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Astaxanthin at the Crossroads of Type 2 Diabetes and Chronic Diseases: From Mechanistic Insights to Clinical Prospects

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ABSTRACT:

Chronic hyperglycemia, oxidative stress, and systemic inflammation are all linked to type 2 diabetes mellitus (T2DM), a complex metabolic disease that can lead to debilitating microvascular and macrovascular complications such as retinopathy, neuropathy, nephropathy, and cardiovascular disease. Current therapeutic strategies mainly focus on glycaemic control, yet they fall short in addressing the oxidative and inflammatory milieu that drives long-term complications. Astaxanthin (ASX), a naturally occurring xanthophyll carotenoid, has emerged as a potent nutraceutical with broad-spectrum antioxidant, anti-inflammatory, and cytoprotective properties. Its unique molecular structure enables efficient scavenging of reactive oxygen species (ROS) and stabilization of cellular membranes, while also modulating redox-sensitive signalling pathways such as NF-κB, MAPK, and Nrf2-ARE. Preclinical and clinical studies highlight ASX's ability to mitigate oxidative damage, preserve mitochondrial function, reduce fibrosis, and improve vascular health, positioning it as a promising adjunct in the management of diabetic complications. Beyond diabetes, ASX demonstrates therapeutic potential in chronic disorders including cardiovascular disease, chronic kidney disease, and neurodegenerative conditions. However, despite encouraging experimental evidence, clinical validation remains limited. Future research should focus on establishing optimal dosing, long-term safety, and therapeutic synergies with conventional treatments. Collectively, this review integrates current mechanistic insights and translational findings, underscoring ASX's potential as a novel nutraceutical intervention at the crossroads of T2DM and chronic disorders.

1. Introduction

Antioxidants are a diverse class of bioactive molecules that play a pivotal role in protecting biological systems from oxidative damage. Even at relatively low concentrations, these compounds can effectively neutralize reactive oxygen species (ROS) and other free radicals, which are inherently unstable and highly reactive. Uncontrolled ROS activity can result in lipid peroxidation, protein oxidation, and nucleic acid damage, ultimately compromising cellular integrity and function. By interrupting or delaying oxidative chain reactions, antioxidants preserve the structural and functional stability of biomolecules. Their protective actions extend across cellular membranes and into subcellular compartments, where they counteract oxidative insults and contribute to the maintenance of tissue integrity and systemic homeostasis.[1]

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Oxidative stress arises when the production of reactive oxygen species (ROS) exceeds the capacity of the body's antioxidant defenses. While ROS serve important roles in normal metabolism and cellular signalling, their excess can damage lipids, proteins, and DNA, compromising cellular integrity. This imbalance has emerged as a common thread in the pathogenesis of chronic and degenerative diseases, including cancer, cardiovascular disease, and neurodegenerative disorders. It also contributes to skin aging by accelerating both structural deterioration and visible signs of decline. Thus, oxidative stress is increasingly recognized as a central mechanism linking metabolic imbalance to disease and aging.[2]

Within the broader spectrum of natural antioxidants, carotenoids constitute a particularly potent group of lipid-soluble pigments. These compounds are synthesized by photosynthetic organisms, including higher plants, algae, and certain microorganisms, and are characterized by their conjugated double-bond systems that confer both vibrant coloration and antioxidant efficacy. Carotenoids counter oxidative stress through a variety of mechanisms: they are capable of quenching singlet oxygen, scavenging a wide range of free radicals, and disrupting the propagation of lipid peroxidation reactions, particularly within the lipid bilayers of cellular membranes where oxidative damage can be particularly deleterious. [3,4]

Among the most studied dietary carotenoids are β-carotene, lycopene, lutein, and zeaxanthin. These compounds have been extensively evaluated for their antioxidant potential and for their capacity to support and reinforce endogenous cellular defense mechanisms.[5] Beyond their antioxidant properties, carotenoids are increasingly appreciated for their broader contributions to human health. Epidemiological data and clinical investigations have linked carotenoid-rich diets with reduced incidence of chronic disease, enhanced immune function, and improved cognitive and visual health outcomes.[6]

Of relevance to dermatological and cosmetic sciences is the ability of carotenoids to accumulate in the skin. This dermal deposition allows them to contribute to photoprotection by absorbing ultraviolet (UV) radiation and reducing photooxidative stress, which plays a significant role in extrinsic aging. Moreover, carotenoids have been associated with improvements in skin hydration, elasticity, and overall tone, underscoring their dual function in maintaining both the physiological health and cosmetic appearance of the skin.[7]

Owing to these multifaceted bioactivities, carotenoids are emerging as promising agents for therapeutic and cosmeceutical development. Their potential for disease prevention and health maintenance, particularly in the context of oxidative stress-related conditions, has made them the subject of growing scientific inquiry. Nonetheless, further investigation remains essential to optimize their clinical application. Specifically, a more nuanced understanding of their molecular mechanisms, pharmacokinetics, and bioavailability is needed to fully leverage their therapeutic promise.[8]

