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Review Article

Oncology Section

Importance of Retinoic Acid Derivatives in Breast Cancer: A Literature Review

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ABSTRACT

Due to its specific accumulation in breast tissue and lower hazardous effects, Retinoic Acid (RA) has become increasingly popular in the treatment of Breast Cancer (BC). RA modulates the proliferative activity of BC cells and aids in the redifferentiation of cancer cells into normal breast epithelial cells. The HOXA5 regulates RA (homeobox A5) gene through Retinoic Acid Receptors (RAR) and Retinoid X Receptors (RXR) (-α, -β and -γ) and governs numerous cellular processes, including cellular metabolism and both primary and secondary programmed cell death. RA impairs oestrogen signalling in BC by activating Lysine-Specific histone Demethylase 1 (LSD1) proteins. RA downregulates the survivin protein when combined with other drugs like tamoxifen, taxol and interferon, thereby sensitising BC cells and promoting the progression of cell death. Through cadherin-mediated junction formation, RA regulates mammary gland homeostasis, causing BC cells to undergo lactogenic differentiation, which results in an epithelial phenotype. In the third phase of a mammary carcinoma prevention trial, retinoids reduce the incidence of second BC in older women by modulating the levels of Insulin-like Growth Factor (IGF-I) and Insulin-Like Growth Factor Binding Protein (IGFBP-3), which is its main binding protein, both of which have been connected to an increased risk of BC. Women taking tamoxifen with fenretinide experience a significantly lower rate of hot flashes compared to those taking tamoxifen alone. All-Trans Retinoic Acid (ATRA) reduces the hypercoagulation markers when taken alongside tamoxifen; hence, this combination is recommended for preoperative BC patients. RA derivatives combined with immunotherapy delay the recurrence of BC by increasing lymphocytes and natural killer cells. Targeting Breast Cancer Stem Cells (BCSC) is an effective strategy for BC management, with retinoids acting against BC by targeting BCSC. Thus, RA may help prevent chemotherapy resistance and reduce the recurrence of BC in multiple ways; still, further research is essential for an in-depth understanding of RA and BC.

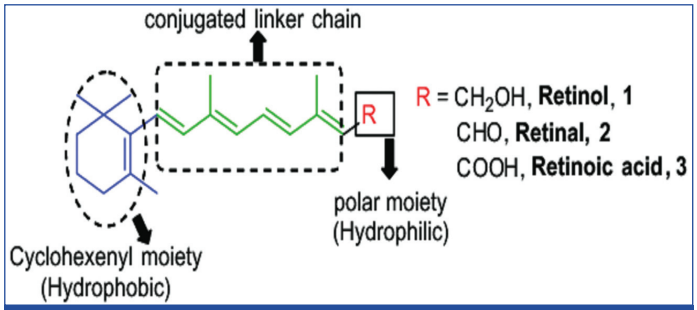
Keywords: Lysine-specific histone demethylase 1 proteins, Retinoic acid receptor, Retinoid X receptor, Survivin protein

INTRODUCTION

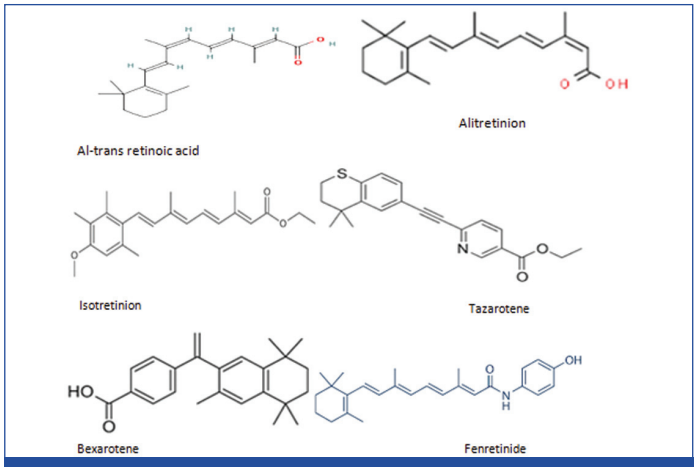
The RA (a vitamin A derivative) is involved in processes such as cellular proliferation, modification, embryogenesis, programmed cell death, the formation of neural cells, immune function and regulating skin functions, which include epidermal keratinisation, reducing inflammation, decreasing wrinkle formation, providing a rosy texture to the skin, fading age spots and unclogging pores [1]. The development of organs such as the liver, eyes, heart, kidneys, limbs, and intestine also requires the contribution of retinoids. Since retinoids play a significant role in eye development, they are used to treat a condition known as "night blindness." Retinoids cannot be synthesised by mammals; thus, they must be obtained from external sources such as meat, eggs, dairy products (milk, cheese, butter, etc.,), and other non vegetable items in general, or processed from vitamin A. Retinyl palmitate is the initial form of vitamin A, which is further metabolised to retinol and subsequently to RA. RA is a well-established compound for treating cancer [2]; therefore, it is essential to study its structure.

