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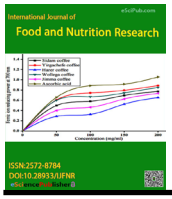

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Astaxanthin: The possible effects of this carotenoid on disease, inflammation and aging control. A meta-analysis

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ABSTRACT

Astaxanthin (ATX), a red pigment that belongs to the xanthophyll subclass of carotenoids, has a strong antioxidant ability and can eliminate singlet oxygen (O2-) as well as hydrogen peroxide (H2O2) and lipid peroxidation. ATX can also prevent mitochondrial dysfunction by permeating and co-localizing within the mitochondria and inhibit the release of cytochrome c resulting from mitochondrial permeabilization and, thus, prevent mitochondrial-mediated apoptotic cell death. Due to its antioxidant capacity and modulating properties of cell signaling, ATX exhibits a variety of beneficial biological activities among them protection against UV damage, anti-inflammatory and immunomodulatory activity, metabolic syndrome (MS) relief, cardioprotective effects, antidiabetic activity, prevention of neuronal damage, anti-aging and anticancer activity. The aim of the present study was to evaluate what has been published about ATX in PubMed/Medline between 2020-2021. The results were distributed in four Tables as follows: Table 1-Publication types; Table 2- Proposal for evaluating the article in vivo; Table 3- Cells markers used in clinical studies in vivo; Table 4- Astaxanthin in human clinical trial. We could observe that the interest of the scientific community has been growing in relation to the benefits of ATX. The results presented in the articles evaluated in this meta-analysis showed us that AXT is already a reality as an option in treatments for various diseases, including glaucoma, heart and vascular injury, type 2 diabetes and fatty liver. We conclude that ATX may not only be a promising nutraceutical as an ally to alternative treatments of the pathologies mentioned above, but also as a powerful prophylactic in elderly individuals in prevention of diseases associated with aging.

Keywords: Astaxanthin; Inflammation; Oxidative Stress; Mitochondria; Aging

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Introduction

Astaxanthin (ATX), a red pigment that belongs to the xanthophyll subclass of carotenoids, has a strong antioxidant ability and can eliminate singlet oxygen ($O2^-$) as well as hydrogen peroxide ($H2O2$) and lipid peroxidation [1]. Due to its antioxidant capacity and modulating properties of cell signaling, ATX exhibits a variety of beneficial biological activities and effects among them, protection against UV damage [2], anti-inflammatory and immunomodulatory activity [3], relief of the metabolic syndrome (MS) [4], cardioprotective effects [5], antidiabetic activity [6], prevention of neuronal damage [7], anti-aging [8] and anticancer activity [9], as well as inhibition of cell membrane peroxidation [10]. In general, ATX has an inhibitory effect on the development of diseases associated mainly with oxidative stress and mitochondrial dysfunction. Since mitochondria are a source of ROS, this can be a target in pathological conditions [11].

ATX can reduce oxidative stress and maintain the integrity of mitochondria [12]. Sztrety et al (2019) have proven that ATX supports mitochondrial function, protecting the redox balance in this organelle [12]. ATX significantly reduces the oxidative stress that occurs physiologically and keeps the mitochondria in a reduced state, even after stimulation with $H2O2$ [13]. It also prevents the loss of the mitochondrial membrane potential in the escape of electrons and increases the consumption of mitochondrial oxygen [12]. ATX also can prevent mitochondrial dysfunction by permeating and co-localizing within the mitochondria [14]. In an in vivo study of geriatric dogs, oxidative damage was mitigated and impaired mitochondrial function was restored in treatment with ATX [15]. In this study, Park et al. (2013) suggests that ATX prevents aging by increasing mitochondrial efficiency in

ATP production and respiratory chain complex activity. Isolated mitochondria from ischemic myocardium in mice also showed higher levels of both ROS and mitochondrial membrane depolarization, in addition to edema in this organelle [16]. However, treatment with ATX has been shown to be effective in reducing the production of mtROS and depolarization and swelling of the mitochondria [11, 16].

