International Journal for Vitamin and Nutrition Research

*Int. J. Vitam. Nutr. Res.* **2026**; 96(3): 50989
https://doi.org/10.31083/IJVNR50989

*Review*

# Emerging Biomarkers in Breast Cancer: Prevention and Therapy With Vitamin A and Carotenoids

Sapna[1], Suresh Babu Kondaveeti[2], Hitendra Singh Batra[2], Chirag G. Makvana[3], Kumud Madan[4], Subbulakshmi Ganesan[5], Lalita Chopra[6], Subhashree Ray[7], Shivam Pandey[8,9], Vivek Kumar Garg[10,*], Ranjay Kumar Choudhary[11,*], Harpal Singh Buttar[12]

[1]Saraswati College of Pharmacy, SGC Group, 140413 Mohali, Punjab, India
[2]Department of Biochemistry, Symbiosis Medical College for Women, Symbiosis International (Deemed University), 412115 Pune, Maharashtra, India
[3]Department of Chemistry, Faculty of Science, Gokul Global University, 384151 Sidhpur, Gujarat, India
[4]School of Pharmacy, Sharda University, Knowledge Park III, 201310 Greater Noida, Uttar Pradesh, India
[5]Department of Chemistry and Biochemistry, School of Sciences, JAIN (Deemed to be University), 560069 Bangalore, Karnataka, India
[6]Department of Chemistry, University Institute of Sciences, Chandigarh University, 140413 Mohali, Punjab, India
[7]Department of Biochemistry, IMS and SUM Hospital, Siksha 'O' Anusandhan (Deemed to be University), 751003 Bhubaneswar, Odisha, India
[8]Centre for Research Impact & Outcome, Chitkara College of Pharmacy, Chitkara University, 140401 Rajpura, Punjab, India
[9]Lloyd Institute of Engineering & Technology, Knowledge Park II, 201306 Greater Noida, Uttar Pradesh, India
[10]Department of Medical Lab Sciences, University School of Allied Health Sciences, Rayat-Bahra University, 140104 Mohali, Punjab, India
[11]Department of Medical Laboratory Sciences, College of Applied and Health Sciences, A'Sharqiyah University, 400 Ibra, North Al Sharqiyah Governorate, Sultanate of Oman
[12]Department of Pathology and Laboratory Medicine, Faculty of Medicine, University of Ottawa, Ottawa, ON K1N 6N5, Canada
*Correspondence: vivekgargpgi@gmail.com (Vivek Kumar Garg); r.choudharymt@gmail.com (Ranjay Kumar Choudhary)
Academic Editor: Torsten Bohn
Submitted: 13 February 2026 Revised: 14 May 2026 Accepted: 26 May 2026 Published: 25 June 2026

**Abstract**

Fat-soluble vitamins, such as vitamin A (VitA) and carotenoids, are crucial micronutrients with strong antioxidant and anti-inflammatory properties that mitigate oxidative stress and inhibit cancer progression. Breast cancer (BC) is the most prevalent cancer among women, and the anti-tumor properties of VitA and carotenoids are gaining increasing attention, particularly because BC risk is strongly influenced by lifestyle factors, including unhealthy dietary habits. Although VitA and carotenoids may exert preventive effects on BC development and progression, there is limited evidence supporting the practical application of these micronutrients in the detection and prevention of BC. Mechanistically, high doses of carotenoids reduce reactive oxygen species (ROS) directly or indirectly through the modulation of transcription factors such as NF-κB and Nrf2–, and through activation of nuclear hormone receptor pathways, including like retinoic acid receptors (RAR), retinoid X receptors (RXR), and peroxisome proliferator-activated receptors (PPARs). These pathways modulate retinoic acid receptor signaling and inhibit oncogenic pathways including PI3K/Akt/mTOR, thereby enhancing apoptosis and suppressing proliferation in BC cells. This review examines the roles of VitA and carotenoids in BC, as well as methods for assessing VitA status. Additionally, this review highlights how genetic variation in the metabolism of VitAand carotenoids is associated with cancer and other pathological conditions. We also discuss how VitA and carotenoids are linked to BC development, how these micronutrients influence cancer-related mechanisms, and how recent advances in clinical research have made VitA and carotenoids promising candidates for BC treatment. This review also underscores the preventive and therapeutic potential of VitA and carotenoids in the initiation and progression of BC.

**Keywords:** breast cancer; nuclear receptors; multidrug resistance; vitamin A; carotenoids; retinol binding protein; reactive oxygen species

## 1. Introduction

The fat-soluble vitamin A (VitA) is found in both plant and animal sources and is distinguished by its unsaturated isoprenoid ring structure. All forms of VitA share a common framework and perform similar physiological roles in living organisms. These substances are also classified as retinoids, comprising both synthetic and natural compounds that share a four-isoprenoid unit arrangement. At first glance, several synthetic derivatives of VitA do not resemble the natural isoprenoids, but their chemical structures conceal the fundamental VitA backbone, and their interactions with retinoid receptors are comparable to those of other retinoids [1]. In contrast to water-soluble vitamins, all of these substances are lipid-soluble and readily accumulate in the body, particularly in hepatocytes and fatty tissue. One benefit of this is that there are no clinical symptoms linked to temporary restriction of VitA intake; nonetheless, buildup and subsequent toxicity may occur [1].

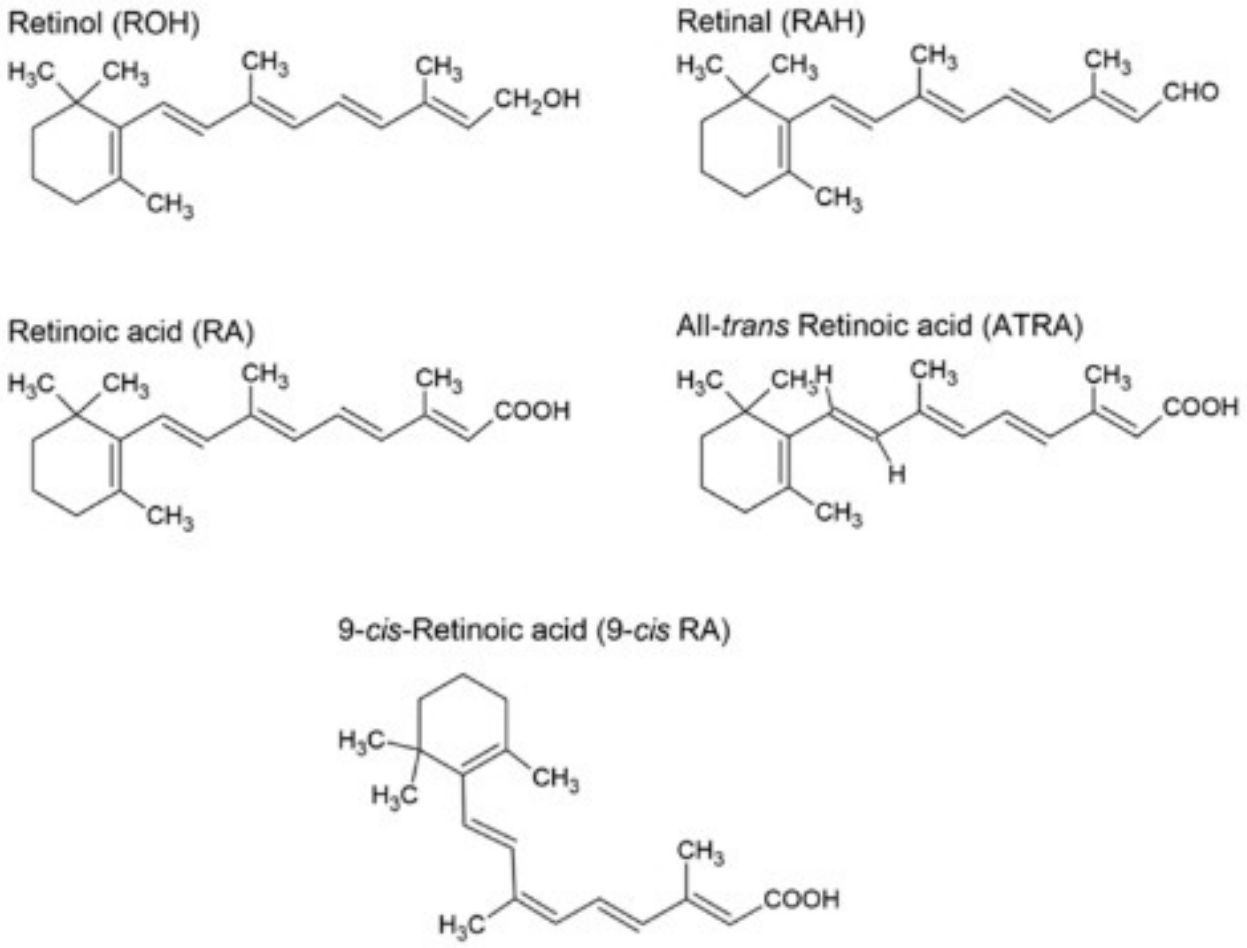


**Fig. 1. Structures of retinol, retinal, retinoic acid, all-trans retinoic acid, and 9-cis retinoic acid [2].**

VitA occurs in vegetables and fruits as provitamin A, namely carotenoids, and in animal sources as retinol. Although retinol is the most common retinoid and is commonly referred to as VitA, its oxidized derivatives, 11-cis-retinal and all-trans-retinoic acid (ATRA), are the primary biologically active molecules. Various forms of VitA (Fig. 1, Ref. [2]) and carotenoids (Fig. 2, Ref. [2]) are illustrated [2].

Many fruits and vegetables contain carotenoids, organic pigments that range in colour from yellow to orange. In addition to their association with VitA, these compounds are renowned for their antioxidant properties. The most widely recognized carotenoids include lutein, lycopene, cryptoxanthin, β-carotene, and α-carotene. Unlike diterpenoid retinoids of animal origin, carotenoids are tetraterpenoids, though they may ultimately be converted to retinol. However, not all carotenoids can be converted by the body into VitA. Provitamin A is found only in molecules that include at least one unsubstituted β-ionone chain [3].

It is widely acknowledged that VitA is linked to several advantageous biological functions, including oxidative stress regulation, immune system enhancement, and protection against photoenergy [4]. Additionally, carotenoids and VitA control the development, differentiation, and proliferation of malignant cells [5]. VitA and carotenoids have been shown to have protective benefits against a variety of chronic conditions and carcinogenesis through a variety of epidemiological examinations [6].

According to the World Health Organization (WHO), cancer is the second leading cause of death globally. In 2020, 2.26 million new cases of breast cancer (BC) were identified worldwide, making it the most common type of malignant tumour among women [7]. BC development and recurrence are characterized by genetic mutations and molecular complexity including impairment of key signaling pathways that involve mitogen-activated protein kinase (MAPK) signaling system and the PI3K/AKT signaling pathway which control cell growth, apoptosis and survival rate [8]. In addition, the growing data shows that the role of oxidative stress and reactive oxygen species (ROS) play an important role in tumor formation and progression by causing genomic abnormalities and DNA destruction [9].