Structure of Retinoic Acid (RA)

Every retinoid, including RA, is formed by three components: a polar portion (carboxylic acid terminal), a bulky hydrophobic region (trimethylated cyclohexane ring), and a conjugated tetraene side chain [Table/Fig-1] [3]. RA exists in multiple isomeric forms, each performing various functions upon binding to receptors. Some retinoids are naturally occurring, while others can be synthesised. 9-cis RA (alitretinoin), ATRA, isotretinoin, tazarotene, bexarotene, etretinate and fenretinide are some of the isomers of retinoids [3] [Table/Fig-2]. RA exerts its effects through specific receptors, namely the RXR and the RAR [4]. Upon ligand binding, these receptors function as ligand-dependent transcription factors and can assemble into heterodimers to activate their downstream targets by binding to RA Response Elements (RARE), which is considered the classical or genomic pathway of RA. This pathway



[Table/Fig-1]: Structure of retinoic acid [3].



[Table/Fig-2]: Structure of retinoic acid isomers [3].

stimulates cell differentiation, halts the cell cycle, and ultimately induces programmed cell death [5].

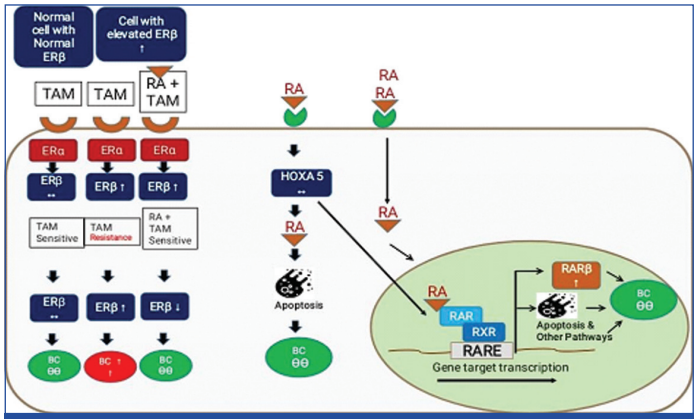
Epidemiology of Breast Cancer (BC)

The BC affects more females worldwide than any other type of carcinoma, accounting for 11.9% of all carcinoma cases. It is projected to overtake pulmonary cancer as the primary cause of cancer incidence globally in 2020 [6]. According to epidemiological studies, there will be approximately two million BC cases worldwide by the year 2030, and by 2050, new cases and deaths are expected to increase by 38% and 68%, respectively [7-9]. In India, the cervix was the primary site of cancer in 1990. However, by the years 2000-2003, the situation had changed, and all cancer registries now list BC as the most common site of the disease, with the exception of some suburban registries [10]. In major cities of India, such as Chennai, Delhi and Mumbai, there has been a noticeable rising trend in BC registrations [11]. In India, there were 536,000 prevalent cases (ranging from 474,000 to 584,000) and an estimated 118,001 incident cases (95% confidence interval: 107,000-130,000) in 2016, with 97.9% of the incident cases occurring in females [12]. The age-standardised incidence rates of BC in women increased by 39.1% from 1990 to 2016 (96% confidence interval: 5.1 to 85.6), with this rise observed across all states of the union [13]. According to Globocan figures for 2020, BC had a cumulative risk of 2.81 and was responsible for 10.6% (90,408) of all fatalities and 13.5% (178,361) of all cancer cases in India. The estimated number of BC cases in the state of Maharashtra was 14,726, 15,522 and 16,358 in the years 2016, 2017, and 2018, respectively [14].