ATX has demonstrated its ability to inhibit the release of cytochrome c resulting from mitochondrial permeabilization and, thus, prevent mitochondrial-mediated apoptotic cell death [11, 17]. In a study with myocardial cellulose, Fan et al. (2017) suggested that ATX inhibited the release of cytochrome c and the apoptosis of myocardial cells, decreasing ROS levels and the consequent formation of protein oxidation products and restoring mitochondrial membrane potential [18]. In the same way, ATX elevated levels of PGC-1α in skeletal muscle, induced the decrease in plasma fatty acids during exercise, and prevented reduction in intermuscular pH due to exercise [19]. ATX also accelerated the utilization of lipids as an energy substrate during aerobic exercise [19]. AXT has demonstrated it elevates the expression of PGC-1α and its downstream proteins, which are involved in the activation of mitochondrial biogenesis, leading to the acceleration of fat utilization during exercise through aerobic metabolism in mitochondria [20]. Therefore, elevation of PGC-1α by ATX may induce the acceleration of lipid metabolism during exercise. Indeed, cytochrome c, a component of the mitochondrial electron transport chain and a major PGC-1α-inducible protein, was also upregulated by ATX [19].

In another study, Nishida et al (2020) demonstrated that ATX activated the AMP Kinase protein (AMPK) in the muscle and upregulated the expressions of a transcriptional coactivator and transcriptional factors, thereby inducing mitochondrial remodeling, including increased mitochondrial oxidative phosphorylation and free fatty acid metabolism [21]. This study suggests that ATX upregulated Pgc-1a gene expression in the skeletal muscle via AMPK activation.

We seek to evaluate, through this present study, what has been published about ATX in the

PubMed/Medline database in the past 2 years (2020/2021) concerning anti-inflammatory activity, immunomodulatory activity, relief of the MS as antidiabetic activity, cardioprotective effects, prevention of neuronal damage, anti-aging and anticancer activity as well as therapeutic dosages, results with significant values, side effects, and others reported in the studies found. The results found in the present study may serve as a basis for further studies, as well as for treatments that require dose adjustment concerning ATX.

Materials and Methods

The material analyzed consists of journal articles on the ATX index in PubMed/Medline, seeking this nutraceutical`s relationship with metabolic activity, aging, cancer, anti-inflammatory and antioxidant activity. The data were collected between 2020 and 2021, totaling 119 articles. The article's search was done through the keywords astaxanthin, anti-inflammatory, antioxidant, cancer, aging control, MS and cardioprotective effects.

Results

The results were distributed in Tables 1-4. In Table 1, we observed a predominance of *in vivo* publications with 28.6%, also considering articles that were elaborated in vitro/in vivo (27.7% only in vivo). Next follows the publications of chemical analysis with 26.1%, and *in vitro* experiments with 21.0%. The results of the review studies of ATX appeared with 19.3%. The significant proportion of 28.6% of in vivo found in this present study demonstrates a notable interest of the scientific community in recent years on the properties of ATX, their therapeutic applications, and the control of aging tissue. Observing the studies only in humans, although our data collection in the year 2021 was only until the month of May, of the six studies found, 4 were in the year 2021, which indicates a growing evidence in the interest of ATX in therapeutic application.

The table 2 shows that the proposal for evaluating the article in vivo in different pathologies. In this table, the inclusion criteria were used to evaluate only articles published in vivo, animals and humans. Studies with ATX were more evident in the search for anti-inflammatory and antioxidant results. A proportion of 22.5% of the 40 articles evaluated were in this group, followed by type 2 diabetes control, with 10%, and cognitive function and cardiac function with 7.5% each.

Table 3 shows the cells markers used only in clinical studies *in vivo* (animal and human). In this table, the inclusion criteria were used to evaluate only articles published in vivo, animals and humans. Caspase-3, nuclear factor kappa beta (NF-kβ), total cholesterol (TC), triglycerides (TG), interleukin-6 (IL-6), low density lipoprotein (LDL), high density lipoprotein (HDL), Malondialdehyde (MDA), glutathione peroxidase (GPx), superoxide dismutase (SOD), tumour necrose factor alpha (TNF-α) appear in four or more articles as metabolic markers for therapeutic evaluation criteria with the use of ATX. This represents 6.8% of the 40 articles evaluated in this table.

Table 4 shows the clinical trials found in humans. In this table, the inclusion criteria were used to evaluate only human clinical trials. Six articles were found and mostly in 2021 (66.6%) with a diversification of interests in the use of ATX, among them cognitive function, cardiac function, semen health, behavior, physical performance, and aqueous humor.

