REVIEW

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The Sources of Essential Fatty Acids for Allergic and Cancer Patients; a Connection with Insight into Mammalian Target of Rapamycin: A Narrative Review

Zhila Arshad[1], Soheila Rezapour-Firouzi[2]*, Mahshid Mohammadian[3], Meysam Ebrahimifar[4]*

Abstract

Background: Disturbance in essential fatty acids (EFA) metabolism plays a key role in autoimmune diseases, but EFA supplementation with sources of borage, evening primrose, hemp seed and fish oils was not effective in atopic and cancer diseases, as that seen in the case of multiple sclerosis. It seems that two complexes of the mammalian target of rapamycin (mTOR) signaling, mTORC1 and mTORC2, are congruent with the two bases of the Traditional Iranian Medicine (TIM) therapy, Cold and Hot nature, which are essential for the efficacy of functional oils for controlling immune responses in autoimmune diseases. **Methods:** We searched PubMed database, Web of Science (WOS), Google Scholar, Scopus and selected studies by predefined eligibility criteria. We then assessed their quality and extracted data. **Results:** The oils controlled by Cold or Hot nature may be helpful in maintaining homeostasis and preventing autoimmune diseases. In summary, studies of randomized controlled trials for allergy and cancer patients found no improvement in the signs or response to tests, despite a remarkable change in EFA fractions in the blood by supplementation with sources of borage, evening primrose, hemp seed and fish oils. In contrast, portulaca oleracea oil exhibited protective effects by anti-inflammatory properties via the PI3K/Akt/mTORC2 pathway with a deviation immune response to Th1 to treat atopic diseases and cancer. **Conclusions:** According to the concept of Traditional Iranian Medicine therapy, in contrast to Cold-nature oils, EFA supplementation with the sources of Hot-nature oilsis not suitable for the treatment of atopic and cancerous diseases.

Keywords: Polyunsaturated fatty acids- cancer- allergy- immune response- Thelper

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Introduction

For several years, the biological association between cancer and allergies has taken epidemiological, oncological and immunological interest to scientists. One theory holds that the effect of diet on the incidence of allergy and cancer is mediated through the quality fatty acids content. The dietary modulation of allergy and cancer risk is mediated through the balance of ω3 to ω6 polyunsaturated fatty acids (omega-3toomega-6-PUFAs) in the diet. Allergy, or atopy, is considered to be a hypersensitivity reactions introduced by specific immunological mechanisms, which includesseveral mediators such as Th2 cell cytokines, chemokines, immunoglobulins (IgE, IgG), as well as activation of the immune system cells including eosinophils, mast cells (Simpson et al., 2002). An increased incidence of cancer may result from frequent tissue inflammation in atopic patients, which in turn could be associated withpermanently impaired tissues (Vena et al., 1985). The mechanistic target of rapamycin (mTOR) pathway is a vital integrator of nutrient-sensing signals in all mammalian cells that plays an essential role in cell growth and metabolism with environmental inputs, including nutrients and growth factors (Saxton et al., 2017). The mTOR pathway forms two distinct protein complexes, known as mTORC1 and mTORC2 (Saxton et al., 2017). The mTORC1 signaling is essential for T helper (Th)1 and Th17 differentiation and, mTORC2 is critical for Th2 differentiation (Delgoffe et al., 2011). The phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K-Akt-mTOR) pathway is persistently activated in many types of cancer and allergy.Thispathway, as a lipid kinase, plays a vital role in many of the cellular and molecular mechanisms driving asthma and cancer pathophysiology and is a key therapeutic target (LoPiccolo et al., 2008; Choi et al., 2013;

*[1]Department of Pathology of Anatomy, School of Medicine, Baku University of Medical Sciences, Baku, Azerbaijan, [2]Cellular and Molecular Research Center, [3]Department of Biochemistry, School of Medicine, Urmia University of Medical Sciences, Urmia, [4]Department of Toxicology, Faculty of Pharmacy, Islamic Azad University, Shahreza Branch, Shahreza, Iran. *For Correspondence: s.rfirozi@gmail.com, ebrahimifar67@gmail.com*

Yoo et al., 2017). A large portion of the immune response is based on the regulation of mTOR activation through fatty acids.The atopic diseases by a tendency to the Th2 cells of the immune system have been linking with cancer progression. So, allergens and allergic foods can increase the risk of cancer. Autoimmune diseases, more than other diseases, have gathered much attention in the field of alternative medicine. Because of this etiopathogenesis is incompletely understood so far, it is necessary to open up many opportunities for misinterpretation. In this review, we evaluate why porulacaoleracea oil has beneficial effects on atopic diseases and cancers, but the sources of borage, evening primrose, hemp seeds and fish oils have not been as successful as if we would expect if proposed EFA-mediated pathophysiological mechanisms central to these diseases. Another purpose of this review is to shorten the present evidence effects ofthe source of PUFAs as functional foods onatopic diseases and cancers to evidences the molecular mechanisms that cause this association. It is still to be investigated whether mTOR can be seen as a therapeutic target for allergic and cancer diseases by protective source of PUFAs on the basis of Traditional Iranian Medicine (TIM) view.Narrative overview of the literature synthesizing the findings of literature retrieved from searches of computerized databases, hand searches, and authoritative texts (Green et al., 2006).This narrative review study was conducted using preferred reporting items.

