal dietary supplements during pregnancy and breast-feeding in preventing the development, enhancing

spontaneous regression, and reducing early progression of fetal and neonatal NBs during pregnancy and breast feeding.

2. Neuroblastoma

Pediatric NBs represent 8–10% of childhood cancers and account for approximately 15% of cancer-related childhood deaths [9]. NBs are slightly more frequent in boys, but no significant differences have been reported in the incidence of NB between ethnicities [10]. The incidence of NB in children less than 1 year old is estimated at 65 cases per million and in children under 15, 11–13 cases per million [11]. Approximately 30% of NBs are diagnosed within the first year of life and the remainder diagnosed before the age of 5 [10]. NBs in adolescents and young adults are rare but carry poor prognosis [12]. NB patients of less than 18 months exhibit more frequent spontaneous regression and enhanced survival rates (86.0% 3-year overall survival and 84.6% 5-year overall survival), whereas survival rates are lower in older individuals (45.9% 3-year overall survival and 36.3% 5-year overall survival) [11,12].

2.1. NB Risk Factors and Pathogenesis

Despite extensive experimental studies, the etiology of NB remains to be elucidated. Hereditary familial NBs are rare (1–2% of all cases) and have been attributed to germline gain of function mutations in anaplastic lymphoma kinase (ALK) [13,14] and germline loss of paired like homeobox 2B (PHOX2B) [13]. NBs develop during fetal development, supporting the hypothesis that maternal exposure to certain substances and conditions prior to or during pregnancy may be important in NB development and early progression. Within this context, the exposure of pregnant women to permanent hair dye during the first and second trimesters is associated with a higher risk of NB development; maternal workplace exposure to solvents [15] and air stable polycyclic aromatic hydrocarbons has also been linked to increased risk of NB development [16]. Furthermore, smoking, alcohol, or the use of drugs during pregnancy have been implicated in increasing the risk of fetal NB development, and nicotine has been shown to promote NB cell proliferation *in vitro* by inducing the expression of brain derived neurotrophic factor and its receptor, Tropomyosin receptor kinase B (TrkB). However, further studies are required to confirm the potential causal relationship during pregnancy, the doses required to enhance risk, and whether the co-consumption of nicotine, alcohol, and illicit drugs increase the risk of NB development [17,18].

On the other hand, breastfeeding from 3 to 13 months has been shown to reduce NB development by providing nerve and insulin-like growth factors that inhibit sympathoadrenal neuroblast proliferation and promote their differentiation during the neonatal period [19].

NBs arise from sympathoadrenal progenitor cells of neural crest origin that normally give rise to the sympathetic ganglia, sympathetic neurons, and adrenal chromaffin cells [5,6,20,21]. NB cells do not respond to differentiation signals and are blocked in a de-differentiated, stress-resistant proliferating state [22]. This state is facilitated by activated oncogenes including MYCN, which is amplified in approximately 20% of primary NBs and carries poor prognosis [23,24]; the hypoxia-regulated oncogenic alternative TrkAIII splice variant of the neurotrophin receptor tropomyosin-related kinase A (TrkA), which exhibits spontaneous intracellular activation and is expressed in advanced stage, relapsed, and metastatic NBs [25,26], aberrant neurotrophin receptor TrkB expression [27], and oncogenic ALK activation [28], to name a few.

2.2. Diagnosis, Risk-Classification, and Current Therapies

The median age of NB diagnoses is 18 months, with 90% of NBs diagnosed prior to the age of 5. Patients <18 months of age exhibit more frequent spontaneous NB regression, whereas NBs in older children are more aggressive and associated with lower survival rates [2,13]. Primary NBs may occur throughout the sympathetic nervous system but

develop more frequently in the adrenal glands [21]. NB diagnosis combines the histological examination of biopsies with imaging and biochemical profiling, and at the histological level, NBs appear as small, round, undifferentiated intensely stained cells [29].