Retinoic Acid (RA) and Breast Cancer (BC)

The RA is extensively used to prevent and treat cancer due to its anticancer, anti-inflammatory and receptor-binding properties [15]. Generally, RA acts as an attacker against cancerous cells in the body. It helps differentiate the cells, blocks their growth and induces apoptosis. As the number of cancerous cells increases, RA can combine with other drugs to form chemotherapeutic agents to combat them. A RA-binding protein is crucial in the fight against BC cells. RA modulates the proliferative activity of BC cells, redifferentiating breast epithelial cells that have been transformed into cancerous cells and preventing further cell transformation in the body [16].

HOXA5 (homeobox A5) is the protein-coding gene regulated by RA through the RAR, which induces programmed cell death in BC [Table/Fig-3] [17].



[Table/Fig-3]: RA mechanism of action in Breast Cancer [17].
TAM: Tamoxifen; ERβ: Oestrogen receptor beta; RA: Retinoic acid; RAR: Retinoic acid receptor; RARE: Retinoic acid response element

Aldehyde dehydrogenase 1A3 (ALDH1A3) promotes the growth of BC through various signalling pathways. RA regulates these signals and helps to prevent the metastasis of BC. Additionally, RA exhibits alterations in oestrogen signalling through the activation of LSD1, which controls gene expression as a transcriptional repressor or activator via cyclic Adenosine Monophosphate (cAMP)-dependent protein kinase in breast carcinoma [18,19]. In combination with other drugs such as tamoxifen, taxol and interferon, RA downregulates survivin through its synergistic effects, which sensitises BC cells and promotes the progression of mitosis, leading to apoptosis [20]. In breast tumour cells, the sensitivity to RA can be enhanced and restored by curcumin, which also shows efficacy in triple-negative breast tumour cells [21].

Tumour-associated cells are known to be inhibited and differentiated by ATRA, thus acting as an antitumour agent. It can also initiate secondary apoptosis if apoptotic cells are not removed by phagocytic cells. ATRA regulates mammary gland homeostasis, causing BC cells to differentiate into lactogenic cells and facilitating cadherin-mediated junction formation to generate an epithelial-like phenotype [22]. RA interacts with the protein kinase C system, which might be a probable mechanism of RA; hence, ATRA combined with PKC inhibitors could be an effective strategy against hormone-independent BC proliferation [23].

Standard BC cell lines, such as MCF-7 and CAL-51, are highly sensitive to RA and show significant cytotoxic and morphological changes compared to normal cell lines like HBL-100. RA's effects on other local BC cell lines, such as AMK 13 (an Iraqi woman-derived breast cell line), indicate that RA is more sensitive than other international BC cell lines [24].

RA mechanism of inhibition of BC: By activating and/or suppressing specific genes, retinoids can prevent the growth of tumours and alter some characteristics of fully transformed malignant cells. RA exhibits both direct and indirect inhibitory effects on malignant BC cells by engaging numerous signal transduction pathways and influencing gene expression. Many cellular processes, such as development, differentiation, and apoptosis, are regulated by the binding of retinoids to nuclear receptors known as RXR and RAR. Each of these receptors has three types, named α, β, and γ, which act as transcription factors triggered by ligands [25].

The prevention of breast tumour cell proliferation accelerated by RA is attributed to the upregulation of RAR-β expression [Table/Fig-3]. This may play a significant role in tumour suppression. In contrast, RAR-β appears to be increased in healthy mammary epithelial cells and seems to be downregulated in BC cell lines and tissues [26].

Relationship between Oestrogen Receptors (ER) and RA receptors: A nuclear receptor called RARα typically binds to RAREs. RARα can bind to chromatin whether its natural ligands, 9-cis RA or ATRA, are present or not [27]. Furthermore, RARα has the ability to bind to several nuclear receptors, including the thyroid receptor [28].

The expression of the oestrogen-induced gene RARα in breast tumours has been found to correlate with the expression of the ER [27]. It has been demonstrated that RARα and ER share a subset of genomic binding sites and that RARα can inhibit ER function in the presence of its ligands, and vice versa. There is competition between the two nuclear receptors for transcriptional activity and RARα and ER may occasionally share cis-regulatory regions [28]. For BC cells to efficiently engage in transcription, various nuclear receptors may cooperate with RARα as a key component of the ER complex, possibly by maintaining ER-co-factor interactions [29].