External variables such as nutrient intake and dietary habits have become increasingly important as overall BC mortality rates have risen. Vitamins are vital micronutrients that function as antioxidants and participate in a vari-

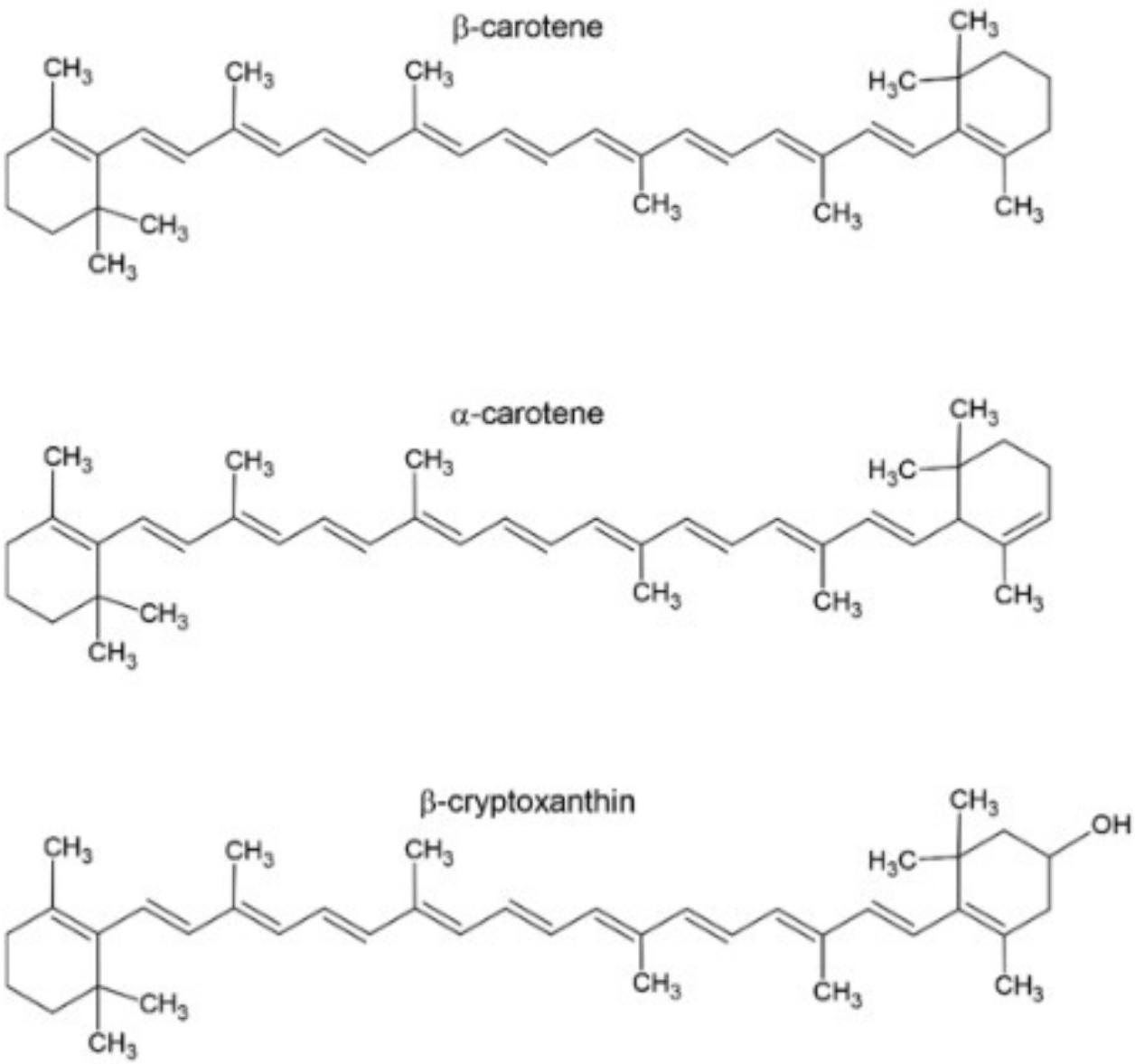


**Fig. 2. Structures of β-carotene, α-carotene, and β-cryptoxanthin [2].**

ety of physiological processes. VitA and carotenoids have recently gained attention as anti-cancer agents that can prevent a variety of tumours. Low dietary and serum concentrations of carotenoids and VitA have been proposed as warning signs for BC in a number of epidemiological investigations [10]. However, due to conflicting findings in the pertinent literature, the precise physiological functions and processes of VitA and carotenoids in the progression of BC remain unclear. VitA status can be readily affected by bioavailability, metabolism, and absorption. The inconsistent results may have been due to a combination of biological variability and the various tests used in VitA evaluation [11]. This article presents epidemiological data supporting the association of VitA and carotenoids to BC risk, their effects on cancer mechanisms, and new developments in clinical practice of VitA or carotenoids as a possible treatment against BC. This study also explores the preventative and therapeutic functions of VitA and carotenoids in BC growth and development.

## 2. VitA and Carotenoids: Composition, Origins, Absorption, and Bioavailability

The 20-carbon molecule referred to as VitA, or retinoids, consists of a conjugated polyene sequence (–C=C–) and an isoprenoid side chain, with a distinct functional group at C15 and a methyl-substituted cyclohexenyl ring (β-ionone ring). When two 20-carbon molecules with β-ionone rings and a polyisoprenoid linkage are joined tail-to-tail, they form carotenoids, known as tetraterpenoids. The chemical structure of carotenoids allows them to be separated into two groups: xanthophylls (like zeaxanthin and lutein), which include oxygen in the form of hy-

droxyl groups, and carotenes (like lycopene, β-carotene, β-cryptoxanthin, and α-carotene), which are hydrocarbons. The intestinal metabolism of dietary β-carotene produces retinal, a natural precursor of retinoids. Retinal is also produced from other retinoids, including retinyl ester and retinol, which are normally derived from the diet. Although retinoid absorption potencies and form-to-form conversions vary, these compounds share comparable molecular structures and activities. These isomers are recognized as transcriptionally functional and include all-trans-retinoic acid (ATRA), 9-cis-retinoic acid, and 13-cis-retinoic acid [12].

VitA must be obtained through diet, either as provitamin A carotenoids or preformed VitA, because the human body cannot synthesize it. The human body absorbs provitamin A carotenoids at a rate of 3% or less, in contrast to the 70–90% absorption of preformed dietary VitA. Additionally, these compounds must undergo multiple steps in human intestinal cells to be converted into a form of VitA [13]. Provitamin A carotenoids are a more volatile and less dependable source of VitA than preformed VitA from animal sources because the transformation of carotenoids into VitA is influenced by a number of circumstances. The nutritional grid, food preparation techniques, and the type and amount of fat in meals all affect the conversion rate. Carotenoids are more bioavailable from foods with a simpler matrix, such as red palm oil and fruits. It has been documented that thermal processing enhances β-carotene's uptake and bioavailability. As a result, cooked vegetables are more bioavailable than raw ones. Furthermore, dietary fats, such as olive oil, facilitate the incorporation of carotenoids into micelles and are necessary for their intestinal absorption. However, dietary fibre or deficiencies in certain micronutrients, such as iron and zinc, limit the conversion of carotenoids to VitA [14]. Only about 40 carotenoids have been identified in plant foods, and about 20 carotenoids have been detected in human blood and tissues, despite the existence of another 600 natural structural variants of carotenoids. β-carotene has the maximum provitamin A action among the six carotenoids that comprise over 95% of the total carotenoids in blood: lutein, β-carotene, β-cryptoxanthin, α-carotene, lycopene and zeaxanthin. Other carotenoids have approximately half the VitA activity of β-carotene. The limited bioavailability of carotenoids in humans is evidenced by the predicted 7–65% absorption of β-carotene from most plant-based foods [15].

There are strict limits on the quantities of carotenoids in food, on their absorption, on their origins, and on the enzymes that convert them to VitA. The carotenoid content of fruits and vegetables is often strongly influenced by ripeness, cultivation practices, location, and the drying process prior to preservation. The scavenger receptor B1 (SRB1) or the cluster of differentiation 36 (CD36) transporter passively diffuses carotenoids into the enterocyte. Through a sequence of processes, carotenoids are converted into retinyl esters or β-carotene, which are then released into the bloodstream in micelle form. These updates by Carazo et al. [1] provide a detailed description of the intestinal absorption and metabolic processes of VitA and carotenoids, as well as the functions of the proteins involved.

## 3. Role of Oxidative Stress in Producing ROS, and Involvement of ROS in Breast Cancer

In order precisely regulate its concentration, oxygen is a crucial component of all biological processes. ROS, a broad class of oxygen-derived tiny molecules that comprise radicals and nonradical species, are created when a variety of endogenous and foreign chemicals undergo enzymatic and nonenzymatic processes. However, certain amounts of the oxygen are partially reduced to ROS [16]. Oxidative stress is the term for the imbalance between free radicals and the antioxidant response caused by the large number of ROS produced under extreme stress circumstances [17]. Excessive levels of oxidative stress may lead to cell death by activating proapoptotic pathways, autophagy, necrosis, and pro-angiogenic events, all of which are thought to be important factors in the progression of a variety of disorders, that include malignancies, cardiovascular, and neurological disorders [17].

Higher ROS concentrations are typically observed in tumour cells, which further exacerbate a malignant phenotype by promoting angiogenesis, metastasis, inflammation, and prolonged cell proliferation. As a result, it is regarded as a known cause of cancer [18]. ROS and oxidative stress contribute to DNA destruction in BC, which can trigger or prevent oncogene activation, transcription, signalling pathways, replication mistakes, and genomic instability. The progression of BC is supported by multiple risk factors linked to ROS induction, including aging, hormonal changes, genetic makeup, and estrogens. These factors cause chromosomal abnormalities and DNA damage [19]. A promising approach to treating BC is to focus on Reduction-Oxidation (REDOX) regulation, given that controlling oxidative stress and maintaining REDOX homeostasis are crucial totumour growth and the response to anticancer treatments [20]. The proper REDOX balance, which shields tumour cells from stress and guarantees their survival in solid tumours, depends on glutathione (GSH) metabolism. Consequently, GSH inhibitors and anticancer treatments may synergize to eradicate cancer cells [21]. Because ROS production is a consequence of mitochondrial dysfunction, changes in mitochondrial biology also play a significant role in cellular metabolism and homeostasis and are associated with the progression of BC [22]. Accordingly, differential ROS generation and reliance by tumour cells are driven by variations in mitochondrial activity among BC subtypes. For example, triple-negative breast cancer (TNBC) has been shown to have elevated ROS levels due to mitochondria; hence, targeting ROS and/or mitochondria may be a plausible treatment option in this subtype of BC [23].

