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Review paper

Vitamin A in prevention and treatment of cancer

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Abstract

Dietary components not only act as chemo preventive agents but also risk factors in the onset of cancer, which stimulating nutritional balance in cancer or non-cancer populations. The supplementation of antioxidant compounds, such as vitamin A (Vit A) and few of its derivatives has been reported to alleviate the oxidative stress in cancer patients. This review focuses on sketching a current scenario on the Vit A role in cancer prevention and therapy. Therefore, we searched for published article on PubMed and Science Direct between 2014 and 2015. The search yielded 75 articles related to Vit A-mediated anti-oxidative or pro-oxidative effects in cancer patients. A low dose-mediated anticancer effect was observed with Vit A in some cancers. The clinical studies showed discrepancies between the low and high doses of Vit A in cancer. In conclusion, precautions are needed in taking Vit A and its derivatives, especially in cancer.

Keywords: *Vitamin A; Oxidative Stress, Cancer.*

1. Introduction

Cancer is a complicated and one of the most lethal diseases throughout the world (Zhang et al. 2010). In order to improve the prognosis, the dietary balance is fundamental (Bozzetti 2015). However, the incorporation of mineral micronutrients, zinc and selenium; and especially the vitamin supplements as well as their derivatives, and analogues have been found to bring some fruitful outcomes in cancer (Chen et al. 2013; Cook-Mills et al. 2013; Oliveira 2015). Being micronutrients and complexity in actions, the use of vitamins in cancer is not common (Barber et al. 2014; Clamon 2015). However, in some non-clinical and clinical studies, the use (both individually and combindly) of vitamins for the prevention and treatment of cancers, is evident (Coulter et al. 2006; Bjelakovic et al. 2013a; Shukla et al. 2014).

Both lipo-soluble and water-soluble vitamins supplied by the organic food materials are extremely necessary for our body homeostasis (Alabdali et al. 2014; Chang et al. 2015). Among them, Vit A (retinol), Vit C (ascorbic acid) and Vit E (tocopherol) are well-known for their antioxidant effect (Bucioli et al. 2011; Greenlee 2012; Celik et al. 2013). Vit A, upon considering as a nurtitional supplement, has been implemented for decades in the prevention and treatment of neoplasms (Rochette-Egly 2015). However, there are reports that telling about the antagonistic effect of Vit A with some antineoplastic drugs along with an involvement in the early cancer development (Demaria et al. 2010; Wong and Lodge 2012; Tang et al. 2014; Doldo et al. 2015).

This text presents a systematic review on Vit A, emphasizing for the prevention and treatment of cancer.

2. Methodology

We searched non-clinical and clinical reports (articles) written in English in the 'PubMed' and 'Science Direct' databases between the years 2014 and 2015. In this regard, the considered keywords were: "vitamin A" or "retinol"' paired with "derivatives," "cancer," "cancer prevention," "cancer treatment," treatment", "clinical study" and "non-clinical study." Figure 1 shows the search, inclusion and exclusion events.

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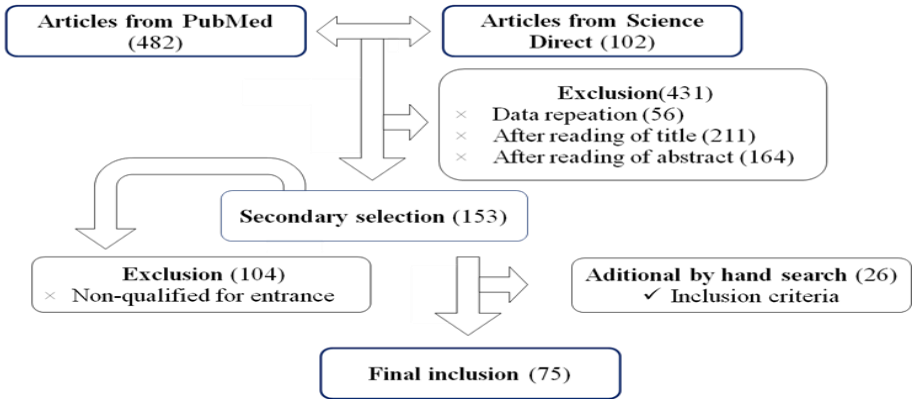


Fig. 1: Schematic Presentation of Search Criteria, Data Analysis, Inclusion and Excluding Events