Discussion

The results of this present work show us that ATX has a remarkable antioxidant and anti-inflammatory potential for several diseases. As we can see in table 1, there are several articles published in vivo, including six clinical trials in humans, predominating in relation to other articles published in the period 2020, 2021. The sum of the in vivo groups shows that 33.6% (40 articles) of the 119 articles evaluated were done in vivo in general. Just for comparison, the revisions appear much lower with 19.3%. That is, there were 40 articles in total in vivo and only 23 review articles. In vitro publications appear with

21% of a total of 25 articles. This demonstrates that the interest of the scientific community in developing clinical trials wich can lead to future therapies with ATX is already a fact.

Table 1: Publication Types

Year	2020	%	2021	%	Total	%
Review	16	18.6	07	21.2	23	19.3
In vitro	22	25.6	03	9.1	25	21.0
In vitro/vivo	01	1.2	-	-	01	0.9
In vivo	24	27.9	09	27.3	33	27.7
Human	02	2.3	04	12.1	06	5.0
Chemical analysis	21	24.4	10	30.3	31	26.1
Total	86	100	33	100	119	100

Astaxanthin and Cognitive Function

ATX has shown promising results in relation to cognitive function, whether used alone or in conjunction with another nutraceutical. In one of the studies analyzed in this present review, Sekikawa et al. (2020) used ATX with tocotrienols on the cognitive function of healthy Japanese adults with memory decline [22]. In this study, 44 subjects were randomly but equally assigned into two groups, the ATX -tocotrienols group and the placebo group. After 12 weeks of intervention, the group that used ATX and tocotrienols showed a significant improvement in composite memory and verbal memory on “Cognitrax” compared to the placebo group. The results of this study demonstrated that taking the combination of ATX -tocotrienols improved composite memory and verbal memory in Japanese adults who experience memory decline [22].

Likewise, in 2012 Katigari et al. had already shown that the extract of Haematococcus pluvialis rich in ATX significantly improved memory in healthy elderly people [23]. In this study, 96 subjects ingested a capsule containing Haematococcus pluvialis extract rich in ATX or a placebo capsule for 12 weeks. In the method used, somatometry, hematology, urine tests and CogHealth and Groton Maze Learning Test were performed before and after every 4 weeks of administration. The following data were evaluated: changes in cognitive performance and the safety of administering the extract of Haematococcus pluvialis rich in ATX. Results showed that CogHealth battery scores improved in the high-dose group (12 mg ATX /day) after 12 weeks. While Groton Maze Learning Test scores showed earlier improvement in the low dose (6 mg ATX/day) and high dose groups compared to the placebo group [23].

The reasons that ATX has been drawing the attention of the scientific community in relation to brain health is its chemical structure [24]. Its unique chemical structure allows it to cross the blood-brain barrier with great efficiency, quickly interacting with neurons in relation to both anti-inflammatory and antioxidant effects [25]. Because of this, many studies have considered the brain as the most important target organ for ATX. In this way, one of the benefits of ATX in neurons is the control of high production of reactive oxygen species (ROS) due to oxidative stress in this type of tissue [24, 25, 26]. Zhu et al. (2020) showed promising results with the use of

ATX in on cognition function, inflammatory response and oxidative stress in vascular dementia mice [26]. In this study, ATX inhibited interleukin-1β (IL-1β) expression and Malondialdehyde (MDA) content, while promoting interleukin-4 (IL-4) expression and SOD activity in a dose-dependent manner.

In our review we found several expressive results of ATX on SOD activity. This shows us that ATX has the ability to protect mitochondria from the production of superoxide ($O2^{-}$) in neurological diseases related to oxidative stress. Controlling SOD is one of the main pathways in the preservation of neurons. ATX also can control the expression of the B-cell lymphoma-2 (Bcl2) and protects neurons from apoptosis mechanisms [27]. In the study by Wu et al. (2013), the authors demonstrated that after administration of D-galactose (D-G) in rats to induce brain aging, the expression of the anti-apoptotic protein Bcl-2 decreased, while the pro-apoptotic protein Bcl-2-associated X protein (BAX) was increased in brains in comparison with the control group. However, treatment with ATX revealed the opposite. It positively regulated the expression of Bcl-2 and reduced the expression of BAX in the brain of aged rats, compared to the D-G group. This result demonstrated that the ratio of Bcl-2 to BAX is correlated with apoptosis in cells. The proportion of Bcl-2/BAX in the D-G group was reduced by approximately 60% compared to the control group ($p < 0.05$), while administration of ATX increased approximately 1-fold the proportion of Bcl - 2 / BAX compared to the D-G group [27].