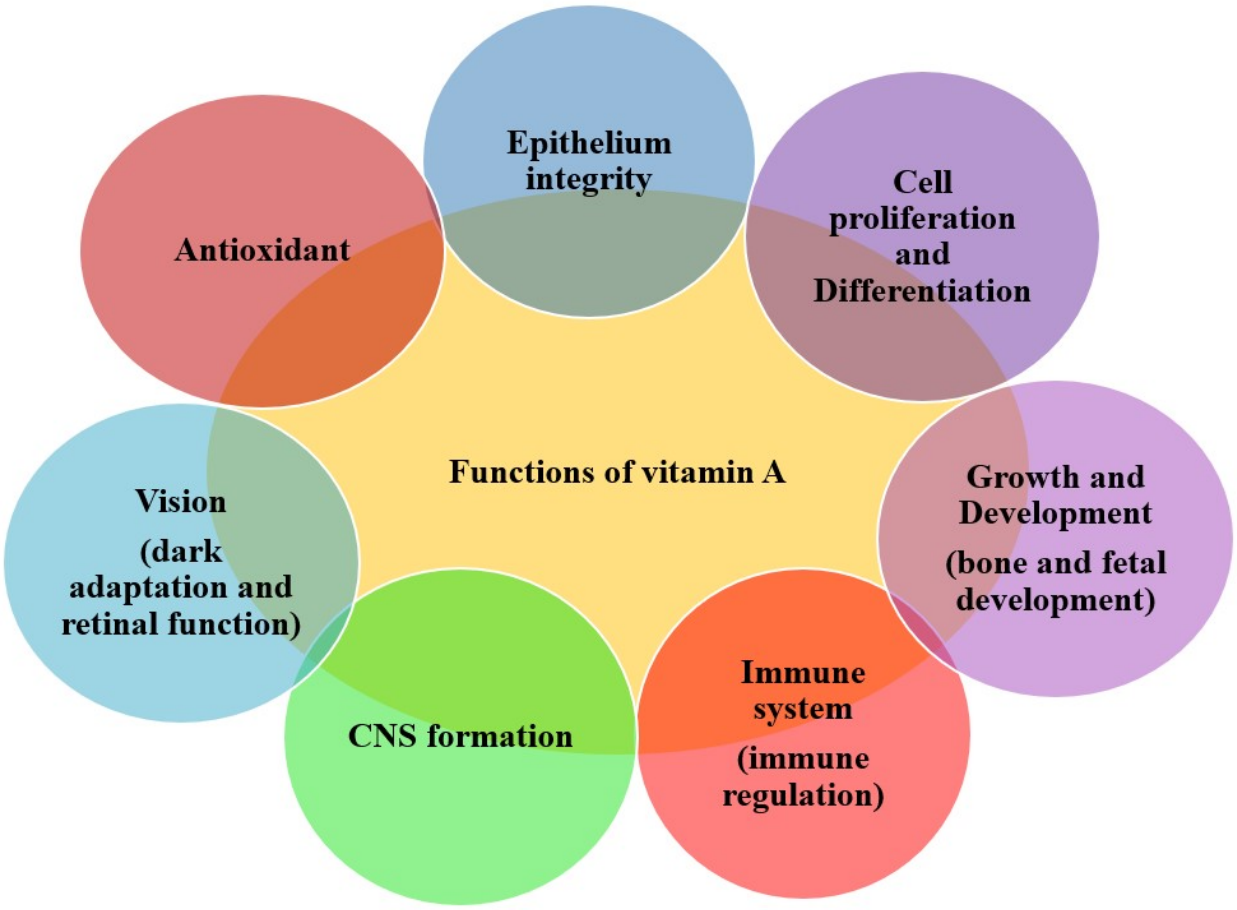


**Fig. 3. Diagrammatic representation of the various physiological functions of VitA.**

## 4. Physiological Functions of VitA

The body uses VitA in various biologically active forms, which confer pleiotropic properties. ATRA is the main active form of VitA, even though retinol, which is also responsible for various functions, is the most prevalent form in the body. Certain metabolites of this vitamin, such as 13-cis-retinol and 9-cis-retinoic acid, are also physiologically active, albeit to a lesser degree. Each vitamin form exhibits specificity for the various tissues and pathways in which it functions. Nonetheless, they share comparable characteristics. ATRA performs many tasks by binding to nuclear receptors and thereby regulating gene expression, whereas retinal serves as a cofactor in numerous enzymatic activities, and 11-cis-retinal plays a role in vision [1]. Fig. 3 provides an overview of the numerous physiological processes in which retinoids are involved. These include corneal and conjunctival development; cell proliferation and division; bone and fetal development; immune system activity; central nervous system (CNS) development; and processes underlying vision in darkness.

Retinoids have been implicated in a number of pathological conditions, including obesity, cancer, osteoporosis, cardiovascular diseases, diabetes mellitus, and skin conditions. Carotenoids also function as antioxidants and anti-inflammatory agents [1].

## 5. Analysis of VitA Status

Stored VitA gets released into the bloodstream as retinol according to the body's requirement. Transthyretin (TTR) and retinol binding protein (RBP) form a compound with retinol that circulates in the plasma. As a result, the patient's physiological condition may impact VitA status and the protein level, for example, due to protein deficiency, hepatic disease, acute infection or inflammatory disorder, and abnormal C-reactive protein levels [24]. VitA absorption or metabolism may be affected by gastrointestinal conditions such as celiac disease, Crohn's disease, pancreatic abnormalities, or specific nutrient deficiencies, such asz-inc and iron. VitA status is frequently assessed by measuring plasma or serum concentrations of carotenoids or retinols after fasting. However, until the liver VitA level decreases markedly or exceeds it, the blood level remains within homeostatic limits, and these levels do not accurately reflect the actual VitA status [25].

Mounting evidence suggests that circulatory carotenoid or retinol levels may be a more promising

indicator of antioxidant activity than dietary amounts. Assessing dietary intake using food frequency surveys has several drawbacks, including inaccurate recall of past diets, individual differences in nutrient absorption, and difficulty accurately reflecting the carotenoid content of foods modified by storage and cooking methods. Because of these limitations, blood levels of carotenoids and retinol have been reported to show a weak to moderate relationship with fruit and vegetable consumption (r = 0.2–0.7 for carotenoids and r = 0.04–0.06 for retinol) [26].

Deficient or hazardous amounts of VitA have been linked to a number of disorders; it is essential to accurately measure the VitA content in the blood. A blue pigment created when VitA combines with trifluoroacetic acid (Neeld–Pearson reaction) or antimony trichloride (Carr–Price reaction) was formerly directly measured to determine the VitA content [26]. These techniques were laborious, difficult to automate, and susceptible to outside influences. Since then, the primary analytical technique has been high-performance liquid chromatography (HPLC) with either spectrophotometric or fluorometric detection. Photometric detection of VitA or carotenoids is based on absorbance at wavelengths of 325 to 450 nm, and peak-height ratios adjusted with internal standards are used for quantification. It has been demonstrated that HPLC techniques outperform earlier photometric techniques in terms of both specificity and sensitivity [27]. However, there are a number of challenges when using HPLC methods to measure fat-soluble VitA and carotenoids; used to identify fat-soluble vitamins, HPLC techniques need concentration and extraction steps to eliminate the oiled material and enhance the desired sample [28]. Sample pretreatment has generally relied extensively on liquid–liquid extraction, solid-phase extraction, and supported-liquid extraction. Because each analyte ionizes in a wide range of ways, it is also challenging to analyze VitA and carotenoids using HPLC. Additionally, because the target analyte's concentration is so low, measuring it requires a significant amount of sample and a punctual runtime [29,30].

A relatively new technique called liquid chromatography combined with tandem mass spectrometry (LC-MS/MS) has become a very selective analytical approach after outperforming other popular techniques. Numerous fat-soluble vitamins can be rapidly and simultaneously analyzed from a small sample using LC-MS/MS technology [31].

Additionally, this technique can analyze multiple components and chemicals in samples and separate and quantify vitamin isomers or epimers. The VitA study can be expanded by examining a variety of specimens with complicated matrix materials. The sophisticated LC-MS/MS technology has made it possible to evaluate VitA status more accurately by streamlining the extraction process, decreasing sample volume, and speeding up testing [32,33].

## 6. Genetic Mutations in Genes Associated With the Metabolism of VitA and Carotenoids

Age and sex affect the amount of VitA required by the body. The Food and Drug Administration (FDA) has suggested that adults should consume 900 µg of Retinol Activity Equivalents (RAE) per day, whereas females should consume 700 µg, pregnant women should consume 770 µg, nursing mothers should consume 1300 µg, and children aged 6 months or less should have 400 µg [34]. The mean intake of a regular diet required to provide adequate nutrition for almost all (97–98%) healthy individuals in a group is known as the Recommended Dietary Allowance (RDA). One µg RAE for each VitA type can be converted to one µg retinol, two µg supplemental β-carotene, twelve µg β-carotene from food, twenty-four µg α-carotene from dietary products, or twenty-four µg β-cryptoxanthin from nutritional sources [34,35]. Numerous proteins interact with VitA during metabolism, transport, and biological activity. Therefore, modifications in genes related to vitamin metabolism may impact the concentration of VitA and human health [36].

Serum retinol levels were associated with rs1667255 in TTR and rs10882272 in Retinol-Binding Protein 4 (RBP4) in a genome-wide association study (GWAS) of 5006 Caucasian individuals. A replication analysis confirmed that the final SNP was highly significant [37]. The RBP-bound form, which binds to TTR and stabilizes the complex, accounts for approximately 95% of retinol in blood. In the coding region of β-carotene 15,15′-monooxygenase (BCO1), R267S (rs12934922), A379V (rs7501331), and two single-nucleotide polymorphisms (SNPs) are recognized to be linked with elevated fasting β-carotene levels and decreased BCO1 activity, which catalyzes β-carotene into two molecules of retinal [38]. GWAS and candidate gene studies have shown that rs6564851, another SNP in the BCO1 promoter region, is associated with fasting β-carotene levels. It has been demonstrated that the SNP influences the binding of intestinal-specific homeobox (ISX), which suppresses β-carotene absorption and its conversion to retinal. Although such SNPs may be associated with β-carotene absorption, they are a crucial concern for vegetarians whose primary source of VitA is β-carotene [39].

The retinol-binding protein 3 (RBP3) gene on chromosome 10q11.22 encodes the 136-kDa lipoglycoprotein known as Interphotoreceptor Retinoid-Binding Protein (IRBP). It accumulates in the interphotoreceptor matrix after being released by photoreceptors. It serves as a retinoid transporter between Müller cells and photoreceptors, and between photoreceptors and the Retinal Pigment Epithelium (RPE). Autosomal recessive Retinitis Pigmentosa (RP) is considered uncommon and is caused by a pathogenic variant in the RBP3 gene. Additionally, such variants may result in atypical retinal dystrophy, character-

ized by childhood-onset high myopia, widespread rod and cone failure, and a negligible fundus appearance [40].

VitA is largely stored in the liver by hepatic stellate cells. An estimated 70% of VitA in the bodies of healthy, well-fed people is thought to be stored in the liver, more precisely in a tiny fraction of cells called hepatic stellate cells [41]. VitA status regulates hepatic Lecithin: Retinol Acyltransferase (LRAT) expression; when retinoic acid levels are high, a positive feedback loop amplifies retinyl ester formation. Patatin-like phospholipase domain-containing 2 (PNPLA2)/PNPLA3 and adipose triglyceride lipase (ATGL) are two lipases that primarily mobilize retinyl ester storage [42]. There are now 11 genetic polymorphisms in ATGL/PNPLA2 that have been linked to myopathy and neutral lipid storage disorder; however, there has been no correlation found between these genetic variations and retinyl ester mobilization [43,44]. A prominent inherited marker of non-alcoholic fatty liver disease (NAFLD) is a missense mutation in the PNPLA3 gene (I148M, rs738409), which increases hepatic retinyl ester levels while reducing blood retinol levels. The only harmful genomic mutation of the PNPLA3 gene is rs738409, despite the fact that 32 missense mutations have been found in the gene [45].

## 7. Epidemiological Studies Showing Relationships Between Carotenoids, VitA and Breast Cancer Risk

It has been reported that the protective benefits of carotenoids against BC risk might vary with oxidative stress-related lifestyle factors such as alcohol consumption or smoking status. Mignone et al. [46] conducted a large-scale case-control study of women living in Wisconsin, New Hampshire, and Massachusetts to investigate the relationship between tumour risk and specific fruits, vegetables, carotenoids, and VA. Five years before the reference date, women were interviewed about their consumption of carotenoid-rich fruits and vegetables [46]. Among premenopausal women, elevated levels of α-carotene ($p$ for trend = 0.07, 95% CI: 0.68–0.98, OR: 0.82), lutein/zeaxanthin ($p$ for trend = 0.02, 95% CI: 0.68–0.99, OR: 0.83), VA ($p$ for trend = 0.01, 95% CI: 0.68–0.98, OR: 0.82), and β-carotene ($p$ for trend = 0.009, 95% CI: 0.68–0.98, OR: 0.81) were negatively correlated. Postmenopausal women did not show an inverse association. However, the analyses of association were not statistically significant; these outcomes were higher among premenopausal women who admitted to smoking than among those who never smoked. The study's findings, consistent with those of other prospective studies, indicate that excessive carotenoid consumption may reduce the incidence of BC before menopause but not after, especially in smokers [46].