Mechanism of action ofPUFAs in Pro-inflammatory Eicosanoids

The PUFAs (ω3 and ω6) have significant roles in membranes structure and function; in cell signaling and regulation of gene expression. Furthermore, they play important roles as substrates for the synthesis of lipid mediators involved in inflammation, immunity, and many other physiological responses (Gurr, 1998). It is likely that the fraction of ω3/ω6 fatty acids incoming the cellular pool from nutritional sources can modify the fraction of eicosanoid precursor fatty acids (FAs) in tissue membrane phospholipids (PLs).The ω3 family of PUFAs includes alpha-linolenic acid (ALA), eicosapenaenoic acid (EPA), and docosahexaenoic acid (DHA) whereas the ω6 family includes linolenic acid (LA) and arachidonic acid (AA). EPA and DHA are precursors for anti-inflammatory lipid mediators, while AA is a precursor for pro-inflammatory lipid mediators. Taken together, PUFAs play crucial roles in maintaining cellular homeostasis, and distresses in the nutritional intake or PUFA metabolism can affect the risk and progression of cellular dysfunction and contribute to cancer (Azrad et al., 2013) or allergy (Horrobin, 2000). Clinical trials have shown that supplementation with PUFAs or oils high in PUFAs can affect markers of inflammation, immune function in cancer and allergy (Manku et al., 1982; Horrobin, 2000; Azrad et al., 2013). LA (ω6) and ALA (ω3) are the main essential fatty acids (EFAs) in the human species. Delta-5-desaturase (D5D) and Delta-6-desaturase (D6D) are vital enzymes for the desaturation and elongation of long chain (LC)-PUFA in mammals. D6D is the first enzyme of the sequence forming the gamma-linolenic acid (GLA) and stearidonic acid (SDA) by adding a double link to LA and ALA respectively (Manku et al., 1984). GLA is rapidly converted to dihomo gamma-linolenic acid (DGLA) by elongase enzyme. The reaction catalyzed by D6D enzyme is the slowest and most rate-limiting step of the reaction in the metabolic pathway of LA. The synthesis of PUFAs is catalyzed by desaturases for incorporating them into cell membranes, which thereby affect the fluidity, permeability and functional properties of the cells (Nakamura et al., 2004). LA and AA, through the enzyme system of elongation and desaturation, by cyclooxygenase (COX) and lipoxygenase (LOX), a large number of biologically active molecules including proinflammatory eicosanoids prostaglandins (PGs) and leukotrienes (LTs) are produced (Borgeat et al., 1985). AA is a precursor of proinflammatory PGE2, while EPA is a precursor of anti-inflammatory PGE3; in addition, GLA and DGLA are precursors of anti-inflammatory PGE1 and PGE3 respectively. Although the activity of D6D is impaired by viral infection, aging, high blood pressure, high alcohol intake, high level cholesterol, stress-related hormones, radiation, nutritional factors (deficiencies of Zn+, Mg+, vitamins: C, B5, B6, B3 and high level of trans fatty acid), diabetes, genetic deficient (inactive D5D and D6D enzymes) (Bates., 1988; Horrobin., 1990; Horrobin., 1992), there will be a reduced DGLA production and then of PGE3. Their relative deficits may release AA from membranes and the formation of high activity of pro-inflammatory eicosanoids including PGE2 and LTB4. The PGE2 and LTB4 are respectively drawn from the AA through the COX2 and the LOX2 pathway, whereas, in normal people, the free AA concentration is low (Ruzicka et al., 1986). From the DGLA, the PGE3 is produced through the COX3 enzyme, which has anti-inflammatory potential and modulates with a mechanism of negative feed-back AA release in free form (Borgeat et al., 1985). For the inhibition of releasing AA free, the ideal ratio of ω3/ ω6 fatty acids should be 1: 2.3; this ratio needs to be obtained because these two groups of EFAs complete distinct and complementary functions (Roncone et al., 2010). Because of this, ω3 and ω6 EFAs should be given together (Aragona et al., 2005). Present studies estimates of the ω3/ω6 PUFAs ratio in developed nations are as few as 1:25 advising people (Delaleu et al., 2008). A cellular concentration ratio of ω3/ ω6 is 1:1.5. It is the most optimal homeostatic levels; however, it is difficult to reach this ratio.For these reasons, it is usually necessary to intake an additional dietary supplementation of ω3 to achieve a balanced ratio of ω3/ ω6 fatty acids (Simopoulos., 2009).