Astaxanthin: from nature to nutrition

Astaxanthin (ASX), a lipid-soluble xanthophyll carotenoid, stands out within the carotenoid family for its remarkable biological potency. Beyond its striking red-orange pigmentation, ASX is renowned for its broad spectrum of biological activities, earning recognition as one of the most powerful natural antioxidants discovered to date. These unique properties have positioned ASX at the centre of scientific interest, particularly for its potential roles in combating oxidative stress and promoting health.[9]

As a staple of the Okinawan diet, a way of living often linked to exceptional longevity and reduced illness, ASX has drawn attention for its potential to promote healthy aging. Emerging evidence suggests that ASX plays a role in modulating critical regulatory pathways, such as the insulin/IGF-1 axis, and activating transcription factors like Forkhead box O3 (FOXO3), which are associated with longevity, stress resistance, and metabolic homeostasis.[9]

A growing body of experimental and clinical research has begun to elucidate the metabolic benefits of ASX supplementation. Data indicate that ASX improves insulin sensitivity and facilitates better glycemic control by lowering fasting blood glucose levels. Concurrently, it has been shown to positively influence lipid metabolism. Studies report reductions in total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglycerides, along with occasional increases in high-density lipoprotein cholesterol (HDL-C). These

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effects appear to be intimately linked to ASX's capacity to counter oxidative and inflammatory stressors, which are known contributors to metabolic dysfunction.[10]

At the mechanistic level, ASX's therapeutic actions are multifactorial. Its polyene structure allows it to efficiently scavenge a variety of ROS, thereby mitigating the oxidative stress that underlies insulin resistance, β-cell dysfunction, and tissue degeneration. Beyond its antioxidative role, ASX exerts potent anti-inflammatory effects. It downregulates the expression of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β), while also inhibiting key enzymes involved in inflammation—namely cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS). This is achieved, in part, through suppression of the nuclear factor-kappa B (NF-κB) signalling pathway, a major transcriptional regulator of inflammation and immune responses.[11]

ASX also supports cellular survival and integrity through modulation of apoptotic signalling. It has been shown to reduce the expression of pro-apoptotic proteins such as Bax and simultaneously enhance the expression of anti-apoptotic proteins like Bcl-2. This shift in the Bax/Bcl-2 ratio promotes cell survival and has particular significance in preserving the functionality of insulin-producing pancreatic β-cells, as well as protecting renal tissues from hyperglycemia-induced damage.[11]

History of astaxanthin (ASX): a novel regulator

Astaxanthin (ASX), a xanthophyll carotenoid of marine origin, was first identified in 1938 by Kuhn and Soerensen during their chemical investigation of crustaceans. At the time, its significance was primarily associated with pigmentation; it was widely utilized in aquaculture to enhance the reddish coloration of commercially valuable species such as salmon and trout. This visual enhancement not only improved market appeal but also became standard practice in the seafood industry.[12]

Despite its early discovery, ASX's biological potential remained largely unexplored for several decades. It was not until the latter part of the 20th century that its pharmacological properties began attracting serious scientific interest. Investigations revealed that ASX possessed remarkably potent antioxidant capabilities substantially more effective than well-known antioxidants like β-carotene and vitamin E. This discovery repositioned ASX from a pigment additive to a promising bioactive compound, prompting exploration of its broader biological relevance.[12]

Subsequent research has shown that ASX is far more than a coloring agent; it is now recognized as a dynamic regulator of biological systems. It influences critical pathways involved in redox balance, mitochondrial bioenergetics, lipid metabolism, cellular signalling, and gene expression, earning it a reputation as a "novel regulator" with potential applications in managing chronic diseases and promoting healthy aging.

Distribution and molecular characteristics of astaxanthin

Chemically, ASX is a C_{40} tetraterpene with the molecular formula $C_{40}H_{52}O_4$. It belongs to the xanthophyll subclass of carotenoids distinguished by their oxygenated functional groups. Structurally, the molecule features two terminal β-ionone rings linked by a polyene chain composed of 13 conjugated double bonds. This conjugation contributes to its intense reddish hue and exceptional ability to quench singlet oxygen and scavenge a range of reactive oxygen species (ROS).[13]

ASX differs from other carotenoids like lutein, zeaxanthin, and β-cryptoxanthin because each terminal ring has both hydroxyl (-OH) and keto (=O) functional groups. These moieties give the molecule amphipathic properties, which enable it to interact with environments that are both lipophilic and hydrophilic. Therefore, ASX may efficiently embed its hydrophobic core into the lipid phase and anchor its polar ends at membrane interfaces to insert itself into phospholipid bilayers.[14]

This structural orientation permits ASX to protect biological membranes from oxidative insult on both sides of the bilayer. Its location and structure enable it to neutralize free radicals in aqueous cytosolic and extracellular environments, as well as within the hydrophobic lipid milieu of membranes.[15] The molecule's extensive polyene system is central to its efficacy in singlet oxygen quenching and free radical scavenging. Comparative analyses underscore ASX's superior antioxidative capacity. In vitro studies have demonstrated that it is approximately 10 times more