NBs exhibit highly heterogeneous biological and clinical characteristics [30]. NB risk-classification, established by the International Neuroblastoma Risk Group (INRG), is based on precise prognostic factors (INRG stage, age at diagnosis, histologic category, grade of tumor differentiation, MYCN alterations, 11q aberrations and ploidy) and delineates pretreatment risk-groups [31]. Low- and intermediate-risk NB patients have the best prognosis and, in most cases, surgery alone is curative. Therapeutic strategies for high-risk NBs are divided into three treatment blocks: induction, consolidation, and post-consolidation therapy. The induction phase involves the use of chemotherapeutic agents (cisplatin, cyclophosphamide, doxorubicin, etoposide, topotecan, vincristine) and resection of the primary tumor. Consolidation therapy consists of high-dose chemotherapy in combination with external-beam radiotherapy, and autologous stem cell transplant [32], and post-consolidation therapy with anti-ganglioside 2 immunotherapy and cis-retinoic acid is used to treat minimal residual disease [31]. Conventional therapeutic approaches for high-risk patients are rarely curative and are associated with frequent relapses and low overall survival rates. Recent advances in the molecular mechanisms involved in NB pathogenesis and progression has resulted in the development of novel targeted therapies against activated ALK and Trk oncogenes, with the aim of improving the quality of life and overall survival of patients with advanced stage refractory and metastatic NB, and are currently in clinical trials [33]. A recent article has reported an exceptional durable response (of >5 years) to compassionate targeted entrectinib ALK/TrkA inhibitory therapy in an infant with relapsed refractory metastatic NB within a context of exhausted therapeutic options [34]. Considering that an effective cure for advanced stage NB is highly challenging, recent research efforts have also begun to focus on the potential of maternal nutraceutical and vitamin supplements to prevent NB development and impair early NB progression.

3. Nutraceuticals and Their Role in Neuroblastoma

The term “nutraceutical” was coined in 1989 by Stephen De Felice, who defined a nutraceutical as a “food, or parts of a food, that provides medical or health benefits, including the prevention and/or treatment of a disease”. Nowadays, nutraceuticals are considered to be natural molecular dietary alternatives to pharmaceuticals that provide physiological benefits [35]. Several nutraceuticals have been shown to exhibit anticancer properties including the inhibition of tumor cell invasion and metastatic progression [36], without detrimentally affecting normal cells [8]. Due to their biological anti-cancer activities, interest is increasing in the potential use of nutraceutical supplements in association with conventional treatments for both cancer prevention and anti-cancer therapy. Nutraceuticals exhibiting inhibitory activity in NB models *in vitro* and *in vivo* are listed in Table 1.

Table 1. Overview of the anticancer activities of nutraceuticals in NB models.

Bioactive Compound	Main Source(s)	Molecular Mechanism/Target(s)	Reference
Curcumin	Turmeric	Inhibition of cell growth and apoptosis induction by p53 upregulation	[37]
		Apoptosis induction by PTEN upregulation	[38]
		Apoptosis induction by HSP60 downregulation	[39]
		Inhibition of tumor progression and migration by Atx downregulation	[40]
		Inhibition of tumor cell migration	[8]
		Inhibition of cell migration and invasion by MMP-2 downregulation and TIMP1 activation	[41]

Table 1. Cont.