Peng et al. [47] found 48–110 metabolites linked to plasma concentrations of estimated-VA-potential, zeaxanthin/lutein, α-carotene, lycopene, β-carotene, and β-cryptoxanthin. These contained metabolites that were primarily positively correlated and connected with in redox status (glutamine, plasmalogens), immune function (tryptophan), epigenetic mechanisms (methylated/ acetylated metabolites), and metabolites that were largely inversely correlated and implicated in β-oxidation (carnitines) (false discovery rate (FDR) ≤0.05) [47,48]. Measuring ≥10 years prior to diagnosis, the β-carotene metabolomic sigatures ($p$-trend = 0.02, Q4 vs. Q1 relative risk (RR) = 0.74) and predicted VA potential ($p$-trend = 0.02, Q4 vs. Q1 RR = 0.74) were linked to a decreased risk of BC [47].

Prognostic prediction for BC now relies heavily on stratification by human epidermal growth factor receptor 2 (HER2) status, estrogen receptor (ER), and progesterone receptor (PR) [49]. In contrast to ER-negative BC ($p$-trend = 0.051, 95% CI = 0.37–1.97, OR = 0.86), Wang et al. [50] showed an opposite relationship between α-carotene and ER-positive BC ($p$-trend = 0.054, 95% CI = 0.43–0.93, OR = 0.63) [26]. According to Bakker et al. [51], the likelihood of having ER-negative tumors was 39–59% lower for those with the largest percentile of α-carotene and β-carotene concentrations (α-carotene, $p$-trend = 0.02, 95% CI = 0.39–0.98, OR = 0.61; β-carotene, $p$-trend = 0.002, 95% CI = 0.26–0.65, OR = 0.41 ), but there was no discernible correlation for ER-positive tumors (α-carotene, $p$-trend = 0.28, 95% CI = 0.49–1.19, OR = 0.77; β-carotene, $p$-trend = 0.91, 95% CI = 0.66–1.57, OR = 1.02) [26]. The highest plasma carotenoid percentile was associated with a 30–40% reduction in the risk of ER-positive BC, but only a clinically significant reduction in the risk of ER-negative BC, according to another investigation [52]. Regardless of hormone receptor type, Sanlier et al. [53] found that serum levels of lutein/zeaxanthin were negatively associated with various cancers and other diseases including BC risk. Certain carotenoids suppressed the proliferation of both ER-positive and ER-negative cells, as reported by Prakash et al. [54]. Nevertheless, some studies indicated that ER status has little bearing on the risk of BC [26].

Higher levels of both α-carotene and β-carotene were shown to be substantially linked to a greater than 50% lower risk of BC with nodal metastases (α-carotene, $p$-trend = 0.002, 95% CI = 0.22–0.71, OR = 0.39; β-carotene, 95% CI = 0.24–0.82, OR = 0.45), according to Tamimi et al. [55]. But Eliassen et al. [52] showed that carotenoids and BC risk were unrelated to tumour size and/or nodal involvement [52]. There are many human studies which showed the association of various carotenoids and BC shown in Table 1 (Ref. [56,57,58,59,60]).

## 8. Potential Role of Vitamin A and Carotenoids as Biomarkers in Breast Cancer

VitA and carotenoids are found as potential biomarkers because they play a very crucial role in oxidative stress management, retinoid signaling pathways, and cancer biol-

**Table 1. Summary of human studies on the relationship between carotenoids and breast cancer.**

| Author | Year | Study type | Population | Biomarkers | Key findings |
|---|---|---|---|---|---|
| Dorjgochoo et al. [56] | 2009 | Nested case-control study (Shanghai Women's Health Study) | 365 breast cancer cases and 726 controls | Plasma carotenoids, tocopherols, retinol | Overall no associated is found with the risk of breast cancer but some carotenoids subtypes like lycopene isomers and α-cryptoxanthin shows, an adverse association |
| Eliassen et al. [57] | 2015 | nested case-control study (Nurses' Health Study) | 32,826 women gave blood samples; 2188 instances of breast cancer were found during the 20-year follow-up. | Plasma carotenoids (α-carotene, β-carotene, lycopene, lutein/zeaxanthin, total carotenoids) | Higher levels of α-carotene, β-carotene, lycopene, and total carotenoids were linked to an 18–28% reduction in breast cancer incidence and recurrence |
| Peng et al. [58] | 2021 | Nested case–control study (Nurses' Health Study I & II) | 1919 breast cancer cases and 1695 controls | Circulating carotenoids | Elevated level of carotenoids has been linked with low risk of breast cancer, particularly in women with high hereditary risk and mammography density |
| Yan et al. [59] | 2016 | Hospital-based case–control study | 521 breast cancer cases and 521 control (women aged 25–70 years) | Serum carotenoids (α-carotene, β-carotene, lutein/zeaxanthin, lycopene and β-cryptoxanthin) | Higher level of α-carotene (OR 0.44), β-carotene (OR 0.27), lutein/zeaxanthin (OR 0.26), and lycopene (OR 0.41) had a stronger inverse relationship with breast cancer, but β-cryptoxanthin has no effect |
| Darouei et al. [60] | 2025 | population-based case-control study | 600 breast cancer and 600 healthy controls (women aged 18–75 years) | Dietary carotenoids (α-carotene, β-carotene, lutein/zeaxanthin, lycopene, β-cryptoxanthin, phytofluene, phytoene, total carotenoids) | An increased dietary consumption of overall and specific carotenoids, especially lycopene, phytofluene lutein/zeaxanthin, phytoene, and total non-provitamin A carotenoids, is strongly related with a lower risk of BC |

BC, Breast cancer; CI, confidence interval; OR, odds ratio.

ogy. The circulating carotenoid levels are associated with BC risk according to various epidemiological studies [26]. Dehnavi et al. in 2024 [61] found a negative correlation between circulating total carotenoids, like α-carotene, β-carotene, lutein, lycopene, and β-cryptoxanthin, and the risk of BC. Each 10 µg/dL of total carotenoids (α-carotene, β-carotene, and β-cryptoxanthin) was linked to a 2%, 22%, 4%, and 10% decreased risk of BC, respectively [61]. These compounds serve as predictive and prognostic biomarkers because high levels of circulating carotenoids improve the antioxidant status and reduce the BC risk. Furthermore, carotenoids may also act as a response-monitoring biomarker, as alterations in their circulating levels may indicate variations in oxidative stress and treatment outcome during therapy [61].

The circulating biomarkers include plasma or serum carotenoids as well as retinol and tissue-based biomarkers, like retinoic acid receptors (RAR/RXR) expression and carotenoid-mediated signaling pathways in breast tumor cells; both of which may be included in biomarker analysis. These biomarker categories emphasize the role of VitA and carotenoids in BC risk prediction, cancer assessment, and customized therapy methods [62].

## 9. Regulatory Role of VitA and Carotenoids in Cell Signalling and Nuclear Receptor Activity in Breast Cancer

Retinoids bind to the nuclear receptors for steroid hormones, known as receptors (RARs) and retinoid X receptors (RXRs), mediating the many actions of VitA. These activated receptors modulate the expression of genes encoding structural proteins, enzymes, and binding substances. Retinoid-mediated carcinogenesis is believed to be linked to alterations in RAR and RXR expression levels [63]. All three RAR and RXR isotypes (α, β, and γ) were inactivated in premalignant and malignant tissues, and the retinoid content of these cancer cells was lower than that of normal

cells. RARβ2 mRNA levels were lower in several solid cancers, especially BC. In fact, patients with BC had higher methylation levels at the RARβ2 gene promoter. RARβ2 gene expression can cause growth inhibition and apoptosis through both retinoid-dependent and -independent mechanisms. Retinoids inhibit BC proliferation *in vivo* by binding to RARα and activating RARβ, which in turn promotes genes involved in cell division and apoptosis (Fig. 4, Ref. [26]). The research found that three weeks of all-trans-retinoic acid treatment initially increased RARβ in 33% of BC patients. RARβ2 may have tumour-suppressive effects, as evidenced by observations that 9-cis- and 13-cis-retinoic acid therapy activated RARβ2 and that elevated RARβ2 concentrations were associated with therapeutic response. The growth-inhibitory action of retinoids can be overcome by BC cell lines that do not express RARβ2 [26].

It has been found that ER-positive BC has higher RARα levels and is sensitive to retinoids, whereas ER-negative BC has lower RARα levels and is resistant to retinoids, depending on the cancer cells' hormone receptor status. Through its interaction with ERα, unliganded RARα paradoxically promotes estrogen-dependent cell proliferation in ER-positive malignancies. On the other hand, retinoid-bound RARα exhibits anti-estrogenic activity because it is unable to interact with Erα. Recent research indicates that ER-negative cancers have considerably higher RARβ mRNA expression than ER-positive tumours, despite having little to no RARα [26]. ATRA-dependent growth inhibition may result from acquired ATRA sensitivity brought on by high RARβ expression. According to one *in vitro* study, retinoids may limit tumour cell growth in both ER-positive and ER-negative BC, but in distinct ways. Retinoids induce senescence and cell cycle arrest in ER-positive malignancies by inhibiting cyclin D and telomerase. Retinoids cause growth inhibition in ER-negative tumours by increasing the expression of p53, p21, and retinoblastoma protein. Nevertheless, a clinical study involving individuals suffering from hormone-responsive metastatic BC (level 1 proof) revealed no positive outcomes when retinoids and hormonal therapy were combined. ATRA with paclitaxel used to treat individuals with metastatic BC demonstrated 76.4% beneficial effects in another clinical trial (level 2 proof) [26].

When cellular signalling pathways are dysregulated, BC cells can have the capacity to multiply, infiltrate, and survive (Fig. 5) [26]. The protein kinase B (PKB or Akt), mammalian target of rapamycin (mTOR), and phosphoinositide 3-kinase (PI3K) pathways are among the cancer signalling pathways that stimulate cell proliferation and contribute to tumour development and progression. PI3K/Akt/mTOR signalling stimulation promotes cell movement and starts the BC cells' metastatic phenotype [64]. The serine/threonine kinase extracellular signal-regulated kinase 1/2 (ERK1/2) promotes tumour invasion. A pro-inflammatory transcription molecule, nuclear factor-κB (NF-κB) can be activated by phosphorylating ERK1/2 [65,66]. This promotes the production of anti-apoptotic genes in the nucleus, such as B-cell lymphoma-extra-large (Bcl-xL) and Bcl-2, which prevent cell death and increase survival. Circulating tumour cells in metastatic BC exhibit markedly reduced apoptotic pathway activation [67].

Through the regulation of these signalling pathways, carotenoids cause BC cells to undergo apoptosis. Carotenoids suppress RAS/RAF/MEK/ERK1/2 signalling and downregulate the PI3K/Akt/mTOR pathway, which inhibits cell motility and growth [68]. Additionally, carotenoids inhibit IKK phosphorylation, thereby preventing IκB from degrading. Pro-inflammatory mediators are prevented from being transcribed by blocking NF-κB activation and storing reactive oxygen species [69]. Additionally, pro-death proteins (Bax, Bak, and p53) are stimulated by carotenoids, whereas pro-survival proteins (Bcl-xL and Bcl-2) are inhibited. Activation of pro-death proteins stimulates caspase activity, thereby inducing apoptosis in cancer cells [70,71]. The process underlying the preventive effects of carotenoids on the carcinogenesis of BC has been the subject of numerous studies. By reducing inflammation, carotenoids can lessen the transformation of cells into cancer [72]. Through the inhibition of the PI3K/Akt/mTOR pathway and consequent blockage of the translation of the MYC protein, which is crucial for oncogenesis, astaxanthin inhibits the proliferation of BC cells [73]. Furthermore, lycopene increased the production of proteins associated with apoptosis and arrested cell cycle progression. In human BC cell lines, lycopene reduced Akt and mTOR phosphorylation, which increased the production of p53 mRNA and pro-apoptotic Bcl-2-associated X protein (Bax) [74].