As the brain is the organ most susceptible to aging, it can provide a sensitive environment for the development of neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease [28]. Therefore, exploring methods to slow or reverse brain aging with nutraceuticals such as ATX may be a promising avenue for the near future, as this carotenoid exhibits potent antioxidant, anti-inflammatory and neuroprotective effects.

Table 2: Proposal for evaluating the article *in vivo* with astaxanthin alone or with another nutraceutical in different pathologies

Year	2020		%		2021		%		Total	%
Proposal	H	A	H	A	H	A	H	A	H	A
Cognitive function	1	2	3.6	7.1	1	1	8.3	8.3	5	7.5
Muscle activity	-	-	-	-	1	1	8.3	8.3	2.5	2.5
Cardiac function	1	3	3.6	10.7	-	-	-	-	2.5	7.5
Liver function	-	1	-	3.6	-	1	-	8.3	-	5.0
Cancer	-	1	-	3.6	-	-	-	-	-	2.5
Antiinflam./anti-oxid. Act.	-	6	-	21.4	-	3	-	25	-	22.5
Glaucoma	-	2	-	7.1	-	-	-	-	-	5
Diabetes/pancreatite	-	4	-	14.3	-	-	-	-	-	10
Other		7	-	25	2	2	16.75	16.75	5	22.5
Total = 40 articles	**2**	**26**	**7.2**	**92.8**	**4**	**8**	**33.35**	**66.65**	**15**	**85**

Astaxanthin as Antioxidant and Anti-inflammatory

Oxidative stress is one of the determining factors in cell aging and the generation of diseases [29]. The formation of ROS in the mitochondrial matrix damages structures not only of DNA, RNA and proteins, but mainly of mitochondrial DNA (mtDNA), causing serious consequences to the metabolism as a whole [30]. In this way, in table 3, 161 cell metabolism markers were found, which were used in 40 in vivo studies, including clinical trials in humans of the 119 articles evaluated in this present meta-analysis. Some markers have appeared in several studies with remarkable significance with the administration of ATX.

The ability of ATX to decrease inflammatory processes as well as reduce free radicals has been extensively reported in scientific literature. In our present review we found several studies in animals and humans where ATX had remarkable results in enzymes activity such as SOD [31, 32, 33], GPx [27, 34], transcription factor signaling proteins such as AMPK [33], control of inflammatory processes by inhibiting NF-kβ [35], TNF-α [36, 37] among others. These markers appeared four or more times in published in vivo works found in this review. We could observe that ATX can control the mechanisms of apoptosis in some diseases, such as dementia [33], non-alcoholic hepatic steatosis [37], type 2 diabetes [34], glaucoma [38, 39], myocardial mitochondrial dysfunction [40], myocardial injury [41, 42] traumatic brain injury [33], muscular dystrophy [43], pancreatitis [44] and among many others. These mechanisms in most cases are associated with the control of NF-kB, TNF-a and consequently caspase-3.

The effect of ATX in the pathologies mentioned above can be attributed to its ability to maintain preserved mitochondrial functions. ATX has been shown to be extremely effective in restoring the activity of GPx enzymes, as well as SOD in removing ROS and preserve mitochondrial structure [27, 34]. Some studies in the past have linked the effects of ROS production to the shortening of telomeres [30]. Passos et al. (2007) stated that mitochondrial superoxide production increases with replicative age in human fibroblasts. In other words, mitochondrial dysfunction is accompanied by impaired calcium homeostasis and other indicators of a retrograde response in senescent cells, with replicative senescence of human fibroblasts being delayed by moderate mitochondrial uncoupling of the uncoupling protein 2 (UCP2). This process reduces the generation of mitochondrial superoxide, reduces telomere shortening [30]. This shows that the mitochondrial production of ROS acts as one of the causes of replicative senescence [45]. Passos et al. also reported that by classifying early senescent cells from cultures of young proliferating fibroblasts, they showed that these cells have higher ROS levels, dysfunctional mitochondria, and shorter telomeres. Still in this study, the authors stated that mitochondrial ROS is the major determinant of telomere-dependent senescence at the single-cell level that is responsible for cell-to-cell variation in replicative life expectancy [30], and ATX can restore mitochondrial metabolism in control ROS and decrease oxidative stress [27, 32].