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potent than β-carotene and up to 100 times more effective than α-tocopherol in neutralizing oxidative stress.[16]

ASX is biosynthesized by diverse organisms, including microalgae, yeast, and fungi, and is further accumulated by marine animals such as krill, crab, shrimp, and salmon through their diets. Among all known sources, the freshwater microalga Haematococcus pluvialis remains the richest reservoir, capable of concentrating ASX to levels exceeding 4% of its dry weight under stress conditions such as intense light, nutrient deprivation, or increased salinity. In these extreme environments, ASX functions as a potent protective molecule, safeguarding cellular structures against oxidative damage.[17]

Owing to these distinctive physicochemical and biological properties, ASX has emerged as a highly promising candidate for nutraceuticals, pharmaceuticals, and cosmeceuticals, especially in conditions where oxidative stress, inflammation, or metabolic dysregulation play a central pathogenic role.

metabolic signalling, apoptosis regulation, and gene expression related to longevity. The following sections detail the mechanisms underlying these effects: **(Fig:1)**

1. Antioxidant defense

ASX functions as a highly effective antioxidant due to its extended system of conjugated double bonds. This enables it to directly scavenge ROS including hydroxyl, peroxyl, and superoxide radicals and to quench singlet oxygen. By integrating into cell membranes, ASX shields structural components such as lipids, proteins, and DNA from oxidative degradation. This is especially relevant in oxidative stress-associated diseases such as insulin resistance, neurodegenerative disorders, and cardiovascular conditions.[12]

2. Anti-inflammatory action

Inflammation is a common pathological feature of many chronic diseases, and ASX exhibits substantial anti-inflammatory activity.

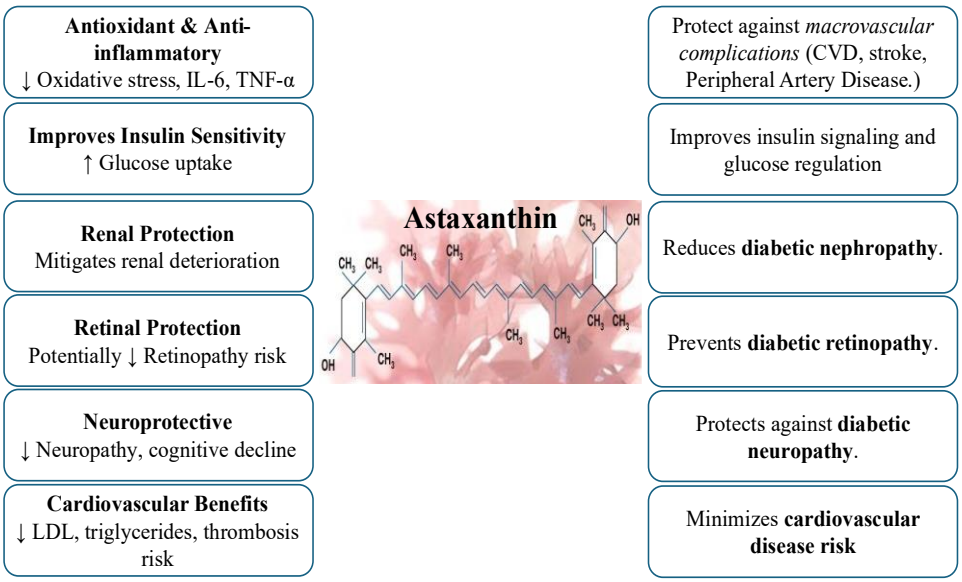

Fig:1- Pleiotropic protective effects of astaxanthin in diabetes and its complications

Mechanism of action of astaxanthin

Astaxanthin's wide-ranging biological actions are mediated through its interaction with several interconnected molecular pathways. While it is best known for its antioxidative efficacy, its influence extends into inflammation modulation, mitochondrial protection,

It achieves this by inhibiting the nuclear factor-kappa B (NF-κB) pathway, a master regulator of pro-inflammatory gene transcription. ASX downregulates the expression of cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β). Additionally, it suppresses key inflammatory enzymes, including cyclooxygenase-2

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(COX-2) and inducible nitric oxide synthase (iNOS), thus attenuating the chronic inflammatory state that underlies metabolic and cardiovascular disorders.[18]

3. Activation of redox-sensitive pathways

Beyond direct radical scavenging, ASX enhances endogenous antioxidant defense mechanisms by activating the Nrf2 (nuclear factor erythroid 2–related factor 2) signalling pathway. Nrf2 regulates the expression of a suite of cytoprotective enzymes such as superoxide dismutase (SOD), glutathione peroxidase, and heme oxygenase-1. Activation of this transcriptional network enhances cellular resilience to oxidative insults and improves redox homeostasis.[19]

4. Mitochondrial stabilization

Mitochondria are both generators and primary targets of ROS. ASX contributes to mitochondrial integrity by reducing mitochondrial ROS production and preserving mitochondrial membrane potential. It stabilizes mitochondrial membranes, prevents the release of pro-apoptotic factors like cytochrome c, and supports efficient ATP generation. These effects collectively enhance energy homeostasis and protect against cell death in metabolically active tissues.[20]