Mechanism of action of PUFAs in Cancer

Epidemiologic studies offeravaried picture of the relationship between nutritional PUFAs and cancer risk progression.Identifying the type of PUFA source for cancer provides an opportunity to follow dietary interventions to control cancer. Specifically, a Western diet with a high intakes of ω6 PUFA and lower intakes of ω3 PUFA plays an important role in carcinogenesis and cancer (Gerber., 2012). It is believed that eicosanoids derived from AA play amajor role in these courses (Carter et al., 1983), and ω3 PUFAs to the diet can block the

promotional effects of AA - ω6 PUFAs (Birt, 1990).In contrast ω6 PUFAs, especially AA, are much richer in our daily diet and are relatedto many adverse effects on the human body, including cancer. For example, a high intake of ω6 correlates with a high risk of breast, prostate, and coloncancer prevalence inmany studies, and the low ratio of ω3/ω6 was suggested as a predictor of cancer development (Sauer et al., 2007; Brown et al., 2010; Sakai et al., 2012). Results were found that large amounts of ALA are found in walnuts and flaxseed, which significantly reduced tumor size in mice fed walnuts compared to controls in animal model of the breast (Hardman et al., 2008; Hardman et al., 2011) prostate (Davis et al., 2012), and colon cancer (Nagel et al., 2012). The enzyme 5-LOX converts AA to LTB4. In normal physiological situations, 5-LOX is not naturally expressed, but it is upregulated through inflammatory reactions and tumorigenesis. As such, LTB4 levels have been shown to be higher in human colon and prostate cancer tissues (Il Lee et al., 2011). In normal tissues, COX-1 is constitutively expressed at low levels and COX-2 is unnoticeable but is inducible during inflammatory responses. In cancer cells, COX-2 is often expressed as a result of production of high levels of PGE2 (Wang et al., 2010). PGE2 is linked to breast cancer (Diaz-Cruz et al., 2005). In the prostate cancer COX-2 expression and PGE2 biosynthesis motivate PI3k/Akt/mTOR pathway (Vo et al., 2013). EPA, which can be derived from the metabolism of ALA or through the intake, produces anti-inflammatory eicosanoidsof PGE3 and LTB5 by the COX and LOX pathway, respectively. In contrast to the actions of PGE2, PGE3 and LTB5, they do not induce cancer cell multiplying and instead downregulate the expression of PGE2 and LTB4 in competition with AA (Bagga et al., 2003). Nutritional DHA reduces tumor size in a dose-response method in animal model of breast cancer (El-Mesery et al., 2009). EPA and DHA (Long chain ω3-PUFA) may modulate the production of pro-inflammatory eicosanoids, thereby inducing local inflammatory status, which is essential in cancer development. Genes involved in the desaturation of fatty acids, including D6D and D5D, as well as the genes encoding enzymes responsible for eicosanoid production, are known to be involved in tumor development (Lenihan-Geelset al., 2016). Intake of saturated and trans-unsaturated fatty acids,animal sources of fat, are associated with all-cause morbidity and mortality due to many kind of cancers (Azradet al., 2013; Pelseret al., 2013).