In fact, AXT has shown to interact remarkably in the biochemical markers evaluated in this meta-analysis, being a promising supplement both in the control of ROS by increasing the activity of SOD and GPx, and in the control of inflammatory processes as seen in the inhibition of NF-kB and TNF-a. The results found in this meta-analysis make ATX a promising supplement in the control of diseases associated with oxidative stress and in inflammatory processes.

Astaxanthin and Metabolic Syndrome

Diseases related to MS directly reflect two crucial processes, oxidative stress [46] and inflammation [47]. By observing the effects of AXT in the control of many inflammatory processes, its therapeutic potential involving MS were observed in this review. The study by Kato et al. (2020) showed that the administration of 12mg of ATX decreased the oxidative stress in the

serum marker Diacron reactive oxygen metabolite (dROM) in heart failure patients, although the urinary marker 8-hydroxy-2′-deoxyguanosine (8-OHdG) did not present significant changes [48]. On the other hand, the randomized study by Park et al. (2010) demonstrated that the administration of 8mg of ATX for 8 weeks in human health female dramatically reduced DNA damage biomarker 8-OHdG as well as the blood inflammatory marker C-reactive protein (CRP) [49].

Table 3: Cells markers used in clinical studies in vivo (animal and human) with astaxanthin

Markers Found:

In only one study	Total	%	In two studies	Total	%	In three studies	Total	%	In four or more studies	Total	%	Grand total	%
HDAC9, p21, MEK, MMP-1, Cyclins D, D1 and E, MUC1, MUC2, 16RNA, P65, INF-γ, IL-10, ocludin, claudin-1 and ZO-1, 4-HNE, GSK-3β, NOX2, NLRP3, NLRP3, Insulin, FOXO, Col5A1, Nqo1, Notch2, IP-1, TP, GCC, TMT, HSP70, HSTF-1, JNK-1, HMGB-1, Neurophil, TLR2, TLR4, MVC, MP, mTOR, P70S6K, TPP, CRC, NQQ1, HDAC4, SRBP1, MPO, Caspase-8, XOD, ADA, GLUT-9, URAT-1, OAT-1, OAT-3, ABCG-2, CKMT, IL-10, VEGF, Urea, IB, VLDL, STAT-3, SCARB-1, VLDLR, S-DNA, FSH, MMP-S, GLUT4, HOMA-IR, IL-1α, MCP-1, HSP90, HSP27, HSP72, HSF-1, GR, GST, Albumin, TNF-β, ITGL-1, Ca, Collagen exp., IL-2, PGSK-3β, Bcl-xL, PGC-1α, TFAM, mtDNA, Lipase, PPAR-α, HBP, HMGCR, FXR, RXR, BAD, IL-15, , OHdG, CRP, BNP, LVEF, HbA1c, Amilase, CK, UA, Cholinesterase, DB, LAP, LD, Hemogram, RVSP, LVESVI, TIMP-1, ERK, ATM, CGC.	115	71.5	ATM, ERK, BAX, TLR4, MyD88, PI3K, GSH, MAPK, IL-4, Nrf-2, COX-2, BUN, Creatinine, PPAR-γ, TGF-B1, CAT, IGA, TB, α-SMA, TP, GGT, ALP, SC, BAD	24	14.9	Caspase-9, Bcl-2, Akt, HO-1, iNOS, Glucose, IGG, IGM, ALT, AST, MMP9.	11	6.8	Caspase-3, NF-kβ, TC, TG, IL-6, LDL, HDL, MDA, GPx, SOD, TNF-α.	11	6.8	**161**	**100**