Bioactive Compound	Main Source(s)	Molecular Mechanism/Target(s)	Reference
Resveratrol	Grape skin and seeds, wine, peanuts, tea and berries	Apoptosis induction by caspase 3 activation, cell cycle arrest at S-phase by cyclin E upregulation and p21 downregulation	[42]
		Apoptosis induction	[43]
		Apoptosis induction and inhibition of cell proliferation by p53 activation	[44]
		Inhibition of oncogenic signals through prevention of ROS production and TrkAIII activation	[45]
Allicin	Garlic	Apoptosis induction and cell proliferation inhibition by ODC1 downregulation	[46]
S-allylcysteine (SAC)		Apoptosis induction and cell growth inhibition through mitochondrial permeability induction	[47]
Diallyl disulfide (DADS)		Apoptosis induction and cell proliferation inhibition	[48]
		Cytoskeletal damage, G2/M cell cycle arrest and apoptosis induction	[49]
		Anti-apoptotic effect by PGC1 α activation	[50]
All-trans retinoic acid (ATRA)	Vitamin A metabolite–	Differentiation activity	[51]
9-cis-retinoic acid (9-cis-RA)	Animal products, vegetables and fruits	Reduction of tumor growth in vivo	[52]
		Differentiation effect in amplified NMYC cell lines	[53]
Epigallocatechin-3-gallate (EGCG)	Green tea	Apoptosis induction through caspase and calpain activation	[54]
		Inhibition of tumor relapse and resistance to chemotherapy	[55]
		Enhanced efficacy in combination with 6-OH-11-O-hydroxyphenanthrene	[56]
Bergamot essential oil: BEO, BEO-TF, BEO-TFi	Bergamot (Citrus)	Apoptosis induction by p53 phosphorylation, increased of Bax and decrease of Bcl-2, reduced phosphorylation of p38	[57]
Bergamottin, 5-Geranyloxy-7-methoxycoumarin		Increase apoptosis and ROS levels, increase of BAX, p53, CASP9 and CASP3, decrease of Bcl-2 and Bcl-XL	[58]
Caffeine	Coffee, tea	Apoptotic induction by increasing caspase-3 activity	[59]
Berberine (BRB)	Medicinal plants	Enhanced apoptosis p53-mediated	[60]
		Apoptosis induction in combination with As ₂ O ₃	[61]
		Promoting differentiation through increased expression of MAP2, β -III tubulin, NCAM and downregulation of stemness marker as CD133, beta-catenin, notch2, MYCN, and SOX2	[62]

The absorption of nutrients required for fetal growth, development, and health originate from maternal nutrition and arrive at the fetus via the placenta. Both mother and fetus, therefore, are in potential danger of experiencing micronutrient deficiency during the period of gestation due to fetal growth requirements. For this reason, maternal nutrient supplementation is frequently prescribed in order to offset these potentially adverse outcomes for both mother and child, should micronutrient levels fall below a critical level. These supplements contain all of the most important components for the healthy development of the fetus [63].

In the following sections, we review relevant nutraceuticals with NB inhibitory activity, with particular reference to curcumin, resveratrol, garlic compounds, vitamin A, green tea, and other compounds such as caffeine, berberine, and bergamot. We review the main molecular mechanisms through which these nutraceutical compounds exert their NB inhibitory activity (Figure 1). We also review the importance of maternal multivitamin and multiple-micronutrient supplements to offset nutritional deficiencies, with the aim of not only providing dietary information for optimizing maternal health and fetal development during gestation and breast feeding, but also to lower the potential risk of developing NB.