Th2 immune deviation has an active role in tumor progression

Cancer has always been the most important of all diseases. The types of cancers include ovarian cancer, breast cancer, lung cancer, brain cancer and gastric cancer (Amiri et al., 2016; Ebrahimi Far et al., 2017; Izadi et al., 2016; Kanaani et al., 2017; Poy et al., 2016; Poy et al., 2018). In the majority of studies, to establish the efficacy of clinical treatments using chemotherapy in combination with other drugs for clinical using,on the cell line, has not been paid to the immune system tendency to treat cancer (Sajjadiyan et al., 2016; Mohamadi et al., 2017; Mohammadian et al., 2017). Immune cells that tend to promote tumor progression through immunosuppression include Th2 CD4+ cells, activated B cells, and neutrophils (de Visseret al., 2006; Verbekeet al., 2011; Biragyn et al, 2012). Typically, T helper cell differentiation Th1 and Th2 cell populations are reproducing from naïve Th0 cells. If Th0 cells differentiate into Th1 cells; are those normally related to the cytotoxic function: Tumor necrosis factor (TNF)-α,interferon(IFN)-γ.Conversely, Th2 cells arise from the differentiation of Th0 cells exposed to interleukin (IL)-4 and IL-13. Th1 cytokines enhance the cytotoxic capabilities. Th2 cells are associated with allergic responses by high levels of the IL-4, IL-5, IL-10, and IL-13 cytokines. IFN-γ and other Th1 cytokines inhibit transcription of IL-4, while IL-4 induces expression of Th2 cytokines and inhibits the expression of IFN-γ (Amsen et al., 2009). In cancer, immune responses signals not only suppress Th1 cell maturity but also promote Th2 maturity, further inhibiting T-cell-mediated cytotoxicity, to promote humoral immune responses (Pollard., 2004; DeNardo et al., 2010). Furthermore, Th2 cells suppress the differentiation of cells with Th1 profile responses, induce IgE production and, consequently, contribute to humoral immunity (Adkins et al., 2004; Bettelli et al., 2007). Cancer cells promote the production of IL-4 and down-regulate the production of IFN-γ (Sheu et al., 2001). Quantitatively, expressed high amounts of Th2-type cytokine mRNA were detected at the tumor site (Asselin-Paturel et al., 1998). The expansion of a peculiar subset of 'Th2-1ike' cells with increased IL-4 production was also found in patients with B helper cell chronic lymphocytic leukemia (Shurin et al., 1999).Thus, these studies have been shown that a shift from Th1- to Th2-type of T cell response may play a significant role in the development and progression of cancer.

Mechanism of action of PUFAs in Atopic Diseases

Atopic diseases are a range of syndromes in the individual including allergies, eczema, asthma, hay fever or migraine. The defects in the immune system of atopic patients suggest a relationship between genetic factors and various environmental cues. There are many indicators for the unusual metabolism of EFAs and PGs in atopic diseases (Tricon., 2006). Changes in EFAs consumption have paralleled increases in childhood asthma and atopy. EFAs play vital roles in skin structure and physiology. EFA insufficiency reproducessigns of atopic dermatitis (AD) (Manku et al., 1982; Wright, 1991; Horrobin, 2000). AD patients have a deficiency and defect in the activation of the D6D enzyme, which affects the conversion of LA to GLA (Wright, 1991; Horrobin, 1992). Since GLA is rapidly metabolized to DGLA in the cells by the elongate enzyme (Chapkin et al., 1986; Horrobin, 1992; Ziboh et al., 2000), GLA supplementation enhances DGLA levels in the skin cells, which leads to the increased production of DGLA metabolites includinganti-inflammatory eicosanoids PGE1, PGE3, and 15-hydroxyeicosatrienoic acid (15-HETE or 15-OH-DGLA) (Manku et al., 1982; Wright, 1991; Horrobin, 1992; Ziboh et al., 2000). DGLA seems to have a role in maintaining AA in cell membranes, as well as being converted to anti-inflammatory eicosanoids,

where it has desirable actions.Furthermore, the presence of high levels of DGLA prevents themetabolism of AA to proinflammatory eicosanoids (Horrobin, 1992). AD is associated with increased levels of LA, AA, and reduced levels of the metabolites of GLA and DGLA (Galli et al., 1994). There was evidence that the ratio of maternal PUFAs to later atopy and wheeze was related to low levels ω3/ ω6 PUFAs ratio (Pike et al., 2012). Concentrations of LA tend to be elevated in the milk, blood, and adipose tissue of patients with atopic eczema (AE), whereas the concentrations of ALA products are significantly reduced. This shows reduced LA metabolism to GLA, while GLA administration has been found to improve the clinically assessed skin problem (Horrobin, 1992). Low levels of ALA and total ω3 LC-PUFAs in the milk of mothers appear to be associated with atopic sensitivity of in childhood, as well as relative disturbances between the ω3-PUFAs and the ω6-PUFAs in mature milk, which revealed the atopic status in the mothers. Variations in the EFA's composition of maternal milk could clarify some of the protective effects of breast-feeding against atopic conditions (Duchen et al., 1998). Disturbances of the lung function appear to be related to increased LTB4 formation in patients with atopic asthma (Borgeat et al., 1981). LTB4 is a pro-inflammatory agent with a chemotactic power towards polymorphonuclears, eosinophils, and monocytes that was found to be enhanced in the skin areas with the AD eczematous lesions (Ruzicka et al., 1986). The most pro-inflammatory product of AA is LTB4. Low levels of eicosanoids of DGLA metabolism may be involved in AD. DGLA, which cannot itself be metabolized to LTs, can produce a 15-OH-DGLA derivative that inhibits the conversion of AA to LTs (Vanderhoek et al., 1980). PGE1 and PGE3 derived from DGLA, are supposed to prevent the mobilization of AA from cell membranes PLs (Feinstein et al., 1977). Therefore, a functional EFA inadequacy will lead to deficiencies in T suppressor cell function and an enhanced risk of allergic responses (Settipane et al., 1974).