Total = 40 articles

Total cell markers = 161

LAP - Leukocyte Alkaline Phosphatase; **LD** - Lactic Dehydrogenase; **IB** - Indirect Bilirubin; **DB** - Direct Bilirubin; **UA** - Uric Acid; **RVSP** - Right Ventricular Systolic Pressure; **LVESVI** - Left Ventricular end-Systolic Volume Index; **LVEF** - Left Ventricular Ejection Fraction; **BNP** - B-type natriuretic peptide; **SC** - Serum creatinine; **8-OHdG** - 8-hydroxy-2′-deoxyguanosine; **HSP70** - heat stress protein 70; **BAD** - Bcl-2-Associated Death Protein; **FXR** - Farnesoid X Receptor; **RXR** - Retinoic X Receptor; **HBP** - Lipoprotein Binding Protein; **HMGCR** - 3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase**; LDL** - Low Density Lipoprotein; **VLD**L - Very Low Density Lipoprotein; **VLDLR** - Very Low-Density Lipoprotein Receptor; **HDL** - High Density Lipoprotein; **TC** - Total Cholesterol; **TG** - Triglycerides; **ALP** - Alkaline Phosphatase; **ALT** - Alanine Aminotransferase; **AST** - Aspartate Aminotransferase; **GGT** - Gama-Glutamyl Transferase; **TB** - Total Bilirubin; **TP -** Total Protein; **IP** - Inorganic Phosphate; **BUN** - Blood Urea Nitrogen; **ITGBL1** - Integrin Subunit Beta Like 1; **TIMP-1** - Tissue Inhibitors of Metalloproteinase-1; **α-SMA** - Alpha-Smooth Muscle Actin; **TGF-β** - Transforming growth Factor- Beta 1; **HSP72** - Heat Shock Protein 72; **HSP27** - Heat Shock Protein 27; **HSP90** - Heat Shock Protein 90; **HSF1** - Heat Shock Factor 1; **MMP** - Mitochondrial Membrane Potential of Spermatozoa; **SCARB1** - Scavenger Receptor Class B Type 1; **TLR4** - Toll-like Receptor 4; **GPx** - Glutathione Peroxidase; **GR** - Glutathione Reductase; **GST** - Glutathione S-Transferases; **AMPK** - Adenosine 5′-Monophosphate–Activated Protein Kinase; **Ckmt** - Creatine Kinase Mitochondrial; **XOD** - Xanthine Oxidase; **ADA** - Adenosine Deaminase; **iNOS** - Nitric Oxide Synthase Isoform; **ERK** - Extracellular Signal-Regulated Kinases; **ATM** - ATM Serine/Threonine Kinase; **MDA** - Malondialdehyde; GSH - Glutathione; **SOD** - Superoxide Dismutase; **MPO** - Myeloperoxidase; **BNP** - B-Type Natriuretic Peptide; **NQO1** - NAD(P)H quinone dehydrogenase 1; **Nrf2** - Nuclear Factor Erythroid 2-Related Factor 2; **HO-1** - Heme Oxygenase 1; **CRC** - Ca2+ Retention Capacity; **TPP** - Tetraphenylphosphonium ion; **MP** - Metabolic Performance; **MVC** - Maximal Voluntary Contraction; **SREBP1** - Sterol Regulatory Element-Binding Protein 1; **JNK1** - c-Jun N-Terminal Kinase 1; **HSTF1** - Heat Shock Transcription Factor 1; **HSP70** - Heat Shock Proteins 70; **HDAC9** - Histone Deacetylase 9; **PI3K** - Phosphoinositide 3-Kinase; **GSK3β** - Glycogen Synthase Kinase 3-Beta; **ATM** - Ataxia-Telangiectasia Mutated Kinase; **MEK** - Mitogen-Activated Protein Kinase; **ERK** - Extracellular Signal-Regulated Kinases; **MMP-1** - Matrix Metallopeptidase-1; **MMP9** - Matrix Metallopeptidase 9; **ZO-1** - Zonula Occludens-1; **p21** - Cyclin-Dependent Kinase Inhibitor; **Nf-kB** - Nuclear Factor Kappa-Beta; **MUC1** - Mucina-1; **MUC2** - Mucina-2; **4-HNE** - 4-Hydroxynonenal; **CGC** - Ganglion Cell Complex; **TMT** - Trial Making Test; **Bcl-2** - B-Cell Lymphoma 2; **Bcl-Xl** - B-Cell Lymphoma-Extra Large; **BAX** - Bcl-2-Associated X Protein; **16rRNA** - 16S