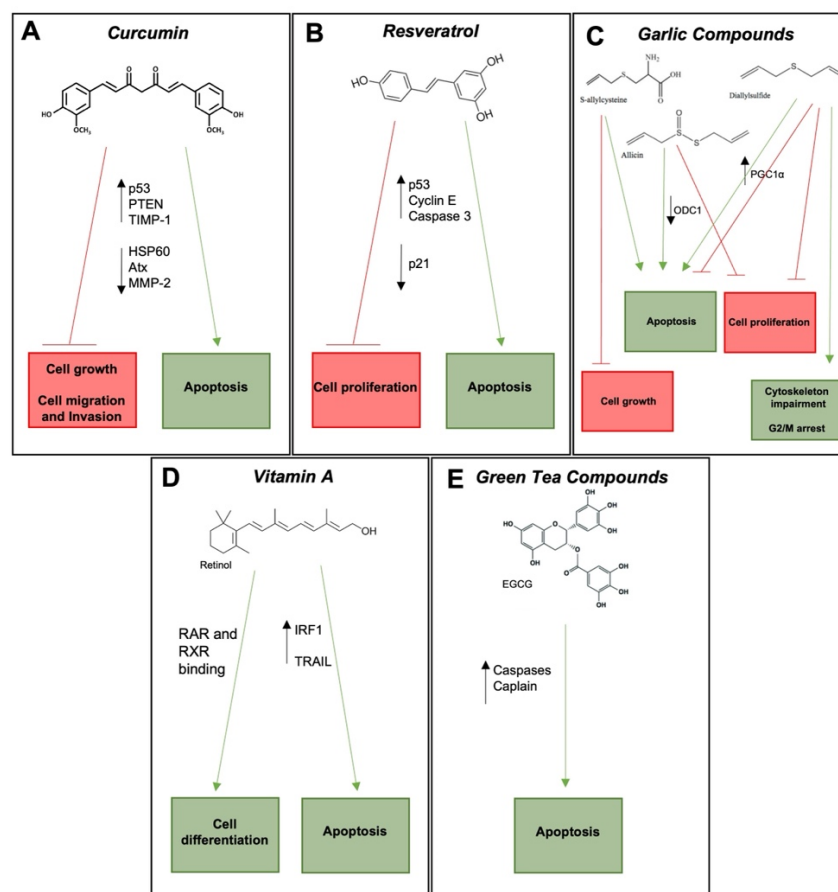


Figure 1. Schematic representation of the main molecular mechanisms responsible for the nutraceuticals' anti-cancer activity in NB.

3.1. Curcumin

The natural polyphenol curcumin (diferuloylmethane) is the most important nutraceutical component extracted from the rhizome of native Indian plant turmeric (*Curcuma longa*) [64], commonly used for its characteristic color and flavor in curries and mustards [65,66]. Turmeric preparations contain carbohydrates, proteins, essential oils, fat, minerals, curcuminoids, and traces of vitamins [65]. The curcuminoids include curcumin, dimethoxycurcumin, and bis-dimethoxycurcumin, of which curcumin is the most abundant [64]. Curcumin exists in tautomeric bis-keto and enolate forms, and at acid and neutral pH, is mainly in a hydrogen donating bis-keto form while at basic pH, it is mainly in enolic form [67]. The therapeutic potential of curcumin stems from reports of anticancer [68], anti-inflammatory [69,70], antioxidant [71], and antimicrobial activity [72]. Curcumin's anti-cancer properties include the inhibition of tumor promotion, tumor-associated angiogenesis, and tumor growth [73]. However, curcumin exhibits poor bioavailability due to low absorption and rapid metabolism, and is rapidly eliminated from tissues and blood, regardless of the administration route [74]. Co-administration with adjuvants and nano-formulations have been developed to overcome these problems [75].

In NB models, curcumin inhibits MYCN-amplified NB cell proliferation and induces P53-dependent apoptosis (Figure 1A) [37]. Curcumin also promotes NB cell apoptosis by upregulating phosphatase and tensin homolog (PTEN) expression, decreasing phosphorylated Akt levels and increasing Foxo3a nuclear translocation, resulting in pro-apoptotic p27, Bim, and Fas-L expression [38]. In addition, curcumin reduces HSP60 expression in NB cells, which is involved in pathogenesis and progression and reduces HSP60 S-nitrosylation, increasing the folding capacity, and implicating HSP60 in curcumin anti-cancer activity [39]. Curcumin also inhibits NB cell migration [8], motility factor autotaxin (Atx) expression in MYCN-amplified and non-amplified NB cells [40], and matrix metalloproteinase-2 (MMP-2) expression and activates the MMP inhibitor TIMP-1 [41], which together characterize curcumin as a potent inhibitor of NB cell migration and invasion.

3.2. Resveratrol

The polyphenolic stilbene phytoalexin resveratrol (3,5,4'-trihydroxystilbene) is produced in damaged plants and is abundant in grapes, wine, peanuts, tea, and some berries [76,77]. Red grapes are a principal source of resveratrol, and resveratrol concentrations in red wine range from 1.5 to 3 mg L⁻¹ [78]. Resveratrol exists in cis and trans forms, and trans-resveratrol is the more stable and abundant isoform [77]. The majority of studies have focused on the biological properties of trans-resveratrol [79]. The beneficial properties of dietary resveratrol include antioxidant, cardio-protective, and chemo-protective activity. In addition, resveratrol exhibits anti-inflammatory, antiviral, neuroprotective [80], and anti-cancer activity. Resveratrol exhibits tumorigenesis inhibitory activity in vitro and in vivo that is consistent with a cancer preventing function [81,82], and could be used in combination with standard chemotherapy because of its antioxidant and anti-inflammatory properties [82].