3. Results and discussion

3.1. Antioxidant activit of vitamin A

The physiological roles of Vit A are individualized and complex, related to numerous processes such as recognition and molecular signaling, basal body metabolism, immune response, replacement of epithelial cells and mucosal tissues, reproduction (e.g. – spermatogenesis), and maintenance of vision (Lee et al. 2010; Von Lintig 2012; Doldo et al. 2015). The-carotene, β-carotene, β-cryptoxanthin, retinol (Vit A), retinoic acid (RA) and retinaldehyde are some of the terminologies that correspond to natural, synthetic and pro-Vit Compounds (Donkena et al. 2010; Bushue and Wan 2010). The chemical structures are so varied, where Vit A metabolites can attribute to the following conformations: cis, 9-cis retinoic acid; and trans, all-trans retinoic acid (ATRA) (Grune et al. 2010; Szabo et al. 2013; Connolly et al. 2013; Varshosaz et al. 2013).

However, the activity of each analogue or derivative depends on some factors, including specificity and molecular identification. The immune response by the Vit A and its derivatives are linked to the interaction with free radicals, such as reactive oxygen species (ROS: superoxide anion, hydroxyl radicals and hydroperoxyl). The ROS scavenging capacity is also plugged to save the cellular macromolecules such as – carbohydrates, proteins, lipids and genetic materials (e.g. - DNA/RNA), which is helpful to manage cancer. Vit A also acts as a potent modulator of progression or even initiation of cancer. It can prevent cell proliferation and tissue invasiveness (Zeegers and Goldbohm 2001; Doldo et al. 2015).

Vit A stimulates the steroidal nuclear protein receptors, such as retinoic acid receptors (RARs) and retinoic-X receptors (RXRs); those are evident to influence the gene transcription in cancer (Lee et al. 2010; Bushue and Wan 2010). Vit A also stimulates some other proteins such as retinol-binding protein (RBP), cellular retinol-binding protein (CRBPs) / cellular retinoic acid-binding protein (CRABPs) and retinol-binding plasma proteins; Stra6, a gene associated with p53 in the induction of cellular apoptosis, which is essential for the control of cell proliferation and tumoral tissue invasion (Mahalingam et al. 2010; Liu et al. 2011; Li et al. 2011; Carrera et al. 2013; Khillan 2014; Doldo et al. 2015).

Much attention has been given on natural product-based cancer therapy by these days (Connolly et al. 2013). Notably, cancer therapies available to date are restricted, individualized, complex and differentiated, leads to large deficits in public health as a whole, include some dangerous side effects such as alopecia, dietary and circulatory disorders, blood, liver and heart toxicity, and so on (Tykwinska et al. 2013; Lqubal et al. 2014; Tang et al. 2014).

The ATRA is evident to act as an antitumor agent in some in vitro and ex vivo non-clinical studies, especially in the primary cells of patients with chronic lymphocytic leukemia (CLL) (Holmes 2012; Fernández-Calotti et al. 2015). ATRA in HepG2 and A549 cells is evident to reduce DNA methyltransferase (DNMT) activity through the DNA methyltransferases, resulting in an activation and regulation of p53 gene through the ubiquitination of the mouse double minute 2 homolog (MDM2) (Shukla et al. 2014; Meloni 2014). In some studies, ATRA is found to exert an apoptotic cell death in a number of cancer cells (Heo et al. 2015; Carmona-Gutiérrez et al. 2011; Circu and Aw 2012; Guicciardi et al. 2013; Johansson et al. 2010), as observed in figure 2.

Vit A analogues / derivatives also have impacts on protein signaling, that can be identified and detected by using biosensors in some disorders, including glaucoma, chronic cardiovascular diseases, intraepithelial neoplasias or even cancers such as colorectal, uterine cervix and breast (Zanon-Moreno et al. 2013; Brown et al. 2014; Khan et al. 2015). Although, the effects of macro nutrients on neoplastic disorders are needed to be distinguished, health research suggesting beneficial effects of antioxidants in cancer (Table 1) (Neuzil et al. 2007; Dorjgochoo et al. 2008; Apraiz et al. 2011).