ERα-expressing tissues include the pituitary, vagina, uterus and breast, while ERβ-expressing tissues include the ovary, prostate and lung. There has been ongoing discussion regarding the significance of ERβ in mammary development and carcinogenesis because it is present in the breast, albeit at lower concentrations than ERα [30]. The expression of ERα varies depending on the stage of development of the mammary gland; however, 55% to 75% of breast epithelial cells express ERβ at all stages of breast development [31].

When BC first appears, an analysis of the ERα to ERβ ratio shifts. Individuals who have relapsed and are resistant to tamoxifen show higher expression of ERβ [32]. Most attention in clinical strategies for treating hormonally responsive BC has been focused on ERα and its target genes. However, resistance to tamoxifen has limited this strategy, and other treatments targeting different signalling pathways are required to combat resistance. The expansion and proliferation of ERβ in breast tumour cells can be inhibited by RA [33-35].

RAR expression has been significantly improved in gastric cancer patients; thus, RAR overexpression may serve as a diagnostic tool in gastric cancer [36]. Similarly, RAR overexpression in breast tissue may be an alarming sign for the manifestation of BC.

Safety and tolerability of RA derivative: According to a thorough review of the phase III trial, decreased dark adaptation (cumulative incidence: 19%) and dermatological conditions such as itchiness, urticaria and dryness of the skin and mucous membranes (18.6%) were the most frequent side-effects [37]. Gastrointestinal problems (13%) and changes to the ocular surface (10.9%) were less frequently reported. In the control group, decreased dark adaptation, dermatological illnesses, digestive problems and alterations to the ocular surface were reported in 2.9%, 5.4% and 3.2% of cases, respectively.

Interestingly, it was noted that adverse effects diminished most of the time and were significantly more prevalent in postmenopausal women. However, there were no events that could have been fatal, and only 64 of 1,435 females (4.4%) discontinued treatment due to medication toxicity [38]. In a study addressing this issue, chronic administration of fenretinide (a synthetic retinoid derivative) was not shown to be linked with appreciable changes in the bone mineral density of the forearm [39]. Patients with modifications to the Goldmann weekers test showed a low rate of complaints regarding decreased dark adaptation [40]. Older and heavier women experienced a greater reduction in retinol induced by fenretinide and were consequently more likely to report ocular complaints [41].

RA derivatives role in other disease conditions: High-affinity RAR ligand (LGD 1550) activates RARs and inhibits activator protein-1. It is relatively well tolerated in patients, with few adverse reactions and shows modest activity in cervical cancer and epidermoid cancer. TAC-101, a selective retinoid for the RAR alpha, has been shown to be toxic to the musculoskeletal system and to cause hypertriglyceridaemia and an increased thrombotic risk in human trials [42].

Topical application of retinol and RA exhibits a remarkable antiageing effect on the face by altering the histology of the skin and the expression of genes and proteins associated with skin health. The mechanisms of action of retinol and RA show a similar pathway [43]. In patients with pancreatic cancer, ATRA acts as a stromal-targeting drug alongside gemcitabine and nab-paclitaxel. It is well tolerated and has a dose-limiting hazard of grade 4 thrombocytopenia [44].

In a controlled study of patients treated for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), 13-cis RA and the recommended treatment protocol significantly reduced mortality and the need for Intensive Care Unit (ICU) care [45]. Retinoids lower the recurrence rate and sensitise therapeutic modalities used for various other carcinomas, including hepatocellular carcinoma, lung cancer, Kaposi's sarcoma, renal cell carcinoma and acute promyelocytic leukaemia [46].

BC and RA clinical studies: Due to their well-known role in regulating cellular metabolism and programmed cell death in in-vitro research, retinoids have been investigated as potential antitumour medications in clinical trials [47]. One distinctive characteristic of retinoids is their ability to accelerate programmed cell death. Retinoids are most frequently studied in clinical trials for BC due to their unique accumulation effect in breast tissue and their comparatively safer profile. In a phase III trial aimed at BC prevention, retinoids were found to modify the levels of circulating IGF-I and IGFBP-3 in premenopausal women, thereby reducing their risk of developing a second case of BC. Both IGF-I and IGFBP-3 have been linked to an increased risk of BC in premenopausal women in various prospective studies [48-50].