In NB models, resveratrol is cytotoxic to NB cells and induces NB cell apoptosis associated with caspase 3 activation (Figure 1B). Resveratrol promotes cell cycle arrest in S phase, probably by downregulating p21 and upregulating cyclin E expression, and arrests NB growth and increases survival in a mouse NB model [42]. Resveratrol also promotes mitochondrial permeability, resulting in mitochondrial cytochrome c and Smac/DIABLO release, resulting in apoptosis through the intrinsic pathway [43]. Resveratrol also inhibits proliferation and induces apoptosis in NB B65 cells through a SIRT1 independent mechanism, consistent with p53 activation and the inhibition of oncogenic signal transduction [44]. The antioxidant activity of resveratrol prevents ROS production and suppresses intra-mitochondrial activation of the oncogenic alternative TrkAIII splice variant in NB cells under conditions of ER stress, reducing stress-resistance, cell survival, and protective glycolytic metabolic adaptation [45].

The combined activity of resveratrol and immune-cytokines has also been investigated in a mouse NB model. Treatment with immune-cytokines alone arrested NB progression, which progressed after the cessation of treatment. Treatment with resveratrol alone resulted in primary tumor regression, but relapse with metastatic progression following the cessation of treatment. In contrast, treatment with resveratrol and immuno-cytokines resulted in primary tumor regression, long-term survival in 61% of mice, and the absence of metastatic progression [83]. This illustrates the need to further evaluate the NB inhibitory effects of resveratrol in combination with other drugs.

3.3. Garlic Compounds

Garlic (*Allium sativum* L. Fam. *Liliacee*) is a native plant of middle Asia, the beneficial effects of which have been known for over 5000 years. In ancient times, garlic was used by many populations, such as the Chinese, Israelis, Greeks, Egyptians to cure hemorrhoids, rheumatism, cough, skin disease, fever, and other diseases [84,85]. Today, garlic is known for its beneficial properties as an antioxidant [86], antibacterial agent [87], and for its anti-hypertensive [88] and anti-cancer properties [89]. Of the more than 2000 bioactive

molecules present in garlic, the medicinal properties of garlic have largely been attributed to molecular organosulfur compounds [90,91], of which alliin is the most interesting.

In chopped or crushed garlic, the non-proteinogenic amino acid alliin is converted into allicin by the release of alliinase, and is then rapidly transformed into ajoene, diallyl sulfide (DAS), and diallyl disulfide (DADS) [84]. Garlic also contains smaller amounts of biologically active *g*-glutamyl-S-allylcysteine (GSAC), S-methylcysteine sulfoxide (methiin), S-trans-1-propenylcysteine sulfoxide, and S-2-carboxypro-pylglutathione and S-allylcysteine (SAC) [92].

However, the antitumoral effects of many molecular garlic components have not been studied. Allicin induces apoptosis and inhibits proliferation in NB cells by downregulating ornithine decarboxylase (ODC1), a direct transcriptional target of the metastasis promoting oncogenes *c*-MYC and MYCN (Figure 1C) [46]. When combined with cyclophosphamide, allicin exhibits greater anti-tumor activity than cyclophosphamide alone in a mouse NB model [92]. The antitumoral effects of the garlic component SAC has also been evaluated in NB cells. SAC promotes apoptosis by inducing mitochondrial permeability and inhibits cell growth [47]. The allicin metabolite DADS induces mitochondrial apoptosis and inhibits proliferation in SH-SY5Y NB cells [48], and the pro-oxidant ROS producing activity of DADS also leads to cytoskeletal impairment, cell cycle arrest in G2/M, apoptosis, protein phosphatase 1 (PP1) activation, and subsequent Tau dephosphorylation [49]. DADS-induced ROS production, however, activates peroxisome proliferator-activated receptor-gamma co-activator 1 alpha (PGC1 α), which exhibits both cancer promoting and anti-cancer activity, and in NB cells induces mitochondrial biogenesis with anti-apoptotic effects, consistent with NB promoting potential [50]. The activity of DADS in NB, therefore, should be better understood.