The oxidative effects of Vit A is evident to overcome the chemotherapeutic resistance in some cancer, such as acute promyelocytic leukemia (APL), suggesting a new therapeutic window in cancer (Johnson and Redner 2015; Uchino et al. 2015). Vit A is also found to exert cytotoxic effects on breast cancer (MCF-7) (Marcato et al. 2015; Flodrova et al. 2015), neuroblastoma (SK-N-BE and SH-SY5Y) (Watters et al. 2013), P19 of embryonal carcinoma (Lee et al. 2015), hepatocellular carcinoma (HTC) (Ionta et al. 2012), primary cells of osteosarcoma (Zhang et al. 2014), pancreatic adenocarcinoma (Panc-1 and Aspc-1) (Guan et al. 2014), prostate cancer (DU145) (Ameri et al. 2011), ovary cancer (A2780) (Doldo et al. 2015), and so on (Guo 2011; Qiao et al. 2012).

However, the clinical evidence suggests that, Vit A at low doses has suppressed effects of genetic mutation (Table 1). In a study, Vit A combined with ATRA (45 mg/day for 2 months) was found to improve cancer situation in APL patients (53) not mutated for the FLT3 / ITD receptor (Hong et al. 2011). Although low dosages are more common, the uses of ATRA at 3,869 to 222,111 IU/day are also found to exert an antitumor effect in 49 patients with head and neck tumors (Colacino et al. 2012).

Moreover, the precursors, derivatives and metabolites of Vit A are also evident to prevent or treat cancers in a number of studies (Table 1). The same combination is also reported to act against melanoma (236,623 patients) and gastric cancer (1, 221, 392) (Zhang et al. 2014; Kong et al. 2014). The retinol palmitate (RP) at 1,500 µg/day combined with β-carotene was found to decrease in risk of lung cancer in 1428 smokers (Cheng et al. 2014). In a meta-analysis (25 clinical studies) Vit A supplement is found to decrease the risk of bladder cancer in 11,580 individuals (Tang et al. 2014).

Vit A and its analogues/derivatives may also impart an apoptotic cell death through association with some other specific proteins (Suntharalingam et al. 2014). It is because they have selective affinity for the organic, usually specific, clusters which can exert toxicity in tumor cells (Circu and Aw 2012; Doldo et al. 2015; Yang 2015).

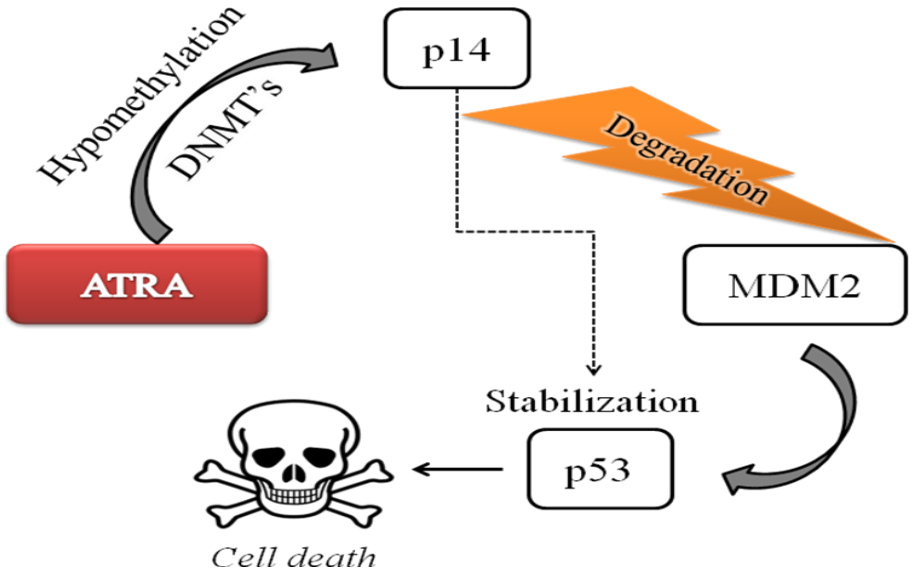


Fig. 2: Therapeutic Action of ATRA, Inducing Hypomethylation of DNMT's. With the Activation of p14 Expression and the Consequent Degradation of MDM2, the Stabilization and Regulation of p53 Promote Apoptosis in Tumor Cells. (Adaptation from: Kwak and Jang, 2015)

Table 1: Therapeutic Effects of Vitamin A and Its Analogues/Derivatives on Cancer in Clinical and Nonclinical Study Models