5. Regulation of apoptosis

Oxidative damage often precipitates programmed cell death, or apoptosis. ASX modulates this process by decreasing the expression of Bax, a pro-apoptotic protein, and enhancing Bcl-2, an anti-apoptotic marker. The resulting decrease in the Bax/Bcl-2 ratio favors cellular survival. This protective modulation is particularly important in maintaining the function of pancreatic β-cells, renal epithelial cells, and neurons under oxidative or hyperglycemic stress.[21]

6. Metabolic modulation

ASX favourably influences metabolic pathways, particularly those involved in glucose homeostasis and lipid regulation. It activates key signalling cascades such as phosphoinositide 3-kinase (PI3K)/Akt and AMP-activated protein kinase (AMPK), which are essential for insulin sensitivity, glucose uptake, lipid oxidation, and energy balance. Through these effects, ASX supports glycemic control and mitigates the development of insulin resistance and metabolic syndrome.[22]

7. Enhancing longevity by modulating gene expression

A unique aspect of ASX's action lies in its ability to modulate transcription factors associated with cellular longevity. Notably, ASX has been shown to upregulate Forkhead box O3 (FOXO3), a key regulator of genes involved in stress resistance, autophagy, DNA repair, and longevity. By promoting the nuclear retention and activation of FOXO3, ASX enhances cellular capacity to respond to metabolic and oxidative stress, suggesting potential applications in age-associated decline and lifespan extension.[9]

Astaxanthin (ASX) as a scavenger of reactive oxygen species (ROS)

Extensive laboratory research highlights astaxanthin (ASX) as a remarkably potent scavenger of reactive oxygen species (ROS), including singlet oxygen, hydroxyl radicals, and organic free radicals. ASX demonstrates about 10 times greater efficacy than other carotenoids like lutein, tunaxanthin, canthaxanthin, zeaxanthin, and β-carotene, and up to 100 times stronger antioxidant activity than vitamin E (α-tocopherol).[23] A key feature of ASX is its ability to prevent lipid peroxidation, a damaging process where free radicals attack lipids in cell membranes with 100 to 500 times greater effectiveness than vitamin E.[12] Notably, ASX maintains its antioxidant function even in aqueous environments, efficiently neutralizing hydroxyl radicals, among the most aggressive ROS.[24]

These powerful antioxidant properties translate into significant physiological benefits. Clinical studies show ASX supplementation markedly reduces oxidation of low-density lipoprotein (LDL) cholesterol, a primary factor in atherosclerosis development, while enhancing high-density lipoprotein (HDL) function, which supports cholesterol removal and protects vascular walls.[25] By preventing LDL oxidation and improving HDL's protective roles, ASX reduces lipid peroxidation–related vascular damage, lowering risks of plaque buildup and cardiovascular events. Additionally, ASX exerts anti-inflammatory effects by downregulating pro-inflammatory cytokines like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which further supports vascular health and endothelial function.[18]

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The role of ASX in mitochondrial function

Mitochondria, the cellular power plants producing ATP, are highly vulnerable to oxidative and nitrosative stress caused by reactive oxygen species (ROS) and reactive nitrogen species (RNS). This stress damages mitochondrial DNA, lipids, and proteins, impairing energy metabolism and contributing to chronic diseases such as neurodegeneration, diabetes, and cardiovascular disorders.[26]

ASX's unique molecular structure with conjugated double bonds and polar end groups makes it amphipathic, allowing it to embed within mitochondrial and cellular membranes. This positioning enables ASX to protect mitochondria from both ROS and RNS, serving as a dual shield against oxidative and nitrosative damage.[27]

Excess reactive nitrogen species, including peroxynitrite, cause nitrosative stress that harms mitochondrial components, disrupting energy production. ASX effectively neutralizes these damaging species, reducing lipid peroxidation, preserving mitochondrial membrane integrity, and safeguarding mitochondrial DNA.[28]

Beyond direct scavenging, ASX boosts endogenous antioxidant defenses by upregulating enzymes like superoxide dismutase (SOD) and catalase, which detoxify ROS and maintain redox balance. This enzymatic support stabilizes mitochondrial membrane potential and sustains efficient oxidative phosphorylation, crucial for optimal ATP synthesis. These mitochondrial benefits are particularly vital in energy-demanding tissues such as cardiac and vascular muscle, where ASX improves mitochondrial efficiency, reduces fatigue, enhances vascular function, and promotes cardiovascular health.[29]

ASX as a novel regulator in disease models: diabetes mellitus and mitochondrial dysfunction

Diabetes mellitus, characterized by persistent hyperglycemia due to defective insulin secretion or action, poses a growing global health threat. The World Health Organization (WHO) projects that by 2030, approximately 578 million people will have diabetes, rising to 1.3 billion by 2050 largely driven by urbanization, sedentary lifestyles, poor diet, and aging populations.[30] The WHO's Global Diabetes Compact seeks to improve equitable access to prevention, diagnosis, treatment, and care, emphasizing early detection and lifestyle interventions. **(Fig: 2)**