The retinoid that has garnered the most attention in clinical studies for chemoprevention is N-(4-hydroxyphenyl) retinamide (4-HPR) fenretinide, a synthetic amide of retinoic acid. Sporn MB et al., examined the biological effects of fenretinide shortly after its creation in the late 1960s [47]. A study demonstrated that this medication preferentially accumulates in the breast rather than in the liver [51]. Fenretinide was initially reported to inhibit chemically induced BC in rats in 1979 [52]. Clinical trials using fenretinide in combination with tamoxifen have shown that this combination appears to be safe and well tolerated in high-risk women, particularly when minimal doses of tamoxifen are used [53]. According to a phase I dose-ranging study, the safe upper limit has been established as 200 mg per day [53].

The National Cancer Institute (NCI) organised a multicentre phase III randomised study with stage I BC patients aged between 35 and 70 years who had undergone surgery for the disease within the previous 10 years without receiving multimodal systemic therapy. Women were randomly assigned to receive either no therapy or a daily dose of 200 mg of a synthetic retinoic acid derivative orally over the course of five years [53]. The onset of contralateral BC and the recurrence of ipsilateral BC were the first and second malignant events, respectively. Findings from an average follow-up of 96 months concluded that fenretinide was significantly more effective for premenopausal women than for postmenopausal women, with no statistically significant difference in hormone receptor-positive and negative BCs [54].

Fenretinide had no impact on the development of contralateral breast tumours and resulted in a negligible 17% decrease in the occurrence of ipsilateral breast tumours. Distant metastases and death were not affected by fenretinide treatment, either overall or in the two categories separately [54]. There was no appreciable overgrowth of a particular tumour in either therapy group [54]. Three cases of ovarian tumours manifested in the fenretinide group after therapy was withdrawn, but there were zero cases during the five-year follow-up period in the fenretinide arm compared to six cases in the control group [55]. An update on fenretinide's impact on ovarian cancer has been provided [56]. Six incidences of ovarian cancer were reported overall in the fenretinide group after a median of 121 months, compared to 10 cases in the control arm. To clarify this and possibly establish a substantial therapeutic effect of fenretinide, more clinical trials are required [57].

Fenretinide may be used as a preventive drug at various phases of breast carcinogenesis, according to the data from the phase III trial. However, the study also demonstrates its inability to halt the emergence of a more malignant phenotype, most likely due to the reduction in retinoid receptor expression [58]. According to a study, the beneficial trend in contralateral breast tumours and ipsilateral breast tumour recurrence in premenopausal females appears to persist after follow-up observations of up to 15 years [59]. This establishes a justification for a phase III primary prevention trial in young women prone to BC.

Trials in synthetic RA and tamoxifen: Contrary to mono-chemotherapy, drug combinations used in poly-chemotherapy are more effective. Similarly, in the fight against BC, research is being conducted on the combination of drugs with different modes of action in an effort to increase efficacy while minimising negative effects. Fenretinide and tamoxifen administered together have been shown in preclinical models to have complementary or synergistic effects in inhibiting the development of MCF-7 cells [60].

In BC clinical studies, the combination of tamoxifen and fenretinide has been tested for safety and tolerability in individuals with metastatic disease [61], in the adjuvant setting [62], and in healthy women at higher risk [62]. A pilot study conducted in 1999 assessed individuals with metastatic BC who had previously received tamoxifen treatment or who had hormone receptor-negative disease for their response to the combination of fenretinide (400 mg daily for 20 out of 26 days) and tamoxifen (a regular dose of 20 mg) [63]. Of the 32 patients who could be analysed, 24 showed no measurable responses to malignancy [63].