mTOR Signaling Pathway, Immune Responses and Fatty Acids Metabolism

The mammalian target of rapamycin (mTOR), an important intracellular pathway, playsa vital role in the regulation of the cell cycle, fundamental metabolic, and physiological processes, such as lipid metabolism (Lamming et al., 2013). The mTOR kinase is known to act as a nutrition sensor of molecular metabolism in cellular homeostasis by altering the cellular metabolic processes and integrating environmental signals (Soliman, 2005; Foster et al, 2010). It is sometimes joked that 'mTOR regulates everything'. Perhaps it is predictable that mTOR is one of the critical sensors of nutritional status at the levels of cells and organisms. The mTOR kinase regulates many major cell cycle processes and is involved in an increasing number of pathophysiological disturbances (Laplante et al., 2012). Thus, it may have a significant effect on the maintenanceof metabolic homeostasis in the whole body. So, it is worthwhile for many processes to be related to nutritional states (Howell et al., 2011). The regulation of mTOR signaling pathway is probably one of the best examples of evolutionarily conserved nutrient-mediated regulation, and dysregulated mTOR signaling has been implicated in major diseases. In response to metabolic signals, two complexes of mTOR facilitate the accumulation of triglycerides by promoting adipogenesis and lipogenesis (Caron et al., 2015). The mTORC1 may be critical for the long-term regulation of lipid homeostasis. Reduced mTORC1 activity increases lipolysis and decreases mitochondrial combustion of FFA (Chakrabarti et al., 2015). The mTOR signaling plays a central role in the regulation of mRNA translation in mammalian cells (Redig et al., 2011) by activating the transcription factor, SREBP (Sterol Regulatory Element Binding Protein) (Brown et al., 2007) which in turn activates acetyl CoA carboxylase (ACC) (Peng et al., 2002), fatty acid desaturase (FASD) (Mauvoisin et al., 2007), and stearoyl CoA desaturase (SCD) (Lamming et al., 2012) enzymes involved in lipogenesis. In vitro, inhibition of mTORC1 by RAPA increases β-oxidation and the expression of enzymes involved in FAs oxidation (Peng et al., 2002; Porstmann et al., 2008). mTORC1 also promotes the expression and activation of peroxisome proliferator-activated receptor γ (PPAR-γ), the principle regulator of adipogenesis (Zhang et al., 2009). The mTORC1-PPARγ pathway is important for the FAs uptake plan in activated CD4+ T cells. This pathway is required for the full activation and rapid proliferation of naive and memory CD4+ T cells. FAs are known to be essential metabolites for maintaining cell activation, proliferation and functioning in rapidly proliferating cells (Angela et al., 2016). FAs have a significant impact on mTORC1 regulation (Yasuda et al., 2014). The mTORC1 is activated by the saturated fatty acids (SFAs), such as palmitate, by enhancing the translocation of mTORC1 to the lysosome and subsequently inducing its activation, while ω3-LC-PUFAs such as EPA inhibit SFA-induced mTORC1 translocation into the lysosome. ω3-LC-PUFAs-mediated function suppresses mTORC1 activity (Zivkovic et al., 2011). Therefore, the quality of fat, including increasing proportions of the ω3 /ω6 fatty acids,could mitigate autoimmune diseases by inhibiting Th1/Th2/Th17 cells through control of mTOR signaling (Sakaguchi., 2004; Yuan et al., 2015; Rezapour-Firouzi., 2017).

mTOR Signaling Pathway in Cancer and Atopic Diseases

It has been shown that a drug that blocks mTORC2 may be useful in treating Th2-mediated asthma or cancer without mitigating Th17 and Th1-mediated antifungal and antibacterial immune responses. In contrast, a selective drug that blocks mTORC1may be useful in MS mediated by Th1 and Th17 cells without diminishing Th2-mediated atopic immune responses (Gamper et al., 2012). Evidence has suggested that mTORC1 tends to promote Th1 differentiation (Delgoffe et al., 2009), while mTORC2 may bias the response to Th2 through AKT phosphorylation (Lee et al., 2010). mTOR signaling effects on B cells are partially imposed by the relative contribution and mTORC1 / mTORC2 ratio. It has been shown that mTORC2 plays a vital role in B cells growth and maturity by AKT phosphorylation (Llorian et al.,