Compound	Test system	Study performed	Dose/concentration	Results	Reference
Retinol	(Revision) In vitro = 2780 ovary cancer cells	Therapeutic efficacy of Retinol	20 μM	It promoted the reexpression of CRBP-1 interfering on the differentiation of the cancerous cells	Doldo et al. 2015
ATRA	Clinical study = 49 patients	Association with DNA methylation in patients with head and neck tumors	3869 - 222111 UI/day	The higher ingestion had a lower association with the methylation of the tumor suppressor gene	Colacino et al. 2012
Retinoic acid	In vitro = HTC cell line	Combined use with cAMP in the treatment of CHC	0.1 µM	Inhibition of HTC cell proliferation and enhancement of differentiation	Ionta et al. 2012
ATRA	In vitro = SK-N-BE and SH-SY5Y cell lines	Indication of the route of carcinogenesis in neuroblastoma	5 µM	Alteration of T-CRs expression levels inducing cell differentiation	Watters et al. 2013
ATRA	In vitro = HT93A cell line	Analysis of cell differentiation in LPA	100 nM	Induction of terminal granulocytic differentiation by the regulation of CD11b and CD34 proteins	Uchino et al. 2015
ATRA	In vitro = Primary cells of osteosarcoma	Analysis of cell differentiation in osteosarcoma	1 µM	Specific binding in E2F1 by RARα inducing osteogenic differentiation	Zhang et al. 2014
ATRA	In vitro = DU145 cell line	Effect on cell proliferation in prostate cancer	1 e 10 µM	Induction of apoptosis by cleavage of p35 and super activation of Cdk5	Chen et al. 2012
ATRA	Ex vivo = 23 patients	Analysis of primary cells of fludarabine-resistant CLL patients	10 µM	Intracellular elevation of hCNT3 by TGFβ1 enhancing cellular apoptosis	Fernández-Calotti et al. 2015
ATRA	Clinical study = 53 patients	Impact on the prognosis of a chemotherapy combination in LPA	45 mg/m^2/day	Better prognosis in non-mutated individuals for the FLT3 / ITD receptor	Hong et al. 2011
Retinol	Meta-analysis 25 studies = 11.580 individuals	Analysis of the preventive effect of diet on bladder cancer	NR	Decreased risk of bladder cancer	Tang et al. 2014
β-carotene + retinyl palmitate	Clinical study = 1.428 individuals	Investigation of the preventive effect of diet in a population at high risk for lung cancer	< 1.500 µg/day AER	Decreased risk of lung cancer in smokers	Cheng et al. 2014
Retinol + β-carotene	Meta-analysis 10 studies = 236,623 individuals	Analysis of the preventive effect on melanoma	NR	Decreased risk of melanoma cancer	Zhang et al. 2014
Retinol + β-caroteno	Meta-analysis 47 studies = 1.221.392 individuals	Analysis of the preventive effect on gastric cancer	1,5 mg/day	Low doses of vitamin can significantly lower the risk of gastric cancer	Kong et al. 2014
ATRA	In vitro = HepG2 and Hep3Bcell lines	Analysis of apoptosis induction in hepatoblastoma and hepatoma	5 µM	Expression of p14, promotion of hypomethylation and induction of apoptosis	Heo et al. 2015
ATRA or 9-cis retinoic acid	In vitro = Panc-1 and Aspc-1 cell lines	Effect of cell proliferation on pancreatic cancer	20 µM	Inhibition of cell migration by the low expression of α-SMA, FAP, IL-6 and decreased production of extracellular matrix	Guan et al. 2014
ATRA and 9-cis retinoic acid	In vitro = MCF-7 cell line	Analysis of invasion and metastasis in breast cancer	0,01 mmol/L and 25 mmol/L	Increased regulation of p27, SmD3 ribonucleoprotein, and cofilin-1, affecting cell migration in the tumor	Flodrova et al. 2015

NR = not related. TCP = head and neck tumot. CHC = hepatocelular carcinoma. ATRA = all-trans retinoic acid.