3.4. Vitamin A and Retinoids

Vitamin A is an essential liposoluble micronutrient, the precursors of which are the provitamin A forms β -carotene e β -canthaxanthin. Forms of Vitamin A include all-trans-retinol, retinal, and retinoic acid (RA), collectively known as retinoids [93,94]. Animal products such as liver, oil, milk, and eggs are the main dietary sources of vitamin A (as vitamin A esters combine with long-chain fatty acids) [95,96], whereas vegetables and fruits such as carrots, tomatoes, spinach, lettuce, parsley, chilies, apricots, and mango, are sources of provitamin A carotenoids [96]. Humans do not synthesize retinoids and are, therefore, dependent upon dietary vitamin A [97]. Following intestinal absorption, retinol is transported by chylomicrons to the liver, which is the primary retinol (retinyl esters) storage site. Retinol is subsequently exported via retinol-binding proteins (RBPs) via the bloodstream to target tissues [93,95].

Vitamin A is essential for physiological processes such as sight, cutaneous integrity, immune system function, reproduction, and fetal development (organogenesis) [98] and has pleiotropic functions due to its biologically active isoforms. Vitamin A deficiency or excess is associated with characteristic symptoms and diseases., including night-blindness and corneal ulcers. Excess vitamin A causes osteosclerosis and teratogenic effects including organ malformation and altered organogenesis [99]. Vitamin A concentration, therefore, must be maintained within a strict range [100]. Vitamin A supplementation is commonly combined in multiple micronutrient integration and rarely alone [63].

Retinoids, as cancer preventing and anti-cancer agents, have been evaluated in NB as apoptosis inducers and pro-differentiation agents (Figure 1D) [94]. All-trans retinoic acid differentiates NB cells in vitro [51] and promotes neuritogenesis consistent with NB cell neural differentiation [101,102]. RA binds nuclear retinoic acid receptors (RARs) and retinoid X receptor (RXR), resulting in the transcription of retinoic acid responsive target genes [99]. Furthermore, retinoids also activate the transcription factor IRF1, a tumor suppressor involved in activating the tumor-selective death ligand TRAIL, leading to apoptosis through the extrinsic apoptotic pathway [103].

Retinoids (particularly 13-cis-RA) are used in high-risk NB as apoptosis and differentiation inducing agents in maintenance therapy for minimal residual disease [104]. Furthermore, the stereoisomer 9-cis-RA has been shown to induce greater differentiation in NB amplified NMYC cells [53]. However, despite its anti-NB activity in a human NB rat xenograft model, 9-cis-RA exhibits higher cytotoxicity, lower bioavailability, and a short half-life, limiting clinical use [52]. The synthetic retinoid fenretinidine is currently in clinical trials [101,104]. Vitamin A is, therefore, considered as a powerful potential NB preventive agent when taken during pregnancy, as discussed below.

3.5. Green Tea Polyphenols

Green tea is a preparation obtained from the dried leaves of the plant *Camellia sinensis*, which contains high levels of the ubiquitous plant polyphenol catechins and expounds numerous health benefits [105,106]. Green tea polyphenols include epicatechin, epigallocatechin (EGC), epicatechin-3-gallate, and epigallocatechin-3-gallate (EGCG) [106], of which EGCG is the most abundant anti-cancer component [55] (Figure 1E). EGCG has been characterized as a potential growth inhibitor in several types of cancer including NB [105], and in SH-SY5Y NB cells induces apoptosis through caspase and calpain activation [54]. In a BE (2)-C NB cell tumor sphere model of high-risk NB, EGCG prevents the formation of tumor-initiating cells, which are considered to be responsible for tumor relapse and therapeutic resistance [55]. EGCG, furthermore, has been shown to improve the anti-tumor efficacy of the retinoid, 6-OH-11-O-hydroxyphenanthrene [56]. EGCG, however, regulates many signaling pathways and, therefore requires further investigation in order to fully understand the mechanisms through which it exerts its anti-cancer activity [55].