2007). These findings indicate that mTORC2 plays a significant role in atopic immune responses (Zhang et al., 2011). In addition, the PI3K-Akt-mTORC2 pathway is a potential target for the treatment of cancers (Vander Haar et al., 2007). Cancer cells consume a lot of glucose. It is reported that glucose transporters are activated only after phosphorylation of PI3K-Akt (Vadlakonda et al., 2013), also enhanced PI3K-Akt-mTORC2 signaling plays a central role in directing immune responses to allergy as well (Wu et al., 2015). The PI3K-Akt-mTORC2 signaling activation is necessary for the onset of asthma and suggests potential targets for asthma treatments (Zhang et al., 2017). Thus, inhibition of PI3K-Akt-mTORC2 signaling activation and Th2 differentiation is targeting for atopic and cancer treatments.

Definition of mTORsignaling in Traditional Iranian Medicine (TIM)

Cold and Hot natures (Mizadj) are accepted as true in TIM and in many other traditional medical theories including Greek, Roman, Arabic, European, Indian, and Chinese traditional medicines (Ott, 1997; Avicenna, 2004). In the study, based on the IL-4 / IFN-γ ratio, it was reported that the trend of people with Hot-Nature was to divert towards Th2 immune responses to higher grade than Cold-nature individuals.Hence, eating of Cold-nature foods (such as portulaca olerace) in a person suffering from an autoimmune disease with a deviation toward Th2 immune responses (such as atopic diseases) may be useful because they can accelerate coldness of nature and deviation to Th1 immune responses. Throughout the world, the influence of warmth or coldness of food and drinks was supported by many traditional medical theories (Shahabi et al., 2008). It seems that two of the signaling complexes of mTOR as a nutrition-sensing conducts immune responses due to nutrients, such that them TORC1 pathway regulates cellular immunity (Th1 immune responses or Cold-nature) and mTORC2 pathway regulates humoral immunity (Th2 immune responses or Hot-nature), respectively. Therefore, differences in nature and temperaments can influence neuroendocrine and immune systems, so medication and nutrition should be prescribed according to the patient's nature and temperament (Mirzaei, 2007). The association between the increasing warmth of nature and the deviation of the immune responses to Th2-like immune responses is in agreement with the view of Iranian physician Avicennathat the smell of a Hot-nature substance such as saffron can lead to rhinorrhea, because it seems that Avicenna was describing a type of allergy (Tadjbakhsh, 2006). Therefore, it is possible that eating, drinking or smelling of Hot-Nature substances can lead to an allergic reaction by shifting the immune responses towards a Th2-like response through phosphorylation of AKT/ mTORC2 (Hertzen, 1998; Holt et al., 2000; Adkins et al., 2001; Upham et al., 2002; Llorian et al., 2007). Since, mTORas a power regulator everything, has a significant influence on maintaining metabolic homeostasis through nutritional cues (Howell et al., 2011; Laplante et al., 2012), in concordance with TIM practitioners' view, both Cold and Hot nature substances have an effect as well on two complexes of mTORC1 and mTORC2, respectively. Therefore, it is necessary to pay attention to the nature of the patients' diet to prevent their acceleration. Further, controlling of healthy people's diet based on Cold or Hot nature may be helpful in the maintenance of homeostasis and prevention of autoimmune diseases (Mirzaei, 2007). With regard to the above, due to deviation toward Th2 immune responses through mTORC2 and acceleration cancer and atopic conditions, EFA or GLA supplementation with Hot-nature oils including borage, evening primrose, hemp seed and fish could not be profitable for cancer or allergy, as we would expect, if proposed EFA-mediated pathophysiological mechanisms are critical to cancer or atopic diseases.

The EFA or GLA Supplementation in Cancer or Atopic diseases

In agreement with TIM practitioners' view, some of the functional oils (sources of EFAs or GLA) were divided to three nature (Ott, 1997; Avicenna, 2004):