3.2. Oxidative effect of vitamin A

Besides, antioxidative Vit A has been recognized for its pro-oxidative effect (Behr et al. 2012), as at high concentration it causes oxidation of the biological molecules (Bowry et al. 1992). It was found to influence on the plasma concentration of antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT) (Schnorr et al. 2014). In some studies, Vit A at 2500 IU/kg /day caused mitochondrial oxidative and nitrosative stress by elevating α-synuclein, β-amyloid protein, RAGE, and tumor necrosis factor alpha (TNF-α) in healthy organisms (Moquin and Chan, 2010; Oliveira et al., 2012). On the other hand, RP at 1000 to 9000 IU/kg/day produced neurotoxic effects by augmenting the production of superoxide anion (O_2•-) in the frontal cortex, cerebellum and hypothalamus of rodents (De Oliveira and Moreira 2007, 2008; De Oliveira et al. 2009).

Cancer progression is dependent on the balance between the induction of cell proliferation or cell death (Nicolau-Galmés et al. 2011; Sadowska-Bartosz and Bartosz 2014). The relationship with the crucial mediators for cell survival, such as tumor necrosis factor kappa B (NFκB) and pro-inflammatory cytokines have been found to link oxidative stress-inducing cell death in Sertoli non-neoplastic cells by altering the mitochondrial electron transfer with Vit A treatment (Zanotto-Filho et al. 2009; Oliveira et al. 2009; Vaseva et al. 2012) (Figure 3). Few evidence suggesting that, RP-mediated imbalance of redox status interfering the basal metabolism of pregnant and lactating adult rats may link to promote teratogenic effects in menopausal women (Schnorr et al. 2011; Behr et al. 2012).

Clinical studies demonstrating inconstancy in the effects of Vit A and its derivatives (Table 2) (Oliveira 2015; Mactier and Weaver 2005). A randomized study of 53 clinical trials suggesting that vitamin supplementation with β-carotene intake at doses above 9.6 mg in 241,883 individuals (age between 18 to 103 years) caused higher mortality rate (Bjelakovic et al. 2013b). Park et al (2011) demonstrated that, in 1400 LPA patients registered at the National Cancer Institute's (NCI) surveillance, continued higher mortality rates even after supplementation of ATRA. On the other hand, Vit A in patients with non-melanoma skin cancer at 25,000 IU significantly increased the risk of developing squamous-cell carcinoma (SCC) (Clouser et al. 2010). Additionally, Bjelakovicet al (2007) reported a β-carotene/Vit A (200,000 IU) induced increased risk of death in 232,606 participants.

To be mentioned that, still there are controversies on the selection and usages of doses of Vit A and its analogues/derivatives (Park et al. 2010; Bjelakovic et al. 2013b). However, the in vitro and ex vivo studies favoring the incorporation of vitamins into at low concentration for chemotherapeutic treatments, while high for pro-oxidant action (Ionta et al. 2012; Tykwinska et al. 2013). This may be due to the balance of production and effects of ROS on cells (Wensveen et al. 2011). However, the Vit A supplementations are not only associated with the maintenance of body homeostasis, but also incorporated into various types of therapies in humans, such as dermatological and oncological disorders (Khillan 2014; Zhang et al. 2014; Hsu et al. 2015). In this regard, the maesured levels of disorders and selection of dose are crucial to Vit A treatment (Behr et al. 2012).