Ribosomal RNA; **P65** - Transcription Factor p65; **MyD88** - Myeloid Differentiation Factor 88; **INF-γ** - Interferon Gamma; **Akt** - Protein Kinase B; **NOX2** - NADPH Oxidase 2; **NLRP3** - NLR Family Pyrin Domain Containing 3; **MAPK** - Mitogen-Activated Protein Kinase; **FOXO** - Forkhead Box O; **TNF-α** - Tumour Necrosis Factor Alpha; **COL5A1** - Collagen Type V Alpha 1 Chain; **NQO1** - Quinone Oxidoreductase; **NOTCH2** - Neurogenic Locus Notch Homolog Protein 2; **IL-1β** - Interleukin-1β; **IL-1α** - Interleukin-1α; **IL-2** - Interleukin-2; **IL-4** - Interleukin-4; **IL-6** - Interleukin-6; **IL-10** - Interleukin 10; **GCC** - Ganglion Cell Complex; **HMGB1** - High Mobility Group Box 1; **TLR2** - Toll Like Receptor 2; **TLR4** - Toll Like Receptor 4; **mTOR** - Mammalian Target of Rapamycin; **p70S6K** - 70-kDa Ribosomal Protein S6 Kinase; **COX2** - Cyclooxygenase-2; **GLUT9** - Glucose Transporter 9; **GLUT4** - Glucose Transporter 4; **URAT1** - Urate Transporter 1; **OAT1** - Organic Anion Transporter 1; **OAT3** - Organic Anion Transporter 3; **ABCG2** - ATP Binding Cassette; Subfamily G Member 2; **PPAR-γ** - Peroxisome Proliferator-Activated Receptor Gamma; **PPAR-α** - Peroxisome Proliferator-Activated Receptor Alpha; **VEGF** - Vascular Endothelial Growth Factor; **STAT3** - Signal Transducer And Activator of Transcription 3; **S-DNA** - Spermatozoid DNA; **FHS** - Follicle-Stimulating Hormone; **HOMA-IR** - Homeostatic Model Assessment for Insulin Resistance; **MCP1** - Monocyte Chemoattractant Protein-1; **CAT** = Catalase; **IgG** - Immunoglobulin G; **IgA** = Immunoglobulin A; **IgM** - Immunoglobulin M; **PGSK-3β** - Glycogen Synthase Kinase 3-beta; **PGC-1α** - Peroxisome Proliferator-Activated Receptor-Gamma Coactivator 1-Alpha; **TFAM** - Transcription Factor A Mitochondrial; **mtDNA** - Mitochodnrial DNA; **CRP** - C-Reactive Protein; **HbA1C** - Hemoglobin A1c; **CK** = Creatine Kinase; **UA** - Uric Acid.

In 2018, Mashhadi et al. published a study with ATX as a potential treatment for MS. This study was an 8-week randomized placebo-controlled trial to investigate the potential effects of ATX supplementation on adiponectin concentration, lipid peroxidation, glycemic control, insulin sensitivity, and anthropometric indices in participants with type 2 diabetes mellitus. The authors found a significant increase in the hormone adiponectin, and consequently an improvement in insulin sensitivity. Likewise, TG and lipopretin VLDL rates dropped significantly, as well as an increase in lipoprotein HDL was also observed [50]. The findings of this study revealed that the dual beneficial effects of ATX are clinically valuable [50]. According to Mashhadi et al., the results offer a new complementary treatment with potential impact on diabetic complications without adverse effects.

What we could observe in the investigated literature of ATX in MS is that, from a molecular point of view, ATX has a direct interaction on the peroxisome proliferator-activated receptor alpha (PPAR-α) [51]. When activated, this receptor is not only one of the most important transcription factors in mitochondrial biogenesis, but also plays a critical role in the modulation of energy balance and regulation of hepatic lipids through mitochondrial metabolism itself [52]. In 2012, Jia et al. had already demonstrated the therapeutic properties of ATX in fatty liver due to its PPAR-α agonist properties [53]. ATX has demonstrated PPAR-α agonist activity similar to fibrates, which are known to decrease the risk of cardiovascular events in patients with MS [54].

PPAR-α, after forming a heterodimer with the retinoid X receptor (RXR), stimulates the transcription of genes that promote mitochondrial fatty acid oxidation and ketogenesis, including carnitine palmitoyl transferases (CPT) 1a and 2, acyl-coenzyme A oxidase and UCP2 [54]. In fact, in 2008, Aoi et al. demonstrated that astaxanthin increased CPT-1 activity in rats when compared to the placebo group, significantly improving fatty acid oxidation when animals were exposed to treadmill exercise [55]. It was also observed that the favorable impact of PPAR-α agonists on human HDL levels was reflected in the induction of apolipoproteins AI and A-II [56]. PPAR-α also stimulated liver production of fibroblast growth factor 21 (FGF21), a hormone that acts on adipocytes to increase their production of adiponectin; the latter, in turn, acts on hepatocytes and other tissues to stimulate AMPK activity [57].