A: Mild nature oil: olive oil

B: Hot-nature oils: borage, evening primrose, hemp seed or fish

C: Cold-nature oils: portulacaoleracea, coriander

In a clinical trial, treatment with olive oil (mild-nature) compared to borage oil (severely Hot-nature) increased the ω3-EPA levels, while the borage oil depicted metabolism away from the ω3-PUFA synthesis pathway and partially reduced EPA levels. EPA is a precursor to anti-inflammatory LTB5, which has anti-inflammatory potential in contrast to LTB4. Further, the higher levels of EPA are associated with release of less AA from cell membranes and the formation of proinflammatory eicosanoids of LTB4 and PGE2 (Don, 2003). In another study, treatment with GLA derived from evening primrose oil (EPO) in the AD has slightly improved clinical conditions and biochemical abnormalities (Manku et al., 1982). Because of much higher of GLA content, borage oil could be more successful than EPO, but results do not the provable or widely approved treatment for the AD. According to the basic conceptions of TIM, evening primrose and borage oils are substances with Hot-nature that can severely accelerate immune responses tendency toward Th2. Hence, as soon as worsening of disease by borage oil is seen, treatment should be discontinued. It is likely that the effectiveness of borage oil will be more in mild-to-moderate AD than in severe conditions (Foster et al., 2010). Studies have shown that borage oil and EPO are not successful in eczema. The limitation of therapeutic efficacy of borage oil and EPO are related to the acceleration of the warmth of nature or severe deviation of Th2-like immune responses. Also, there is little and insufficient evidence to suggest that these two oils have an effective therapeutic effect on cancer. The conflicting findings regarding the safety and efficacy of GLA, ω3 fatty acids, are seen. Three studies on fish and hempseed oils determined the quality of life in atopic eczema. These were not in favor of fish or hempseed oils over placebo. Even though the adverse events were mainly minimal, with no statistically significant differences between the fish and hempseed oils with placebo (Thandar et al., 2014).

In contrast, there are many studies that indicate antitumor activity of Portulaca oleracea L. or purslane. Purslaneoil or extract (Cold-nature) possesses the ability to inhibit cervical cancer cell growth and is a potent nutrient supplement for oncotherapy (Zhao et al., 2017), colon cancer (Jin et al., 2017), cytotoxicity effects and anti-proliferative properties (Liu et al., 2010). Further, treatment with purslane effectively repressed the PI3K/Akt/mTORC2 activation and truly inhibits deviation of the immune responses to Th2 in cancer and atopic diseases. Also, the purslane exhibited protective effects on hepatocellular carcinomas by anti-inflammatory and anti-oxidative properties through inhibition of the PI3K/Akt/mTORC2 pathway (Guoyin et al., 2017).

Discussion

Complementary and alternative medicines (CAM) and herbal remediesare widely used by patients with cancer or allergy (Swarup et al., 2006; Rostaminasab et al., 2015; Bielory, 2018). The role of nutrition in cancer risk and development is probablymorethan ever recognized, mainly in terms of dietary intake of fresh fruit and vegetables, meat products, and fish or fish oils, which may be linked to their effects on inflammatory processes (Baena et al., 2015; Dasilva et al., 2015). Butthis question remained, why dietary fish oil supplements as a means to improve the prognosis of cancer and prevent tumor growth are largely controversial? Orif the disturbance in EFA metabolism plays a key role in autoimmune diseases, why EFAs or GLA supplementation with sources of borage, evening primrose, hemp seed and fish oils is not very effective in atopic diseases or cancer, as in the case of multiple sclerosis (MS)(Rezapour-Firouzi et al., 2013a; Rezapour-Firouzi et al., 2013b; Rezapour-Firouzi et al., 2013c; Rezapour-Firouzi, 2017). It seems that olive oil (OO) without the tendency toward Th1 or Th2 immune responses, is likely to stimulate the generation to Tregulatory cells for the prohibition of autoimmune diseases and imbalance (de Zoeten et al., 2009; Mercer et al., 2009). Probably, substances of Mild-nature such as olive oil naturally activate Treg and modulate the activation of both mTORC1 and mTORC2 complexes, subsequently Th1 and Th2 immune responses. The inhibitory effects on the activation of mTOR kinase by olive oil were clearly observed. In summary, all the evidence strongly supports the idea that olive oil can regulate the altered levels of mTOR activity in order to prevent autoimmune diseases and cancer (Khanfar et al., 2015). In according to the concepts of TIM, the extracted oils of sources with Hot-nature are associated with the phosphorylation of PI3K/AKT/mTORC2 pathway or shift of immune responses toward Th2 and worsening diseases status. Therefore, EPA, DHA, and GLA as essential fatty acids found in fish oil, evening primrose, and borage oilcan inhibit the action of cancer or atopic diseases, after purification and separation from whole oil. This is why, after years of hearing that eating fatty fish or taking fish oil (Hot-nature) supplements was good for the heart, the eyes, and even mood, the public was puzzled by a study that suggested a risk of prostate cancer in men with high levels of ω3 fatty acids obtained from fish sources (Alexander., 2013; Haas-Haseman., 2015). In contrast, the purslane has a potential application in the treatment of cancer and atopic diseases. As a result, makes an attempt at GLA or EFAs supplementation with sources of functional oils to cancer or atopic diseases should be oils and other substances with Cold-nature. In ancient medicine of Iran, purslane is popular as a traditional medicine for the treatment of atopic diseases (Naseri, 2004; Naseri et al., 2004). Purslane has antioxidant and anti-inflammatoryand anticancer properties can be used as functional food in nutritional/pharmaceutical agent in medicine. Various compounds are separated from the purslane, such as EFAs, flavonoids, alkaloids, terpenoids, and sterols. Its medical value is evident from its use for treatment of diseases associated cough, shortness of breath, and skin condition (Zhou et al., 2015). Purslane has been identified as an exceptionally rich source of ALA, DHA, as well as docosapentaenoic acid (ω3-DPA), and a small amount of EPA essential fatty acids, which are useful in reducing the incidence of certain cancers (Simopoulos et al., 1992; Liu et al., 2000; Acedo et al., 2012). Recently, purslane has been identified as the richest vegetable source of ALA and LA, which reached a content ratio to 45.65 % and 12.37 % respectively. This percentage is higher than that found in some leafy vegetables and even higher than that found in some commonly fish species (Simopoulos et al., 1986; Omara-Alwala et al., 1991; Sallam et al., 2015). The positive regulation of mTORC2 by PI3K/Akt signaling pathway was found to be related to the pathologic process of various cancer (Ai et al., 2015). It implies that immune responses all the cancers square measure toward Th2 or warmth nature in ideas of TIM. So, substances like implantation plant act with high health value and shifts immune responses to Th1, as well as repairing cell membranes by EFAs. In result, the purslane plant as a Cold-nature diet is the appropriate treatment for cancer and atopic diseases. The Cold-nature foods can exert a protective effect against the development of atopic diseases or cancer. In contrast, hot-nature foods have a deviation of the immune response toward Th2, which favor the development of cancer or allergy. This review was considered the food sources of EFAs that could play a key role in the development or inhibition of cancer and allergy. In conclusion, this review provided a new term of the molecular and metabolic basis of controlling polyunsaturated fatty acids metabolism in autoimmune diseases related to the mTOR pathway and link these mechanisms in Traditional Iranian Medicine therapy. Factors apart from the deficiency of EFAs or GLA like nature of daily diet may hasaffect the balance of pathophysiological factors and PGs production, it could also be more important than such imbalances. These answers can improve our understanding of cell biology and should facilitate the way we tend to treat several diseases by co-administering typical and ancient medical care together.