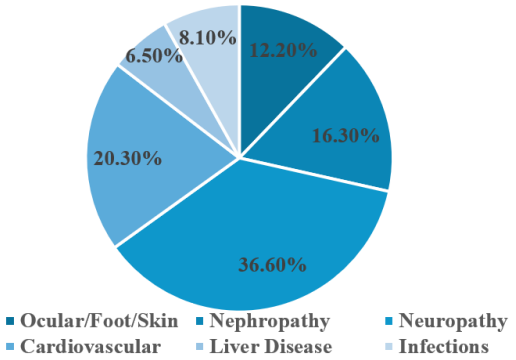

Fig. 2. Prevalence of T2DM complications

Mitochondrial dysfunction is a core factor in type 2 diabetes mellitus (T2DM). Impaired oxidative phosphorylation and ATP production, accumulation of lipid intermediates, and inflammation disrupt metabolic tissues including liver, skeletal muscle, adipose tissue, and pancreatic β-cells promoting insulin resistance and β-cell failure.[31]

At the center of mitochondrial energy metabolism, the electron transport chain (ETC) facilitates NADH reoxidation. ETC impairment leads to NADH accumulation, disturbing the NADH/NAD^+ balance, impairing metabolic enzymes, and weakening antioxidant defenses. This results in elevated mitochondrial ROS production, aggravating oxidative stress, apoptosis, and insulin resistance.[32]

Astaxanthin as a mitochondria-targeted antioxidant

ASX's distinctive molecular traits allow it to accumulate within mitochondria, where it reduces oxidative stress, stabilizes mitochondrial membrane potential, and enhances oxygen consumption rates, thereby preserving mitochondrial function.[33] It preferentially localizes in muscle cell mitochondria, preventing muscle wasting linked to mitochondrial dysfunction. Its therapeutic potential extends beyond diabetes to neurodegenerative, liver, kidney, gastrointestinal, and ocular diseases. ASX's dual antioxidant and anti-inflammatory actions make it a promising candidate for mitochondrial dysfunction–related disorders.[33]

Mitochondrial dysfunction and insulin resistance

Evidence from animal and human studies connects mitochondrial dysfunction to insulin resistance. In obese

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and elderly individuals, fat accumulation in skeletal muscle and liver correlates with reduced mitochondrial size, number, and function. Declined oxidative phosphorylation and impaired fatty acid oxidation lead to the buildup of lipid intermediates, such as diacylglycerol, that disrupt insulin signalling pathways, worsening insulin resistance and advancing T2DM progression.[34]

Targeting mitochondrial health: therapeutic implications

Restoring and protecting mitochondrial function is a promising therapeutic avenue for diabetes and its complications. Interventions like ASX supplementation that enhance mitochondrial biogenesis, and oxidative capacity may sustain energy production, reduce oxidative damage, and preserve cellular integrity.

In diabetic neuropathy, mitochondrial protection supports blood-nerve barrier integrity, potentially slowing or reversing nerve damage. Diabetic retinopathy, a leading cause of blindness in young adults, results from chronic hyperglycemia damaging retinal microvasculature and mitochondria, including mitochondrial DNA damage and decreased expression of essential proteins. This compromises the electron transport chain, fuelling a cycle of oxidative damage. Although retinal cells attempt repair by increasing repair enzyme gene expression, mitochondrial accumulation of these enzymes remains insufficient. Understanding this mechanism underscores the potential of therapies like ASX supplementation to maintain retinal mitochondrial health, potentially inhibiting the progression of diabetic retinopathy and preserving vision.[35] **(Fig : 3)**

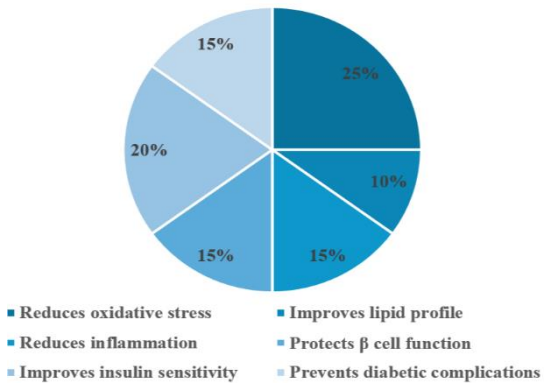

Fig. 3. Effect of astaxanthin on diabetic complications

Nexus between astaxanthin (ASX) and diabetic retinopathy (DR)

Diabetic retinopathy (DR) is one of the most prevalent and debilitating microvascular complications of diabetes mellitus (DM), affecting more than 80% of individuals diagnosed with DM, and is recognized as the most common cause of acquired blindness among adults.[36] DR is a slow-progressing chronic disease whose prevalence escalates with the duration of diabetes. The condition is characterized by a progressive increase in vascular permeability, retinal ischemia, retinal edema, and abnormal neovascularization, ultimately leading to visual impairment and, in severe cases, irreversible legal blindness.[37]