In addition to lycopene, β-carotene promotes apoptosis and inhibits cell cycle progression. According to an *in vitro* investigation, β-carotene inhibits Akt and ERK1/2 signalling, thereby regulating the expression of genes susceptible to oxidative stress. By activating the caspase-3 family of cysteine-aspartic proteases and suppressing Bcl-2 and NF-κB expression, β-carotene induces apoptosis in BC cells [75]. Furthermore, pharmacological administration of fucoxanthin, a xanthophyll found in brown seaweeds, to a BC cell line resulted in concentration-dependent suppression of PI3K/Aktsignalling and NF-κB activity, thereby inhibiting the malignant phenotype [76]. By reducing Bcl-2 activity and increasing Bax and caspase activity, ATRA and its derivatives have been shown in multiple studies to induce BC cell death. Carotenoids and anticancer agents, including doxorubicin, synergize to promote apoptosis in BC cells but not in healthy cells [77].

## 10. VitA and Carotenoids Offer Promising Therapeutic Possibilities for Breast Cancer Management

Antioxidants such as VitA and carotenoids have been used in the management of BC because they help mitigate the adverse effects of chemotherapeutic agents by se-

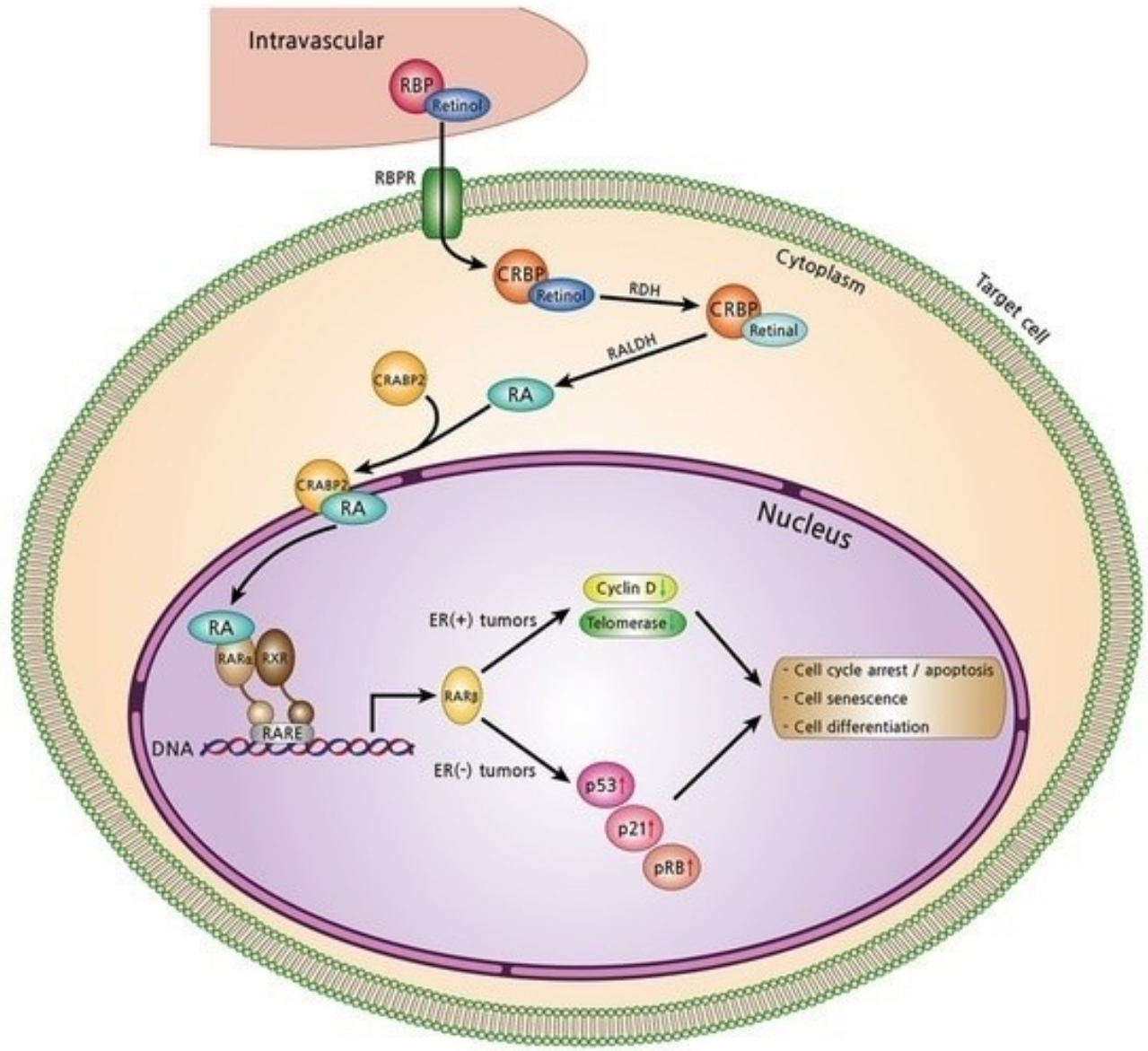


**Fig. 4. The genetic regulation of retinol in the nucleus and its cellular absorption by targeted cells (BC cells)**. Retinol is transported through the bloodstream by binding to RBP. It enters the target cell's cytoplasm via the RBP receptor (RBPR). Intracellular retinol is enzymatically converted into active forms upon binding to cellular RBPs (CRBPs). Retinol dehydrogenase (RDH) converts retinol to retinal, and retinal dehydrogenase (RALDH) then converts it to retinoic acid (RA), which exists as three isomers: all-trans-, 9-cis-, and 13-cis-retinoic acid. RA is transported into the nucleus by cellular retinoic acid-binding protein-2 (CRABP2) when bound to RARα. Retinoic acid response elements (RAREs) in gene promoters are sites where RXRs and RARα dimers bind RA. This complex inhibits growth and induces cell differentiation by promoting the expression of downstream target genes, including RARβ. Cell-cycle arrest and senescence in ER-positive malignancies are driven by suppression of cyclin D and telomerase-related processes. In ER-negative malignancies, senescence and cell death are mediated by activation of the retinoblastoma protein (pRB), p53, and p21 [26].

lectively targeting cancer cells while sparing healthy cells [78]. As naturally occurring antioxidants, carotenoids exert a variety of direct antitumoral effects on tumour cells (Fig. 6). Carotenoids can enhance gap junctional interactions, induce apoptosis, autophagy, or necroptosis, promote cell differentiation, and exhibit antiangiogenic, antimetastatic, multidrug-resistant, and antiproliferative properties. Several studies have shown that VitA and carotenoids work in concert with anticancer medications to maximize apoptosis and inhibit cell growth in BC.

According to a study by Eid et al. [79], fucoxanthin may synergize with chemotherapeutic agents to overcome multidrug resistance in BC cells. Combining carotenoids with anticancer medications increased p53 and caspase activity while decreasing metabolic enzyme activity. By reducing the doxorubicin dose, this approach increased its cy-

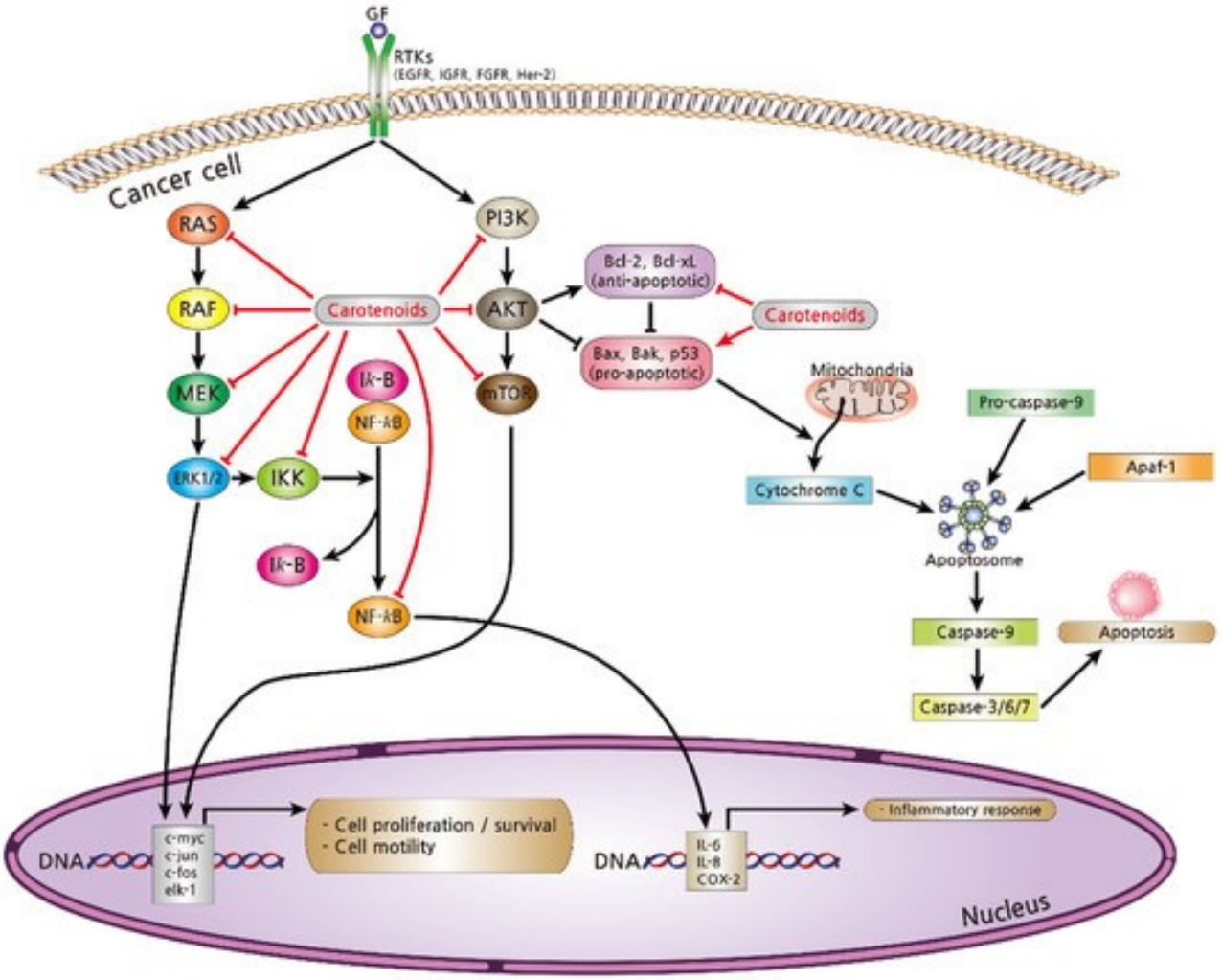


**Fig. 5. Several signalling mechanisms mediate breast oncogenesis**. Growth factors activate the PI3K/Akt/mTOR pathway by binding to receptor tyrosine kinases (RTKs) such as HER2, FGFR, EGFR, and IGFR, thereby increasing cell motility and driving cell proliferation. Akt promotes cell survival by blocking apoptosis, activating anti-apoptotic proteins such as Bcl-2, Bcl-xL, and Bad, and suppressing pro-apoptotic proteins such as Bax and p53. The RAS/RAF/MEK/ERK1/2 pathway is another signalling route that stimulates the expression of transcription factors such as c-Myc, c-Jun, c-Fos, and ELK-1, which are critical for both cell survival and carcinogenesis. ERK1/2 triggers the activation of Iκ-B kinase (IKK), which leads to the proteasomal degradation of Iκ-B, an inhibitory protein bound to NF-κB. Upon activation, NF-κB translocates to the nucleus and induces transcription of IL-6, IL-8, iNOS, and COX-2, thereby triggering an inflammatory response [26].

totoxicity against cancer cells and helped them overcome multidrug resistance [79].