Authorship contribution

Study concepts/study design: all authors; Collection demographic data: all authors; manuscript drafting:

ZhilaArshad; manuscript final version approval and manuscript editing: all authors.

Conflict of interest

The authors declare no conflicts of interest.

Abbreviations

AA	Arachidonic acid
ACC	acetyl-CoA carboxylase
AE	Atopic eczema
AD	Atopic dermatitis
ALA	Alpha-linolenic acid
COX	Cyclooxygenase
CAM	Complementary and alternative medicines
D5D (FADS1)	Delta-5-desaturase
D6D (FADS2)	Delta-6-desaturase
DGLA	Dihomo-gamma-linolenic acid
DHA	Docosahexanoic acid (omega-3 Family)
DPA	Docosapentaenoic acid
EFAs	Essential fatty acids
Elovl	fatty acid elongase
EPA	Eicosapentanoic acid (omega-3 Family)
EPO	Evening primrose oil
FAs	Fatty acids
FADS	Fatty acid desaturase
GLA	Gamma-linolenic acid
15-HETE	15-hydroxyeicosatrienoic acid
HS	Hempseed
HSO	Hempseed oil
IFN-γ	Interferon-γ
Ig	Immunoglobulins (IgE, IgG)
IL	Interleukin (IL-4, IL-5, IL-10)
LA	Linoleic acid (omega-6 Family)
LC-PUFA	Long-chain polyunsaturated fatty acid
LOX	Lypoxygenase
LTs	Leukotrienes (LTB4, LTB5)
MS	Multiple sclerosis
mTOR	mammalian target of rapamycin
mTORC	mTOR complex
PG	Prostaglandin
PGE	Prostaglandin E (PGE1, PGE2, PGE3)
PI3K-Akt	phosphatidylinositol 3-kinase/protein kinase B
PLs	Phospholipids
PPAR-γ	Peroxisome proliferator-activated receptor γ
PUFA	Polyunsaturated fatty acid (ω3-PUFAs, ω6-PUFAs)
RAPA	Rapamycin
SDA (STA)	Stearidonic acid
SFAs	Saturated fatty acids
SREBP	Sterol Regulatory Element Binding Protein
SCD	stearoyl CoA desaturase
Th	T helper (1-2)
TIM	Traditional Iranian Medicine
TNF-α	Tumor necrosis factor-α
ω3-PUFAs	omega3-polyunsaturated fatty acids
ω6-PUFAs	omega6-polyunsaturated fatty acids

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