The absence of timely diagnosis or appropriate therapeutic intervention often results in significant vision loss, ranging from partial blindness to complete visual incapacity, along with other ophthalmic complications that can cause irreversible damage to the visual system.[38]

Pathologically, DR is classified into two main types: Proliferative Diabetic Retinopathy (PDR) and Non-Proliferative Diabetic Retinopathy (NPDR). PDR represents the advanced stage of the disease, marked by the abnormal proliferation of fibrous connective tissue and new blood vessels on the retinal surface, which increases the risk of severe vision loss and retinal detachment. In contrast, NPDR is the earlier stage, characterized by microvascular abnormalities in the retinal capillaries, including microaneurysms, capillary obstruction, edema, and retinal haemorrhages, which result in blurred central vision.[39]

Chronic hyperglycemia plays a pivotal role in DR pathogenesis by inducing oxidative stress in retinal tissues and capillary endothelial cells, thereby causing microvascular damage and retinal dysfunction. Hyperglycemia stimulates the overexpression of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX), leading to excessive cytosolic reactive oxygen species (ROS) production and mitochondrial membrane damage. In diabetic retinal tissues, hyperglycemia-induced oxidative stress also activates the polyol pathway and enhances the formation of advanced glycation end products (AGEs). These changes are accompanied by the activation of protein kinase C

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(PKC), which further amplifies oxidative damage through increased ROS production.[40]

Oxidative stress in the hyperglycemic retina additionally promotes activation of the transcription factor nuclear factor-κB (NF-κB). NF-κB regulates the expression of various pro-inflammatory cytokines, chemokines, and adhesion molecules that contribute to retinal cell injury, vascular inflammation, and the progression of DR. Furthermore, the hyperglycemic milieu impairs the retina's antioxidant defense systems by altering DNA- and histone-modifying enzymes and suppressing the activities of critical antioxidant enzymes such as superoxide dismutase (SOD), manganese superoxide dismutase (MnSOD), catalase, glutathione reductase, glutathione peroxidase, and glutathione (GSH) itself.[41]

Astaxanthin (ASX) has been shown to exert protective effects against the pathogenesis of DR primarily through its potent antioxidant and anti-inflammatory mechanisms. ASX inhibits NF-κB activation by reducing oxidative stress and disrupting the upstream signalling pathways responsible for NF-κB translocation into the nucleus. By preventing NF-κB activation, ASX downregulates the transcription of pro-inflammatory genes, thereby reducing levels of inflammatory cytokines, adhesion molecules, and vascular endothelial growth factor (VEGF). This ultimately mitigates inflammatory damage, prevents excessive vascular leakage, and protects retinal microvascular integrity in the diabetic retina.[42] **(Fig : 4)**

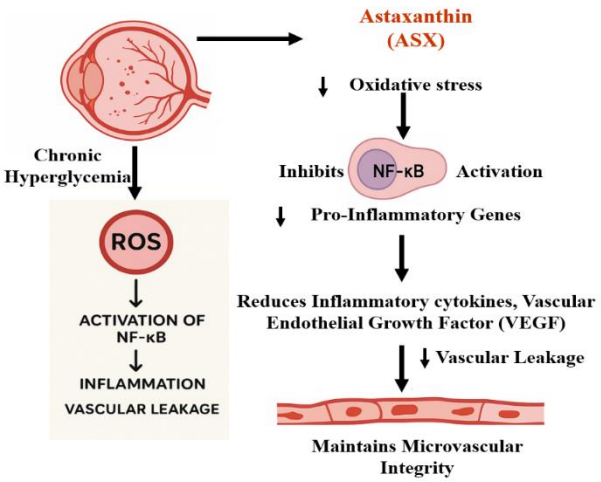

Fig : 4 - Antioxidant and anti-inflammatory role of astaxanthin in retinal protection

Renoprotective effects of astaxanthin in diabetic nephropathy

Diabetic nephropathy (DN) represents one of the most serious microvascular complications of diabetes, characterised by progressive renal dysfunction resulting from structural and functional damage to the glomeruli and tubules. This pathological process is significantly accelerated by persistent oxidative stress and chronic low-grade inflammation, both of which are heightened in the presence of sustained hyperglycaemia. These interlinked mechanisms not only drive the loss of kidney function but also amplify downstream complications. Given its multifaceted biochemical actions, ASX offers a compelling therapeutic prospect in the context of diabetic kidney injury by directly targeting these fundamental drivers of disease progression.