Over the past ten years, numerous initiatives have sought to increase β-carotene bioavailability through nanoformulation techniques. Conventional nanoparticle-based solutions, however, have several disadvantages, including limited entrapment efficiency, short shelf life, and poor bioavailability [80]. Soukoulis and Bohn [81] investigated how the chemical stability and bioavailability of carotenoids could be enhanced by assembling them into a nanoemulsion. Although nanoemulsions present certain challenges, they may increase the bioavailability of β-carotene. For instance, they can be highly detrimental to living organisms, require substantial surfactant and cosurfactant, have a short lifespan, and are unable to dissolve substances with higher melting points [81]. According to research by Dos Santos et al. [82], polymeric nanoparticles are an affordable nanodrug-delivery method for encapsulating carotenoids. Some polymeric nanocarriers composed of biodegradable polymers may exhibit side effects, such as discomfort after subcutaneous, intravenous (IV), and intramuscular administration, as well as a very short shelf life. They may also induce uncontrollable drug release and leakage [82]. According to the research conducted by Rehman et al. [83], carotenoid-based nanoliposomes exhibited reduced size and a lower polydispersity index; however, they

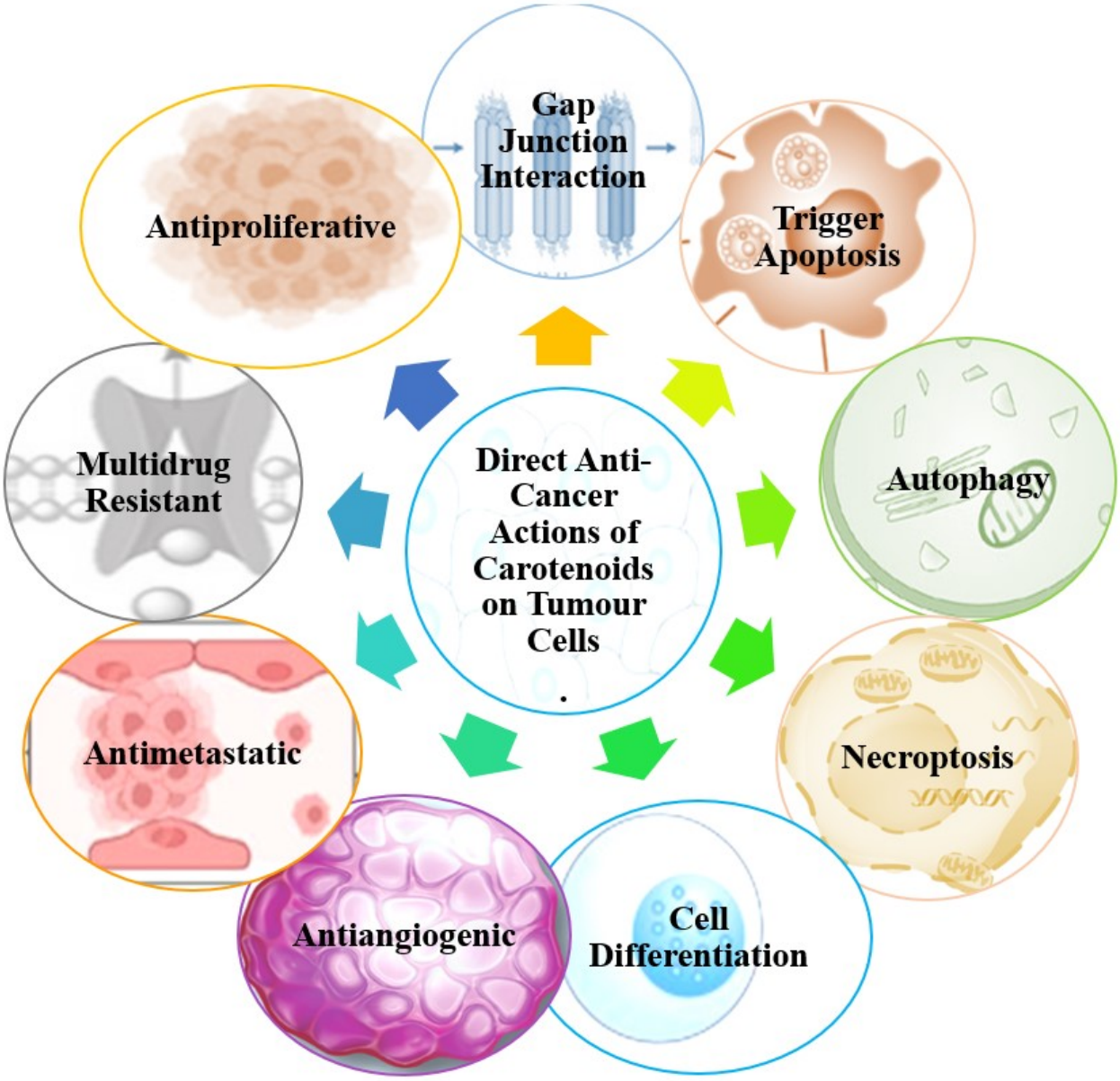


**Fig. 6. Diagrammatic representation of the anticancer actions of carotenoids in tumour cells**.

have significant disadvantages, including low entrapment capacity, limited susceptibility to gastrointestinal enzymes, insufficient solubility, poor consistency, difficulties in regulating liposomal size, and a short half-life.

Although clinical and preclinical studies have demonstrated the protective effects of VitA and carotenoids against the progression of BC, their use in clinical practice remains limited because lipophilic VitA and carotenoids are poorly soluble and have low bioavailability. To improve drug delivery to cancer sites, novel methods for encapsulating carotenoids in various nanocarriers have emerged. BC cells have been shown to be significantly affected by carotenoid-loaded nanotechnologies. When combined with artificial gold nanoparticles (AuNPs), crocin, a naturally occurring carotenoid that gives saffron its colour, dramatically reduced cancer cell growth. Compared with crocin itself, the nanosized liposomal form of crocin exhibits a stronger antitumour effect on BC cells. Nanoparticles can enter cancer cells via leaky tumour microvasculature. In contrast, intact vasculature in other tissues maintains nanoparticles in the circulation [84]. Huang et al. [85] conducted another investigation that showed that, compared with single nanoparticle-loaded medicines, co-delivery of paclitaxel and ATRA using human serum albumin-based nanocarriers significantly reduced the metastatic characteristics of BC cells both *in vivo* and *in vitro*. Retinoids and carotenoids conjugated with nanotechnology not only increase their bioaccessibility to target cells but also slow cancer spread and metastasis, suggesting that this is an innovative approach to cancer treatment [85].

## 11. Conclusions and Future Perspectives

Several epidemiologic studies suggest that increased consumption of fruits and vegetables may reduce the risk of developing breast cancer. Carotenoids and retinol are lipophilic antioxidants and anti-inflammatory agents found in fruits and vegetables, and they have attracted considerable interest in breast cancer prevention.

ROS can be effectively quenched by VitA and carotenoids, which also protect against photooxidative damage. Over the past 20 years, significant efforts have focused on lowering the risk of breast cancer through lifestyle changes. Because studies have reported varying findings on the precise effects of VitA and carotenoids in breast cancer, their therapeutic use in the management of breast cancer remains limited. This review provides a current, comprehensive analysis of the roles and assessment techniques of VitA and carotenoids, as well as the genetic variants associated with cancer and other diseases. Epidemiological evidence supports the beneficial effects of VitA and carotenoids on breast cancer progression, showing reduced risk through inhibition of cell growth, survival, and invasion mediated by retinol and/or carotenoids. Recent research has highlighted the potential of VitA and carotenoids as novel medicinal agents, leveraging their anticancer and antimetastatic properties without adverse effects through various delivery methods. These results indicate an optimistic future for the clinical use of carotenoids and VitA in both the treatment and management of breast cancer. However, further well-designed, randomized, placebo-controlled clinical studies are needed to evaluate the efficacy, safety, and optimal dosing of VitA and carotenoids.

Novel omics technologies are constantly evolving as a result of biotechnological developments, allowing researchers to study data from a variety of sources, including the genome, transcriptome, epigenome, proteome, and metabolome, to mention a few. Precision nutrition is a potential strategy to personalizing dietary plans for breast cancer patients and survivors based on their genetic, metabolic, and microbiome data, as well as tumor and therapy features. Individual dietary responses vary significantly, highlighting the importance of precision nutrition solutions over a one-size-fits-all approach. To fully integrate personalized nutrition into breast cancer care, future research should include huge-scale clinical studies and multi-omics techniques to improve dietary guidelines and assess long-term effects on cancer growth, treatment outcome, recurrence, and survival rates.

## 12. Limitations

This review gives a thorough summary of VitA and carotenoids in BC, but there are some important limitations. Most of the conclusions rely on observational studies and preclinical data, which makes it hard to draw firm conclusions or apply the findings in clinical settings. The review notes that results differ between studies on BC subtypes and patient groups, but it does not look closely at why these differences exist. Also, the manuscript does not describe a systematic approach to searching the literature, discusses VitA toxicity and safety only briefly, and presents the benefits of carotenoids more strongly than the current evidence from randomized clinical trials supports. In addition, issues like how biomarkers are measured, how well these compounds are absorbed, genetic differences, and whether nanotechnology-based delivery systems can be used in practice need more careful discussion. Overall, more solid clinical evidence is needed before VitA and carotenoids can be recommended for regular use in BC prevention or treatment.

## Author Contributions

S: designed and analysis of data for the work ; SBK, HSB, CGM, KM: acquisition of the data; LC, SG, SR, SP: interpretation of the data; VKG, RKC, HSB: conception of the work; HSB: supervised and Validated the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

Not applicable.


## Acknowledgment

We acknowledge the Department of Medical Lab Sciences (USAHS), Rayat-Bahra University, Mohali, for providing the required facilities.

## Funding

This research received no external funding.


## Conflicts of Interest

The authors declare no conflicts of interest.

## References


[1] Carazo A, Macáková K, Matoušová K, Krčmová LK, Protti M, Mladěnka P. Vitamin A Update: Forms, Sources, Kinetics, Detection, Function, Deficiency, Therapeutic Use and Toxicity. Nutrients. 2021; 13: 1703. https://doi.org/10.3390/nu13051703

[2] Kołodziejczyk AM, Karwowski B. Anti-DNA Damage Mechanisms and the Role of Carotenoids, Vitamin A, and Its Derivatives. Nutrients. 2025; 17: 2721. https://doi.org/10.3390/nu17172721

[3] Gebregziabher BS, Gebremeskel H, Debesa B, Ayalneh D, Mitiku T, Wendwessen T, et al. Carotenoids: Dietary sources, health functions, biofortification, marketing trend and affecting factors–A review. Journal of Agriculture and Food Research. 2023; 14: 100834. https://doi.org/10.1016/j.jafr.2023.100834

[4] Huang Z, Liu Y, Qi G, Brand D, Zheng SG. Role of Vitamin A in the Immune System. Journal of Clinical Medicine. 2018; 7: 258. https://doi.org/10.3390/jcm7090258