3.6. Other Compounds

With respect to other nutraceutical molecules with potential anti-NB activity (see Table 1), berberine (BBR) is a natural alkaloid present in the rhizomes and roots of several plants including *Captis chinensis*, *Hydrastis canadensis*, *Berberis aquifolium*, *Berberis aristata*, and *Berberis vulgaris*. In NB in vitro and in vivo models, treatment with BBR leads to a reduction in tumor growth and regulates both differentiation and stemness [62,107]. In addition, BBR induces p53-dependent apoptosis in human SK-N-SH and SK-N-MC NB cell lines [60]. The in vitro cytotoxicity of BBR in cancer cells has also been reported to be enhanced when combined with arsenic trioxide (As_2O_3), a chemotherapeutic drug approved for the treatment of relapsed NB. BBR combined with As_2O_3 induces the apoptosis of SH-SY5Y NB cells by increasing the production of ROS and promoting the fragmentation of DNA, resulting in caspase activation and cell death [61].

The natural alkaloid caffeine, present in coffee, cocoa, tea, cola, guarana, and mate plants, is another potential NB inhibitory nutraceutical. At high concentrations, caffeine has been shown to induce apoptosis in SK-N-MC NB cells via a caspase-3 dependent mechanism [59].

Bergamot, contained within the peel of *Citrus bergamia*, a fruiting plant of the Rutaceae family native to the Southern coast of Calabria (Italy), also exhibits NB inhibitory potential. The essential oil purified from bergamot (BEO) has been shown to reduce the in vitro tumorigenicity of SH-SY5Y NB cells, linked to p53 phosphorylation, enhance the expression and activation of the pro-apoptotic factor BAX, reduce the expression of the anti-apoptotic factor Bcl-2, and reduce the phosphorylation of p38, which promote apoptotic pathway activation [57,58].

4. The Key Role of Dietary Supplements in Pregnancy: Multivitamins and Folic Acid

Multivitamin dietary supplements contain vitamins and minerals, are administered with a healthy and balanced diet, but vary in vitamin and mineral contents. Specific multivitamin supplements are tailored to improve athletic performance, reinforce the immune system, facilitate weight control, reduce cardiovascular risk factors, and improve body fluid drainage [108]. During the gestational period of pregnancy, multivitamin supplements

are used to offset micronutrient deficiency caused by placental and fetal growth and are important for both maternal and fetal health [63,109]. Multivitamin supplements used in pregnancy contain folic acid, vitamin C, vitamin E, vitamin A, β -carotene, and minerals such as iron, calcium and magnesium (Figure 2) [110], with supplements containing vitamin A and folic acid shown to reduce the incidence of NB by up to 30–40% [19,111].