Hyperglycaemia-induced overproduction of reactive oxygen species (ROS) triggers a cascade of deleterious events within the kidney, including increased inflammatory cell infiltration, elevated cytokine release, and upregulated nuclear factor kappa B (NF-κB) activity. Renal inflammation is now widely recognised as a central contributor to the initiation and progression of nephropathy. In parallel, ROS overproduction activates transforming growth factor-beta (TGF-β) signalling, stimulating excessive extracellular matrix (ECM) deposition—an early step towards renal fibrosis and eventual structural deterioration of the kidney.[35]

Animal studies consistently demonstrate the nephroprotective effects of ASX, suggesting its potential utility as an adjunctive treatment for DN. In diabetic models, persistent exposure to elevated glucose levels results in the accumulation of advanced glycation end-products (AGEs), which bind to cellular RAGE receptors and activate pro-inflammatory signalling through the NF-κB pathway and protein kinase C (PKC) cascades. This interaction intensifies oxidative stress and inflammation, further fuelling renal injury.[43]

ASX exerts its protective influence through multiple molecular avenues. It enhances the activity of endogenous antioxidant enzymes such as superoxide dismutase (SOD) and catalase, while reducing the concentration of serum malondialdehyde (MDA)—a lipid peroxidation marker. Notably, ASX shows selective mitochondrial accumulation in human mesangial cells, where it attenuates high-glucose-induced ROS

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generation. This mitochondrial localisation allows ASX to efficiently inhibit transcription factor activation, leading to the downregulation of cyclooxygenase-2 (COX-2), monocyte chemoattractant protein-1 (MCP-1), and TGF-β1. Furthermore, ASX modulates the overproduction of fibronectin (FN) and TGF-β1, thereby limiting ECM accumulation and slowing fibrosis. Emerging evidence highlights the pivotal role of the redox-sensitive transcription factor Nrf2-ARE in these effects—acting as a master regulator of antioxidant defence and cytoprotective responses in diabetic kidneys.[44]

Animal studies reinforce these mechanistic insights. In diabetic models, ASX treatment preserved renal architecture, reduced collagen deposition, and improved glomerular filtration rates, as indicated by decreases in serum creatinine and blood urea nitrogen (BUN). Such improvements were accompanied by mitigation of oxidative injury and inflammation, reflecting ASX's combined antioxidant and anti-inflammatory capacity.[45]

Beyond these systemic effects, ASX's mitochondrial localisation provides an added layer of protection in DN, where mitochondrial dysfunction is a central contributor to renal cell apoptosis and functional decline. By maintaining mitochondrial integrity and supporting ATP production, ASX helps sustain the viability of both tubular and glomerular cells under hyperglycaemic stress. This mechanism has been highlighted not only in diabetic kidney disease but also in other nephrotoxic conditions, such as lithium-induced injury, underscoring its broad renoprotective potential.[27]

Taken together, ASX appears capable of counteracting the triad of oxidative stress, inflammation, and fibrosis that underpins DN progression. By scavenging ROS, suppressing NF-κB activation, inhibiting pro-inflammatory cytokines, and protecting mitochondrial function, ASX may help preserve renal structure and function in diabetes. While preclinical evidence is compelling, well-designed clinical trials are needed to confirm these benefits, determine optimal dosing, and assess long-term safety in human diabetic populations.

Astaxanthin as a potential therapeutic in diabetic neuropathy

Diabetic neuropathy (DNp) is among the most prevalent and disabling complications of diabetes, substantially affecting quality of life. The burden is especially pronounced in countries such as India, where the overall diabetes prevalence is high, and healthcare access, awareness, lifestyle patterns, and socioeconomic conditions contribute to striking variability in DNp prevalence rates ranging from 9.6% to 78% in different population groups.[46]

The condition is clinically characterised by pain, tingling, numbness, and weakness, most often in the extremities. On a pathophysiological level, it arises from a convergence of oxidative stress, chronic inflammation, and mitochondrial dysfunction—mechanisms that progressively damage peripheral nerves and, in some cases, central nervous system pathways.[47] Current therapeutic strategies are largely palliative, focusing on pain relief, with limited efficacy in halting or reversing the underlying neurodegenerative processes. This gap underscores the urgent need for disease-modifying interventions.

ASX demonstrates robust neuroprotective potential in DNp, primarily by addressing the oxidative and inflammatory components of neuronal injury. As a potent free radical scavenger, ASX mitigates ROS-mediated cellular damage, protecting neurons from oxidative stress—a core driver of nerve degeneration. Its anti-inflammatory properties are mediated through the suppression of NF-κB activation, which in turn downregulates the production of tumour necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β), thereby curbing inflammation-driven neuronal injury.[13]

Beyond antioxidant and anti-inflammatory roles, ASX contributes to mitochondrial preservation, a crucial factor in neuronal health. Mitochondrial dysfunction in DNp leads to impaired ATP synthesis and heightened oxidative stress. ASX has been shown to enhance mitochondrial respiratory chain activity and energy production, thereby supporting neuronal metabolism and resilience.