[5] Koklesova L, Liskova A, Samec M, Buhrmann C, Samuel SM,

Varghese E, et al. Carotenoids in Cancer Apoptosis-The Road *from Bench to Bedside* and Back. Cancers. 2020; 12: 2425. https://doi.org/10.3390/cancers12092425
[6] Medina-García M, Baeza-Morales A, Martínez-Peinado P, Pascual-García S, Pujalte-Satorre C, Martínez-Espinosa RM, et al. Carotenoids and Their Interaction with the Immune System. Antioxidants (Basel, Switzerland). 2025; 14: 1111. https://doi.org/10.3390/antiox14091111
[7] Łukasiewicz S, Czeczelewski M, Forma A, Baj J, Sitarz R, Stanisławek A. Breast Cancer-Epidemiology, Risk Factors, Classification, Prognostic Markers, and Current Treatment Strategies-An Updated Review. Cancers. 2021; 13: 4287. https://doi.org/10.3390/cancers13174287
[8] Li H, Prever L, Hirsch E, Gulluni F. Targeting PI3K/AKT/mTOR Signaling Pathway in Breast Cancer. Cancers. 2021; 13: 3517. https://doi.org/10.3390/cancers13143517
[9] Li K, Deng Z, Lei C, Ding X, Li J, Wang C. The Role of Oxidative Stress in Tumorigenesis and Progression. Cells. 2024; 13: 441. https://doi.org/10.3390/cells13050441
[10] Ma E, Iso H, Yamagishi K, Ando M, Wakai K, Tamakoshi A. Dietary Antioxidant Micronutrients and All-Cause Mortality: The Japan Collaborative Cohort Study for Evaluation of Cancer Risk. Journal of Epidemiology. 2018; 28: 388–396. https://doi.org/10.2188/jea.JE20170023
[11] Borel P, Desmarchelier C. Genetic Variations Associated with Vitamin A Status and Vitamin A Bioavailability. Nutrients. 2017; 9: 246. https://doi.org/10.3390/nu9030246
[12] Vašková J, Stupák M, Vidová Ugurbaş M, Židzik J, Mičková H. Therapeutic Uses of Retinol and Retinoid-Related Antioxidants. Molecules (Basel, Switzerland). 2025; 30: 2191. https://doi.org/10.3390/molecules30102191
[13] Harrison EH. Mechanisms involved in the intestinal absorption of dietary vitamin A and provitamin A carotenoids. Biochimica et Biophysica Acta. 2012; 1821: 70–77. https://doi.org/10.1016/j.bbalip.2011.06.002
[14] Yan X, Huang J, Huang L, Luo C, Li Z, Xu P, et al. Effects of dietary lipids on bioaccessibility and bioavailability of natural carotenoids. LWT. 2024; 200: 116171. https://doi.org/10.1016/j.lwt.2024.116171
[15] Milani A, Basirnejad M, Shahbazi S, Bolhassani A. Carotenoids: biochemistry, pharmacology and treatment. British Journal of Pharmacology. 2017; 174: 1290–1324. https://doi.org/10.1111/bph.13625
[16] Mandal M, Sarkar M, Khan A, Biswas M, Masi A, Rakwal R, et al. Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) in plants–maintenance of structural individuality and functional blend. Advances in Redox Research. 2022; 5: 100039. https://doi.org/10.1016/j.arres.2022.100039
[17] Pizzino G, Irrera N, Cucinotta M, Pallio G, Mannino F, Arcoraci V, et al. Oxidative Stress: Harms and Benefits for Human Health. Oxidative Medicine and Cellular Longevity. 2017; 2017: 8416763. https://doi.org/10.1155/2017/8416763
[18] Yu W, Tu Y, Long Z, Liu J, Kong D, Peng J, et al. Reactive Oxygen Species Bridge the Gap between Chronic Inflammation and Tumor Development. Oxidative Medicine and Cellular Longevity. 2022; 2022: 2606928. https://doi.org/10.1155/2022/2606928
[19] Zhao Y, Ye X, Xiong Z, Ihsan A, Ares I, Martínez M, et al. Cancer Metabolism: The Role of ROS in DNA Damage and Induction of Apoptosis in Cancer Cells. Metabolites. 2023; 13: 796. https://doi.org/10.3390/metabo13070796
[20] Li Y, Zhang X, Wang Z, Li B, Zhu H. Modulation of redox homeostasis: A strategy to overcome cancer drug resistance. Frontiers in Pharmacology. 2023; 14: 1156538. https://doi.org/10.3389/fphar.2023.1156538
[21] Liu Y, Cai X, Liu J, Luo Z, Zhang J, Cao Z, et al. The role of redox homeostasis in tumor progression: implications for cancer therapy. Acta Biomaterialia. 2025; 204: 156–186. https://doi.org/10.1016/j.actbio.2025.07.067
[22] Zorov DB, Juhaszova M, Sollott SJ. Mitochondrial reactive oxygen species (ROS) and ROS-induced ROS release. Physiological Reviews. 2014; 94: 909–950. https://doi.org/10.1152/physrev.00026.2013
[23] Sarmiento-Salinas FL, Delgado-Magallón A, Montes-Alvarado JB, Ramírez-Ramírez D, Flores-Alonso JC, Cortés-Hernández P, et al. Breast Cancer Subtypes Present a Differential Production of Reactive Oxygen Species (ROS) and Susceptibility to Antioxidant Treatment. Frontiers in Oncology. 2019; 9: 480. https://doi.org/10.3389/fonc.2019.00480
[24] Akerstrom B. Retinol Binding Protein and Its Interaction with Transthyretin. In Lipocalins, Landes Bioscience (pp. 91–98). CRC Press: Boca Raton. 2020.
[25] Mędza A, Szlagatys-Sidorkiewicz A. Nutritional Status and Metabolism in Celiac Disease: Narrative Review. Journal of Clinical Medicine. 2023; 12: 5107. https://doi.org/10.3390/jcm12155107
[26] Kim JA, Jang JH, Lee SY. An Updated Comprehensive Review on Vitamin A and Carotenoids in Breast Cancer: Mechanisms, Genetics, Assessment, Current Evidence, and Future Clinical Implications. Nutrients. 2021; 13: 3162. https://doi.org/10.3390/nu13093162
[27] Jodłowska S, Latała A. The comparison of spectrophotometric method and high-performance liquid chromatography in photosynthetic pigments analysis. OnLine Journal of Biological Sciences. 2011; 11: 63–69. https://doi.org/10.3844/ojbsci.2011.63.69
[28] Fatima Z, Quinto M, Zhou JL, Li D. Active substances of fat-soluble vitamins: Advances in extraction and analysis approaches. TrAC Trends in Analytical Chemistry. 2023; 167: 117276. https://doi.org/10.1016/j.trac.2023.117276
[29] Zou PC, Zhang Y, Bian Y, Du RZ, Qian M, Feng XS, et al. Triazoles in the environment: An update on sample pretreatment and analysis methods. Ecotoxicology and Environmental Safety. 2024; 286: 117156. https://doi.org/10.1016/j.ecoenv.2024.117156
[30] Badawy MEI, El-Nouby MAM, Kimani PK, Lim LW, Rabea EI. A review of the modern principles and applications of solid-phase extraction techniques in chromatographic analysis. Analytical Sciences : the International Journal of the Japan Society for Analytical Chemistry. 2022; 38: 1457–1487. https://doi.org/10.1007/s44211-022-00190-8
[31] Tang L, Swezey RR, Green CE, Lee MS, Bunin DI, Parman T. A tandem liquid chromatography and tandem mass spectrometry (LC/LC-MS/MS) technique to separate and quantify steroid isomers 11β-methyl-19-nortestosterone and testosterone. Journal of Chromatography. B, Analytical Technologies in the Biomedical and Life Sciences. 2022; 1193: 123165. https://doi.org/10.1016/j.jchromb.2022.123165
[32] Li SW, Luo Y, Chen W, Huang C, Chen Y, Hong XY. A novel liquid chromatography-tandem mass spectrometry (LC-MS/MS) method for quick and efficient quantification of five fat-soluble vitamins. Clinica Chimica Acta; International Journal of Clinical Chemistry. 2026; 579: 120615. https://doi.org/10.1016/j.cca.2025.120615
[33] Wang X, Qin Q, Li F, Fu Y, Liu N. A novel LC-MS/MS method combined with derivatization for simultaneous quantification of vitamin D metabolites in human serum with diabetes as well as hyperlipidemia. RSC Advances. 2023; 13: 34157–34166. https://doi.org/10.1039/d3ra05700c
[34] NIH. Vitamin A and Carotenoids - Health Professional Fact Sheet, Natl. Institutes Heal. 2023. Available at: https://ods.od.nih.gov/factsheets/VitaminA-HealthProfessional/ (Accessed: 27 October 2025).
[35] Institute of Medicine (US) Food and Nutrition Board. What are