One-third of the treated individuals experienced symptomatic nyctalopia and five patients (16%) discontinued treatment due to toxicity [63]. Upon detailed observation, it was shown that in this group of individuals with advanced disease, the combination was unsuccessful, and studies on prevention should not utilise a fenretinide dosage of 400 mg [63]. The high rate of withdrawals (30%) observed in a clinical study of fenretinide (400 mg/day) plus tamoxifen against a placebo and tamoxifen as adjuvant treatment in older women with BC has raised additional concerns about the viability of this combination [63]. In that study, women taking tamoxifen and fenretinide experienced a borderline significantly lower rate of hot flashes compared to those taking tamoxifen and a placebo; however, the combined arm had a greater incidence of grade I–II leucopenia, nyctalopia, hypercalcaemia and genitourinary and respiratory adverse events. Women who have not yet reached menopause and have elevated IGF-I levels in their blood had a higher chance of developing primary [63,64] and secondary [65] BC. In high-risk older women, fenretinide causes a moderate reduction in IGF-I levels. Various clinical studies involving RA derivatives and their combination with other anticancer drugs are summarised in the table [Table/Fig-4] [66-72].

Future scope in BC managments with retinoids: The BCSCs are a key factor responsible for the manifestation, prognosis, metastasis and therapeutic resistance of BC. This small population of cells, present within the heterogeneous cellular population of BC cells, remains active even after exposure to major chemotherapeutic agents and is responsible for the recurrence of BC cells [73,74]. Targeting BCSCs is an effective strategy for BC management [75]. Adapalene, a third-generation retinoid, acts against BC by targeting BCSCs, potentially helping to prevent chemoresistance [76,77]. This recent finding accelerates research into retinoid derivatives as future therapeutic agents in BC management.

S. No.	Drug	Finding
1	All trans Retinoic Acid (RA)+paclitaxel	The use of ATRA and paclitaxel in combination therapy for metastatic BC demonstrates that this is a regimen that is well-tolerated and has low response rates. Duration of the progression and mortality rates comparable to those for paclitaxel and placebo show similar effect with ATRA combination. Data revels that comparatively significant percentages of patients had stable disease [66].
2	Alitretinoin (9-cis-RA)+tamoxifen	The outcome of the preliminary clinical trial demonstrates that the combination of tamoxifen and alitretinoin is safe and effective in treating metastatic BC. 70 mg/m^2/d of tamoxifen combined with 20 mg/d of phase II dosage is advised [67].
3	Tamoxifen (TAM)+13- Cis-Retinoic Acid (CRA) vs Tamoxifen+Interferon alpha-2a (IFN)	The therapeutic effects of TAM in patients with advanced BC are unaffected by its administration [68].
4	ATRA added with tamoxifen versus ATRA versus tamoxifen	Hyper coagulation indicators were reduced in the ATRA+Tam groups compared to Tam alone. These findings imply that preoperative ATRA may regulate BC patients hypercoagulable states under specific circumstances [69].
5	Fenretinide, the derivative of a RA	In women over the age of 50 years, fenretinide causes a moderate drop in Insulin-Like Growth Factor-I (IGF-1) level. To ascertain the connection between IGF-I change and secondary breast tumours, more investigation is required [70].
6	ATRA+Tamoxifen	According to results from phase 1 and phase 2 chemotherapy, patients treated with tamoxifen and ATRA experienced decreases in serum levels of IGF that were similar to those reported in people on tamoxifen only. Some of the patients who had previously progressed while receiving showed objective responses [71].
7	13-cis RA and interleukin-2	In the study, natural killer cells, lymphocytes and the CD4+/CD8+ ratio all showed a steady rise over baseline levels. In conclusion, metastatic BC patients who are not responding after 5-9 sessions of drug dependent cancer therapy, biological response modifier therapy with interleukin-2 and RA is well tolerated, improves lymphocyte, natural killer cells, CD4T+/CD8+T ratio, and seems to stop the recurrence of the disease [72].

[Table/Fig-4]: Important clinical research conducted in Retinoic Acid (RA) along with other drugs for BC [66-72].

CONCLUSION(S)

A thorough evaluation of RA's involvement in the treatment and prevention of BC was conducted. It has been recognised that RA and its derivatives serve as potent tools to sensitise conventional chemotherapy and offer hope in addressing the serious, life-threatening issue known as drug resistance. Although the efficacy of RA derivatives alone presents some drawbacks, their synergistic effects encourage researchers to conduct further studies on their effectiveness. Developing new and more effective RA derivatives is essential in light of the significant increase in the number of BC cases. This review aims to accelerate research related to RA and BC to better understand the link between them.

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