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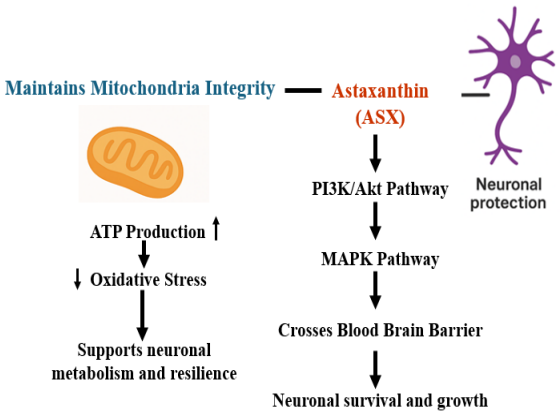

Fig :5 - Neuroprotective mechanisms of astaxanthin

ASX's influence extends to key intracellular survival pathways. By modulating PI3K/Akt signalling, ASX promotes neuronal survival and growth, while potential interactions with the MAPK pathway suggest a role in stress adaptation and apoptosis regulation.[48] An additional pharmacokinetic advantage is its ability to cross the blood–brain barrier, enabling ASX to act not only on peripheral nerves but also on central nervous system structures, broadening its neuroprotective scope to encompass both diabetic neuropathy and other neurodegenerative disorders with similar pathogenic hallmarks. **(Fig: 5)**

Astaxanthin as a cardioprotective agent

Cardiovascular disease (CVD) remains a major cause of morbidity and mortality worldwide, with oxidative stress and chronic inflammation serving as pivotal contributors to its pathogenesis. Increasing evidence supports the therapeutic potential of Astaxanthin (ASX) as a cardioprotective agent, owing to its potent antioxidant, anti-inflammatory, antihypertensive, and lipid-regulating properties.[49]

ASX exerts cardiovascular protection through multiple interrelated mechanisms. A fundamental pathogenic step in CVD development is the oxidative modification of low-density lipoprotein (LDL) cholesterol, which precipitates endothelial dysfunction and accelerates atherosclerotic plaque formation.[50] Compared with other antioxidants, such as vitamin E and β-carotene, ASX exhibits superior efficacy in preventing LDL oxidation. By safeguarding lipoproteins and vascular endothelial cells from oxidative insult, ASX maintains vascular integrity and slows the progression of atherosclerosis.[51]

In addition to its antioxidative effects, ASX modulates key inflammatory pathways implicated in cardiovascular dysfunction. It downregulates pro-inflammatory mediators such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), thereby alleviating vascular inflammation and enhancing endothelial responsiveness.[52]ASX further attenuates inflammatory signalling by inhibiting nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) pathways, contributing to the suppression of atherogenesis.[53]

Clinical studies reinforce the cardioprotective effects of ASX, demonstrating its capacity to improve lipid metabolism by lowering triglyceride concentrations and elevating high-density lipoprotein (HDL) cholesterol levels. Furthermore, ASX supplementation has been shown to enhance vascular blood flow, reduce arterial stiffness, and aid in blood pressure regulation, factors that are crucial for the prevention of hypertension and other vascular pathologies.[51]

At the myocardial level, ASX supports cardiac health by protecting mitochondrial structure and function. Its lipophilic nature allows it to localize within mitochondria, shielding them from oxidative damage, sustaining energy production, and preserving the viability of cardiomyocytes—cells particularly susceptible to oxidative injury.[54] ASX also boosts nitric oxide (NO) bioavailability and upregulates endogenous antioxidant enzymes, further improving endothelial performance.

From a metabolic standpoint, ASX reduces LDL cholesterol and triglyceride levels, raises HDL cholesterol, limits visceral adiposity, and contributes to glucose homeostasis, thereby lowering overall cardiovascular risk.[27] It has also been associated with improved blood rheology, reduced arterial wall thickness, and decreased levels of fibrinogen and L-selectin. In patients with heart failure, ASX may enhance cardiac contractility, increase left ventricular ejection fraction (LVEF), and improve exercise tolerance.

Preclinical studies have demonstrated ASX's ability to protect myocardial tissue from ischemia/reperfusion injury, attenuate foam cell cholesterol accumulation, and

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limit atherosclerotic plaque development. Human clinical trials corroborate these findings, reporting reductions in oxidative stress biomarkers, improvements in hemodynamic parameters, and enhanced cardiac performance. Importantly, ASX has shown a strong safety profile, with no major adverse effects documented.[55]

Conclusion and future perspectives

Astaxanthin (ASX) stands out as a powerful natural compound with the ability to combat oxidative stress and inflammation, two core drivers of diabetes-related complications. In diabetic neuropathy, nephropathy, and retinopathy, high glucose levels over time overwhelm the body's antioxidant defences, damaging mitochondria, fuelling chronic inflammation, and ultimately impairing tissue function.

ASX offers a multifaceted defence. It neutralises harmful reactive oxygen species, preserves the energy-producing capacity of mitochondria, and keeps inflammatory pathways in check. By doing so, it helps protect delicate structures such as peripheral nerves, kidney filtration units, and the retinal microvasculature, all of which are particularly vulnerable in diabetes.

Beyond diabetes, ASX's broad protective potential extends to conditions like neurodegenerative disorders, cardiovascular disease, liver injury, and autoimmune illnesses. Its low toxicity and ability to influence multiple disease pathways make it an attractive candidate for long-term use.

The path ahead lies in translating this promise into evidence-based clinical practice. Well-designed, large-scale human trials are essential to establish optimal dosing, long-term safety, and the best ways to integrate ASX with existing therapies. If these studies confirm its potential, ASX may become an important component of personalized strategies to slow, prevent, or even repair oxidative stress–induced damage, paving the way for healthier aging and improved disease management.

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