In 2019, Choi mentioned in his work the therapeutic implications of ATX in the modulation of PPARs receptors. In this work, the author states that ATX increases the action of PPAR-α and suppresses that of PPAR-β / δ and PPAR-γ. However, it has been confirmed that ATX exhibits opposite effects on PPARs depending on the cell context [58]. In other words, ATX acts as an adaptogen, having a function depending on how the cell metabolism behaves. To understand this mechanism, the anti-inflammatory effects of ATX are mediated by PPAR-γ activation, not PPAR-α. Thus, PPAR-γ induces the expression of pro-inflammatory cytokines in macrophages and gastric epithelial cells, resulting in inhibition of cell growth and

apoptosis in tumor cells [58]. However, this does not occur in normal cells. Simultaneous and differential regulation of PPAR-α and PPAR-γ activity by ATX demonstrated a hepatoprotective effect, maintaining liver lipid homeostasis and preventing related liver problems [59].

Another notable result of AXT in MS can be seen in the work by Nishida et al. (2020). In this study, the authors observed an up-regulation of the Pgc-1α gene and other genes that control mitochondrial biogenesis in muscle tissue from mice treated with ATX [21]. AXT has been shown to induce phosphorylation of the AMPK protein, inducing the expression of Pgc-1 and consequently greater activity of Sirtuin 1 (Sirt1) by increasing NAD+, which is mediated by the enzyme Nampt, and finally activating PGC-1α, the main signaling protein of mitochondrial transcription factors. Thus, ATX stimulated the expression of Nampt and Sirt1 genes, positively influencing NAD+ metabolism [21].

Table 4: Astaxanthin in human clinical trial

Author	Journal	Tittle	Type	Year
Kato et al.	Nutrients. 2020 Jun; 12(6): 1896	Effects of 3-Month Astaxanthin Supplementation on Cardiac Function in Heart Failure Patients with Left Ventricular Systolic Dysfunction	A Pilot Study	2020
Sekikawa et al.	J Clin Biochem Nutr. 2020 Nov; 67(3): 307–316	Cognitive Function Improvement with Astaxanthin and Tocotrienol Intake	A randomized, double-blind placebo-controlled study	2020
Kumalic et al.	Radiol Oncol. 2021 Mar;55(1): 97–105	Effect of the Oral Intake of Astaxanthin on Semen Parameters in Patients with Oligo-astheno-teratozoospermia	A Randomized Double-blind Placebo-controlled Trial	2021
Crosta et al.	Nutrients. 2021 Jan; 13(1): 56.	Improvement of Executive Function after Short-Term Administration of an Antioxidants Mix Containing Bacopa, Lycopene, Astaxanthin and Vitamin B12	The BLAtwelve Study	2021
Kawamura et al.	Antioxidants (Basel) 2021 Jan; 10(1): 113	Astaxanthin-, β-Carotene-, and Resveratrol-Rich Foods Support Resistance Training-Induced Adaptation	A randomized controlled trial	2021
Hashimoto et al.	J Clin Biochem Nutr. 2021 Mar; 68(2): 169–172	The effect of aging on the antioxidative activity of astaxanthin in human aqueous humor	A randomized controlled trial	2021

Conclusion

In our present study, we could observe that the interest of the scientific community has been growing in relation to the benefits of ATX. The results presented in the articles evaluated in this meta-analysis showed us that AXT is already a reality as an option in treatments for various diseases, including glaucoma, heart and vascular injury, type 2 diabetes and fatty liver. Because ATX easily passes through the blood-brain barrier, many neurological treatments have also chosen to use this nutraceutical with promising results. As most pathologies are related to oxidative stress and high inflammatory process, AXT proved to be effective in controlling this metabolic imbalance both by acting as a PPAR-α agonist as well as in phosphorylation of AMPK for its activity, two of the most important cell markers in the control of mitochondrial biogenesis in human metabolism.

AXT has also shown positive results in athletes subjected to physical stress induced by intense training. We observed that AXT has an interesting potential when administered with other nutraceuticals that aid in antioxidative processes. Some works with tocotrienols, resveratrol and beta-carotene were evaluated in our review with great success when combined with AXT. Therefore, we can suggest that ATX may not only be a promising nutraceutical as an ally to alternative treatments of the pathologies mentioned above, where the side effects of drugs do not allow continuity in certain specific cases, but also as a powerful prophylactic in elderly individuals in prevention of diseases associated with aging.

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