Dietary Reference Intakes? In NCBI Bookshelf (pp. 1–2). National Academies Press: US. 1998.
[36] Yuan Y, Chen L. Transporters in vitamin uptake and cellular metabolism: impacts on health and disease. Life Metabolism. 2025; 4: loaf008. https://doi.org/10.1093/lifemeta/loaf008
[37] Mondul AM, Yu K, Wheeler W, Zhang H, Weinstein SJ, Major JM, et al. Genome-wide association study of circulating retinol levels. Human Molecular Genetics. 2011; 20: 4724–4731. https://doi.org/10.1093/hmg/ddr387
[38] Leung WC, Hessel S, Méplan C, Flint J, Oberhauser V, Tourniaire F, et al. Two common single nucleotide polymorphisms in the gene encoding beta-carotene 15,15'-monoxygenase alter beta-carotene metabolism in female volunteers. FASEB Journal : Official Publication of the Federation of American Societies for Experimental Biology. 2009; 23: 1041–1053. https://doi.org/10.1096/fj.08-121962
[39] Graßmann S, Pivovarova-Ramich O, Henze A, Raila J, Ampem Amoako Y, King Nyamekye R, et al. SNP rs6564851 in the BCO1 Gene Is Associated with Varying Provitamin a Plasma Concentrations but Not with Retinol Concentrations among Adolescents from Rural Ghana. Nutrients. 2020; 12: 1786. https://doi.org/10.3390/nu12061786
[40] Georgiou M, Fujinami K, Robson AG, Fujinami-Yokokawa Y, Shakarchi AF, Ji MH, et al. RBP3-Retinopathy-Inherited High Myopia and Retinal Dystrophy: Genetic Characterization, Natural History, and Deep Phenotyping. American Journal of Ophthalmology. 2024; 258: 119–129. https://doi.org/10.1016/j.ajo.2023.09.025
[41] Kamm DR, McCommis KS. Hepatic stellate cells in physiology and pathology. The Journal of Physiology. 2022; 600: 1825–1837. https://doi.org/10.1113/JP281061
[42] Pirazzi C, Valenti L, Motta BM, Pingitore P, Hedfalk K, Mancina RM, et al. PNPLA3 has retinyl-palmitate lipase activity in human hepatic stellate cells. Human Molecular Genetics. 2014; 23: 4077–4085. https://doi.org/10.1093/hmg/ddu121
[43] Lulić AM, Katalinić M. The PNPLA family of enzymes: characterisation and biological role. Arhiv Za Higijenu Rada i Toksikologiju. 2023; 74: 75–89. https://doi.org/10.2478/aiht-2023-74-3723
[44] Missaglia S, Coleman RA, Mordente A, Tavian D. Neutral Lipid Storage Diseases as Cellular Model to Study Lipid Droplet Function. Cells. 2019; 8: 187. https://doi.org/10.3390/cells8020187
[45] Liu M, Park S. The Role of *PNPLA3*_rs738409 Gene Variant, Lifestyle Factors, and Bioactive Compounds in Nonalcoholic Fatty Liver Disease: A Population-Based and Molecular Approach towards Healthy Nutrition. Nutrients. 2024; 16: 1239. https://doi.org/10.3390/nu16081239
[46] Mignone LI, Giovannucci E, Newcomb PA, Titus-Ernstoff L, Trentham-Dietz A, Hampton JM, et al. Dietary carotenoids and the risk of invasive breast cancer. International Journal of Cancer. 2009; 124: 2929–2937. https://doi.org/10.1002/ijc.24334
[47] Peng C, Zeleznik OA, Shutta KH, Rosner BA, Kraft P, Clish CB, et al. A Metabolomics Analysis of Circulating Carotenoids and Breast Cancer Risk. Cancer Epidemiology, Biomarkers & Prevention : a Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology. 2022; 31: 85–96. https://doi.org/10.1158/1055-9965.EPI-21-0837
[48] Black HS, Boehm F, Edge R, Truscott TG. The Benefits and Risks of Certain Dietary Carotenoids that Exhibit both Anti- and Pro-Oxidative Mechanisms-A Comprehensive Review. Antioxidants (Basel, Switzerland). 2020; 9: 264. https://doi.org/10.3390/antiox9030264
[49] Van Asten K, Slembrouck L, Olbrecht S, Jongen L, Brouckaert O, Wildiers H, et al. Prognostic Value of the Progesterone Receptor by Subtype in Patients with Estrogen Receptor-Positive, HER-2 Negative Breast Cancer. The Oncologist. 2019; 24: 165–171. https://doi.org/10.1634/theoncologist.2018-0176
[50] Wang Y, Gapstur SM, Gaudet MM, Furtado JD, Campos H, McCullough ML. Plasma carotenoids and breast cancer risk in the Cancer Prevention Study II Nutrition Cohort. Cancer Causes Control. 2015;26:1233–1244. https://doi.org/10.1007/s10552-015-0614-4
[51] Bakker MF, Peeters PH, Klaasen VM, Bueno-de-Mesquita HB, Jansen EH, Ros MM, et al. Plasma carotenoids, vitamin C, tocopherols, and retinol and the risk of breast cancer in the European Prospective Investigation into Cancer and Nutrition cohort. Am J Clin Nutr. 2016;103:454–464. https://doi.org/10.3945/ajcn.114.101659
[52] Eliassen AH, Hendrickson SJ, Brinton LA, Buring JE, Campos H, Dai Q, et al. Circulating carotenoids and risk of breast cancer: pooled analysis of eight prospective studies. Journal of the National Cancer Institute. 2012; 104: 1905–1916. https://doi.org/10.1093/jnci/djs461
[53] Sanlier N, Yildiz E, Ozler E. An Overview on the Effects of Some Carotenoids on Health: Lutein and Zeaxanthin. Current Nutrition Reports. 2024; 13: 828–844. https://doi.org/10.1007/s13668-024-00579-z
[54] Prakash P, Russell RM, Krinsky NI. In vitro inhibition of proliferation of estrogen-dependent and estrogen-independent human breast cancer cells treated with carotenoids or retinoids. The Journal of Nutrition. 2001; 131: 1574–1580. https://doi.org/10.1093/jn/131.5.1574
[55] Tamimi RM, Hankinson SE, Campos H, Spiegelman D, Zhang S, Colditz GA, et al. Plasma carotenoids, retinol, and tocopherols and risk of breast cancer. American Journal of Epidemiology. 2005; 161: 153–160. https://doi.org/10.1093/aje/kwi030
[56] Dorjgochoo T, Gao YT, Chow WH, Shu XO, Li H, Yang G, et al. Plasma carotenoids, tocopherols, retinol and breast cancer risk: results from the Shanghai Women Health Study (SWHS). Breast Cancer Research and Treatment. 2009; 117: 381–389. https://doi.org/10.1007/s10549-008-0270-4
[57] Eliassen AH, Liao X, Rosner B, Tamimi RM, Tworoger SS, Hankinson SE. Plasma carotenoids and risk of breast cancer over 20 y of follow-up. The American Journal of Clinical Nutrition. 2015; 101: 1197–1205. https://doi.org/10.3945/ajcn.114.105080
[58] Peng C, Gao C, Lu D, Rosner BA, Zeleznik O, Hankinson SE, et al. Circulating carotenoids and breast cancer among high-risk individuals. The American Journal of Clinical Nutrition. 2021; 113: 525–533. https://doi.org/10.1093/ajcn/nqaa316
[59] Yan B, Lu MS, Wang L, Mo XF, Luo WP, Du YF, et al. Specific serum carotenoids are inversely associated with breast cancer risk among Chinese women: a case-control study. The British Journal of Nutrition. 2016; 115: 129–137. https://doi.org/10.1017/S000711451500416X
[60] Darouei B, Bohn T, Vahid F, Amani-Beni R, Haghjooy Javanmard S, Zendehdel K, et al. Dietary carotenoids and breast cancer risk: evidence from a large population-based incident case-control study. Nutrition & Metabolism. 2025; 22: 107. https://doi.org/10.1186/s12986-025-01007-x
[61] Dehnavi MK, Ebrahimpour-Koujan S, Lotfi K, Azadbakht L. The Association between Circulating Carotenoids and Risk of Breast Cancer: A Systematic Review and Dose-Response Meta-Analysis of Prospective Studies. Advances in Nutrition (Bethesda, Md.). 2024; 15: 100135. https://doi.org/10.1016/j.advnut.2023.10.007
[62] Bohn T. Carotenoids and Markers of Oxidative Stress in Human Observational Studies and Intervention Trials: Implications for Chronic Diseases. Antioxidants (Basel, Switzerland). 2019; 8: 179. https://doi.org/10.3390/antiox8060179
[63] Wang K, Mendy AJ, Dai G, Luo HR, He L, Wan YJY. Retinoids activate the RXR/SXR-mediated pathway and induce the endogenous CYP3A4 activity in Huh7 human hepatoma cells. Tox-

icological Sciences : an Official Journal of the Society of Toxicology. 2006; 92: 51–60. https://doi.org/10.1093/toxsci/kfj207
[64] Peng Y, Wang Y, Zhou C, Mei W, Zeng C. PI3K/Akt/mTOR Pathway and Its Role in Cancer Therapeutics: Are We Making Headway? Frontiers in Oncology. 2022; 12: 819128. https://doi.org/10.3389/fonc.2022.819128
[65] Lu N, Malemud CJ. Extracellular Signal-Regulated Kinase: A Regulator of Cell Growth, Inflammation, Chondrocyte and Bone Cell Receptor-Mediated Gene Expression. International Journal of Molecular Sciences. 2019; 20: 3792. https://doi.org/10.3390/ijms20153792
[66] Karfa S, Saurav S, Feng B, Li S, Law BK, Datta PK. The Role of Serine-Threonine Kinase Receptor-Associated Protein (STRAP) Signaling in Cancer. Cells. 2025; 14: 854. https://doi.org/10.3390/cells14120854
[67] Mohammad RM, Muqbil I, Lowe L, Yedjou C, Hsu HY, Lin LT, et al. Broad targeting of resistance to apoptosis in cancer. Seminars in Cancer Biology. 2015; 35 Suppl: S78–S103. https://doi.org/10.1016/j.semcancer.2015.03.001
[68] Li Q, Li Z, Luo T, Shi H. Targeting the PI3K/AKT/mTOR and RAF/MEK/ERK pathways for cancer therapy. Molecular Biomedicine. 2022; 3: 47. https://doi.org/10.1186/s43556-022-00110-2
[69] Novoselova EG, Khrenov MO, Glushkova OV, Lunin SM, Parfenyuk SB, Novoselova TV, et al. Anti-inflammatory effects of IKK inhibitor XII, thymulin, and fat-soluble antioxidants in LPS-treated mice. Mediators of Inflammation. 2014; 2014: 724838. https://doi.org/10.1155/2014/724838
[70] Kaloni D, Diepstraten ST, Strasser A, Kelly GL. BCL-2 protein family: attractive targets for cancer therapy. Apoptosis : an International Journal on Programmed Cell Death. 2023; 28: 20–38. https://doi.org/10.1007/s10495-022-01780-7
[71] Qian S, Wei Z, Yang W, Huang J, Yang Y, Wang J. The role of BCL-2 family proteins in regulating apoptosis and cancer therapy. Frontiers in Oncology. 2022; 12: 985363. https://doi.org/10.3389/fonc.2022.985363
[72] Ávila-Román J, García-Gil S, Rodríguez-Luna A, Motilva V, Talero E. Anti-Inflammatory and Anticancer Effects of Microalgal Carotenoids. Marine Drugs. 2021; 19: 531. https://doi.org/10.3390/md19100531
[73] Lee J, Lim JW, Kim H. Astaxanthin Inhibits Matrix Metalloproteinase Expression by Suppressing PI3K/AKT/mTOR Activation in *Helicobacter pylori*-Infected Gastric Epithelial Cells. Nutrients. 2022; 14: 3427. https://doi.org/10.3390/nu14163427
[74] Teodoro AJ, Oliveira FL, Martins NB, Maia GDA, Martucci RB, Borojevic R. Effect of lycopene on cell viability and cell cycle progression in human cancer cell lines. Cancer Cell International. 2012; 12: 36. https://doi.org/10.1186/1475-2867-12-36
[75] Qiu X, Yuan Y, Vaishnav A, Tessel MA, Nonn L, van Breemen RB. Effects of lycopene on protein expression in human primary prostatic epithelial cells. Cancer Prevention Research (Philadelphia, Pa.). 2013; 6: 419–427. https://doi.org/10.1158/1940-6207.CAPR-12-0364
[76] Wang J, Ma Y, Yang J, Jin L, Gao Z, Xue L, et al. Fucoxanthin inhibits tumour-related lymphangiogenesis and growth of breast cancer. Journal of Cellular and Molecular Medicine. 2019; 23: 2219–2229. https://doi.org/10.1111/jcmm.14151
[77] Adams JM, Cory S. The Bcl-2 apoptotic switch in cancer development and therapy. Oncogene. 2007; 26: 1324–1337. https://doi.org/10.1038/sj.onc.1210220
[78] Uti DE, Atangwho IJ, Alum EU, Ntaobeten E, Obeten UN, Bawa I, et al. Antioxidants in cancer therapy mitigating lipid peroxidation without compromising treatment through nanotechnology. Discover Nano. 2025; 20: 70. https://doi.org/10.1186/s11671-025-04248-0
[79] Eid SY, Althubiti MA, Abdallah ME, Wink M, El-Readi MZ. The carotenoid fucoxanthin can sensitize multidrug resistant cancer cells to doxorubicin via induction of apoptosis, inhibition of multidrug resistance proteins and metabolic enzymes. Phytomedicine : International Journal of Phytotherapy and Phytopharmacology. 2020; 77: 153280. https://doi.org/10.1016/j.phymed.2020.153280
[80] Sridhar K, Inbaraj BS, Chen BH. Recent Advances on Nanoparticle Based Strategies for Improving Carotenoid Stability and Biological Activity. Antioxidants (Basel, Switzerland). 2021; 10: 713. https://doi.org/10.3390/antiox10050713
[81] Soukoulis C, Bohn T. A comprehensive overview on the micro- and nano-technological encapsulation advances for enhancing the chemical stability and bioavailability of carotenoids. Critical Reviews in Food Science and Nutrition. 2018; 58: 1–36. https://doi.org/10.1080/10408398.2014.971353
[82] Dos Santos PP, Andrade LDA, Flôres SH, Rios ADO. Nanoencapsulation of carotenoids: a focus on different delivery systems and evaluation parameters. Journal of Food Science and Technology. 2018; 55: 3851–3860. https://doi.org/10.1007/s13197-018-3316-6
[83] Rehman A, Tong Q, Jafari SM, Assadpour E, Shehzad Q, Aadil RM, et al. Carotenoid-loaded nanocarriers: A comprehensive review. Advances in Colloid and Interface Science. 2020; 275: 102048. https://doi.org/10.1016/j.cis.2019.102048
[84] Dhiman R, Bazad N, Mukherjee R, Himanshu, Gunjan, Leal E, et al. Enhanced drug delivery with nanocarriers: a comprehensive review of recent advances in breast cancer detection and treatment. Discover Nano. 2024; 19: 143. https://doi.org/10.1186/s11671-024-04086-6
[85] Huang H, Shi H, Liu J, Min Y, Wang Y, Wang AZ, et al. Co-delivery of all-trans-retinoic acid enhances the anti-metastasis effect of albumin-bound paclitaxel nanoparticles. Chemical Communications (Cambridge, England). 2017; 53: 212–215. https://doi.org/10.1039/c6cc08146k