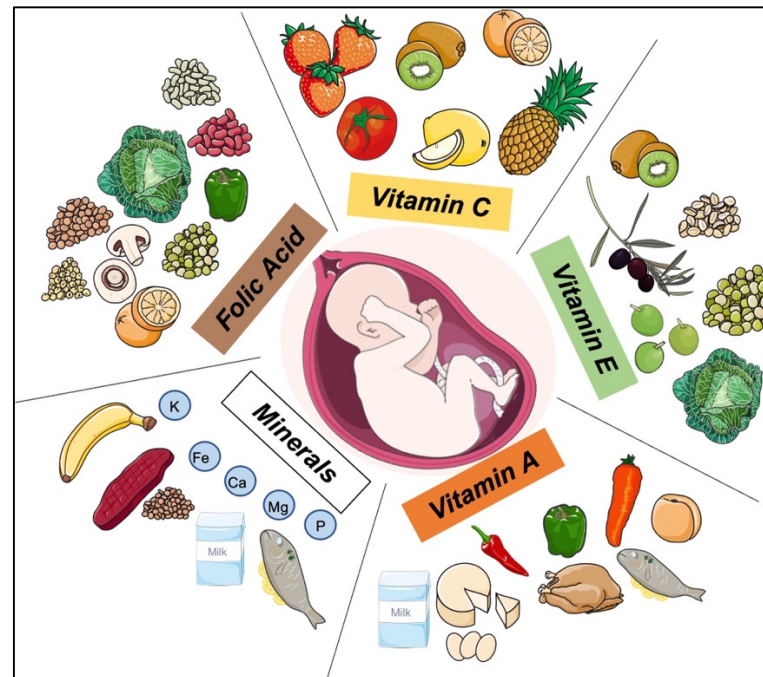


Figure 2. Maternal vitamins and minerals, with related food sources, associated with decreased risk of the development of pediatric cancer. The figure was partly generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license.

Interest in vitamin A as an agent to prevent cancer, however, has waned due to its pronounced cytotoxicity [52]. Therefore, retinoids rather than vitamin A have been recommended by the World Health Organization (WHO) as a component of multivitamin supplements to promote fetal and infant health and decrease the risk of NB in pregnant women [63]. The WHO recommends a daily dose of retinol activity equivalents in pregnant and breastfeeding women of 800 μg [63], with vitamin A concentrations of less than 0.70 $\mu\text{mol/L}$ considered to represent subclinical vitamin A deficiency [112].

Folic acid is a synthetic form of the water-soluble B group vitamin folate [113,114], naturally present in several vegetables including legumes, green leafy vegetables, and some fruits [115]. As folate is more expensive and temperature sensitive, folic acid is more widely used in dietary supplements. The active form of folic acid, 5-methyltetrahydrofolate (5-MTHF), is produced in the liver by folic acid reduction [114], is fundamental for embryonic development. 5-MTHF deficiency during pregnancy, promotes premature birth, and increases the risk of neural tube defects (NTDs) [116,117]. In a 1997 study, the consumption of cereal fortified with folic acid was shown to reduce the number of NB diagnoses in Canada, suggesting a potential role for folic acid in preventing NB. This was supported in a subsequent retrospective folic acid fortification study that also reported a reduction in NB cases [118], later confirmed by a meta-analysis of previous data concerning NB incidence following maternal multivitamin ingestion. However, the different combinations of vitamins and minerals in multivitamin supplements has hampered the identification of the actual components that reduce NB incidence, and no studies have been reported that demonstrate a relationship between a specific multivitamin supplement and NB pathogenesis [119].

5. Discussion and Conclusions

The majority of NBs are diagnosed in advanced stage, and despite aggressive multimodal therapeutic strategies, continue to exhibit a high frequency of post therapeutic relapse, poor prognosis, and low overall survival, making an effective cure highly challenging [30,33]. Although novel targeted therapies may eventually improve response rates and outcomes in advanced stage NB, novel maternal nutritional supplements containing the NB inhibitory nutraceuticals and vitamins reviewed in this article, provide an important additional strategy to reduce NB development, enhance spontaneous regression, and reduce the early progression of NBs during pregnancy and breast feeding. This potential would add to the important aims of using maternal nutritional supplements to augment maternal, fetal, and childhood health and may also extend to the prevention of additional fetal pathologies, exemplified by folic acid prevention of neural tube defects [117,118]. For these potentials to be realized, problems associated with nutraceutical bioavailability, toxicity, and the route of administration must be addressed and resolved [52,75].

In conclusion, the use of novel maternal supplements containing NB inhibitory nutraceuticals and vitamins not only has the potential to prevent NB development, but also to enhance spontaneous NB regression and reduce early NB progression during fetal growth and early childhood. This novel underestimated approach provides a potentially important additional weapon in the battle to defeat this highly challenging pediatric cancer and, therefore, warrants complete and thorough investigation.

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