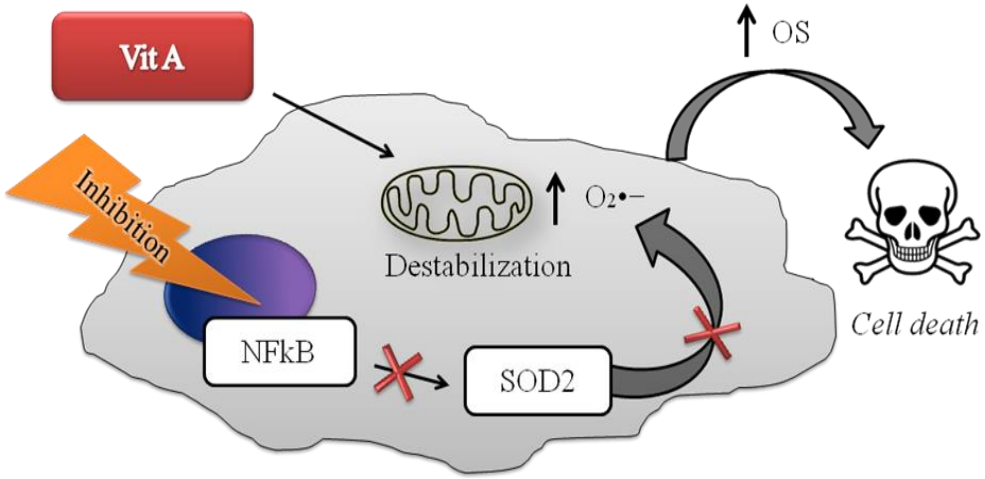


Fig. 3: Vit A-Induced Production and Intracellular Accumulation of Reactive Species and Impacts of Oxidative Stress on Normal Cells. [Vit A by Inhibiting the Nfκb (Tumor Necrosis Factor Kappa B) as Well as SOD2 (Superoxide Dismutase 2) Activity and Eventually Augmenting the ROS (Reactive Oxygen Species) May Impart Mitochondrial Dysfunction by Induction of Oxidative Stress (OS).] (Adaptation from: Zanotto-Filho Et Al., 2009).

Table 2: Oxidative and Adverse Effects of Vitamin A and Its Analogues/Derivatives on Clinical and Non-Clinical Study Models

Compound	Test system	Study performed	Dose/concentration	Results	Reference
β-carotene and vitamin A	Randomized trial of 385 clinical articles = 232,606 individuals	Cancer prevention	1333-200.000 IU	Supplementation increased the risk of death	Bjelakovic et al. 2007
ATRA	Clinical study = 1400 patients	Analysis of the efficacy of LPA treatment	NR	Mortality rates remain high after supplementation	Park et al. 2011
Retinyl palmitate	In vivo = female Wistar rats	Effects of supplementation during menopause in OVX rats	500 ou 1,500 IU kg/day (30 days)	Reduction of SOD/CAT Hypothalamic and frontal cortex, as well as lipid peroxidation of the frontal cortex	Behr et al. 2012
Retinyl palmitate	In vivo = rats	Redox state evaluation	1000–9000 IU/kg/day	Interference on the activity of mitochondrial electron transfer in the cerebellum	De Oliveira and Moreira 2008
All-trans retinol (ROH)	In vitro, ROH-treated Sertoli cells	Protective effect of NFkB against oxidative stress induced by ROH	5–10 µM	Accumulation of reactive species	Zanotto-Filho et al. 2009
Retinyl palmitate	In vivo = adult Wistar rats	Evaluation of interference on neuronal homeostasis	1000–9000 IU/kg/day (28 days)	Induction of nitrosative stress in the hypothalamus	De Oliveira et al. 2009

Retinyl palmitate	In vivo = adult Wistar rats	Evaluation of brain metabolism dysfunction	1000–9000 IU/kg/day (28 days)	Dysfunction of the redox and bioenergetic state in the frontal cortex	Oliveira et al. 2009
Retinyl palmitate	In vivo = adults rats	Evaluation of oxidative and nitrosative stress markers	500-2500 IU/kg/day (3 months)	Dysfunction of the hepatic redox state	Oliveira et al. 2012
Retinyl palmitate	In vivo = adults rats	PSM redox state analysis	1000–9000 IU/kg/day	Mitochondrial dysfunction and cerebral alteration of the cortex and / or cerebellum	De Oliveira and Moreira 2007
β-carotene	Randomized trial of 53 articles = 241,883 individuals	Effects of different doses on mortality rates	> 9,6 mg	High doses significantly increased mortality	Bjelakovic et al. 2013b
Retinyl palmitate	In vivo = female Wistar rats	Effects during gestation and lactation by parameters of oxidative stress	2500-25.000 IU/kg	Supplementation during gestation and lactation may be toxic to mothers with adverse effects on the development of offspring	Schnorr et al. 2011
Retinol	Clinical study = 525 patients	Action against recurrence in patients at risk for non-melanoma skin cancer	25.000 IU	Significant increase in the risk of developing squamous cell carcinoma	Clouser et al. 2010

NR = not related. OVX = ovariectomized. PMS = submitocondrial particles. ATRA = all-trans retinoic acid. ROH = retinyl alcohol.

4. Conclusion

The effects of Vit A and its precursors/analogous/derivatives are found to link with the used dose and individual-dependent. Low dose-mediated cytoprotective while at high dose-mediated pro-oxidative damaging effects in experimental animals are observed in the literature. Besides, a number of influences on the cellular response system, the ROS-induced activity may link to them. Therefore, it is badly needed to understand the levels of oxidation and selection of dosages of them. Additionally, patient's age and pathological conditions are also two other important considerations on vitamin therapy.

5. Conflict of interest

None declared.

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