Am J Cancer Res 2022;12(3):938-960
www.ajcr.us /ISSN:2156-6976/ajcr0140073

Review Article

Retinoids as anti-cancer agents and their mechanisms of action

Ying Jin[1], Soek Sin Teh[2], Harrison Lik Nang Lau[2], Jianbo Xiao[3], Siau Hui Mah[1,4]

[1]School of Biosciences, Faculty of Health and Medical Sciences, Taylor's University (Lakeside Campus), Subang Jaya, Selangor, Malaysia; [2]Energy and Environment Unit, Engineering and Processing Division, Malaysian Palm Oil Board, Kajang, Selangor, Malaysia; [3]Nutrition and Bromatology Group, Analytical and Food Chemistry Department, Faculty of Food Science and Technology, University of Vigo, Ourense Campus, Ourense, Spain; [4]Centre for Drug Discovery and Molecular Pharmacology, Faculty of Health and Medical Sciences, Taylor's University (Lakeside Campus), Subang Jaya, Selangor, Malaysia

Received October 25, 2021; Accepted January 2, 2022; Epub March 15, 2022; Published March 30, 2022

Abstract: Retinoids (vitamin A) have been reported extensively for anti-cancer properties due to their high receptor-binding affinities and gene regulation abilities. However, the anti-cancer potential of retinoids has not been reviewed in recent years. Thus, this review focused on the anti-cancer effects of retinoids and their synergistic effects with other drugs, together with their mechanisms of action in different types of cancers reported in the past five years. The retinoids were well studied in breast cancer, melanoma, and colorectal cancer. Synthetic retinoids have shown higher selectivity, stronger effectiveness, and lower toxicity than endogenous retinoids. Interestingly, the combination treatment of endogenous retinoids with chemotherapy drugs showed enhanced anti-cancer effects. The mechanisms of action reported for retinoids mainly involved the RAR/RXR signaling pathway. However, limited clinical studies were conducted in recent years. Thus, retinoids which are highly potential anti-cancer agents are worth further study in clinical, especially as a combination therapy with chemotherapy drugs.

Keywords: All-*trans*-retinoic acid, combination treatment, RAR/RXR signaling pathway, vitamin A

Introduction

Retinoids, a group of vitamin A derivatives are biosynthetically available in animals and plants, which are consumed as dietary intake by humans [1, 2]. They have been classified into endogenous and synthetic retinoids, with their structures comprised of three units, a bulky hydrophobic region of cyclic end group, a linker unit of the polyene side chain, and a polar end group [1, 2]. Literature showed that retinoids possess numerous biological activities including anti-cancer and anti-inflammatory, as well as maintenance of embryonic development, vision, immune balance, and metabolism [3, 4]. Among them, gene regulation in cancer is one of the crucial biological activities of retinoids [3]. The main anti-cancer regulators among the endogenous retinoids (**Figure 1**) are all-*trans*-retinoic acid (all-*trans*-RA), 9-*cis*-retinoic acid (9-*cis*-RA), and 13-*cis*-retinoic acid (13-*cis*-RA) which are mostly generated in the human body through the retinoid metabolism pathway [4, 5]. Besides, peretinoin, WYC-209, ST1926, bexarotene, tamibarotene, UAB30, and 6-methyl-UAB30 are synthetic retinoids (**Figure 1**) with similar structures as retinol and characterized with higher specificity and effectiveness in their anti-cancer activities than endogenous retinoids [6-9].

Cancer is a complicated and one of the most lethal diseases in the world [10]. Surgical excision, irradiation, and chemotherapy are the three main cancer treatment approaches in which the selection of these methods is depending on the type of cancer and stage of tumor progression [11]. Among them, chemotherapy is the most common drug therapy for local and metastatic cancer, which utilizes a single drug or combination of drugs to kill the rapidly-growing cancer cells in the body [11]. Nevertheless, some of the disadvantages reported include lack of drug selectivity and mul-

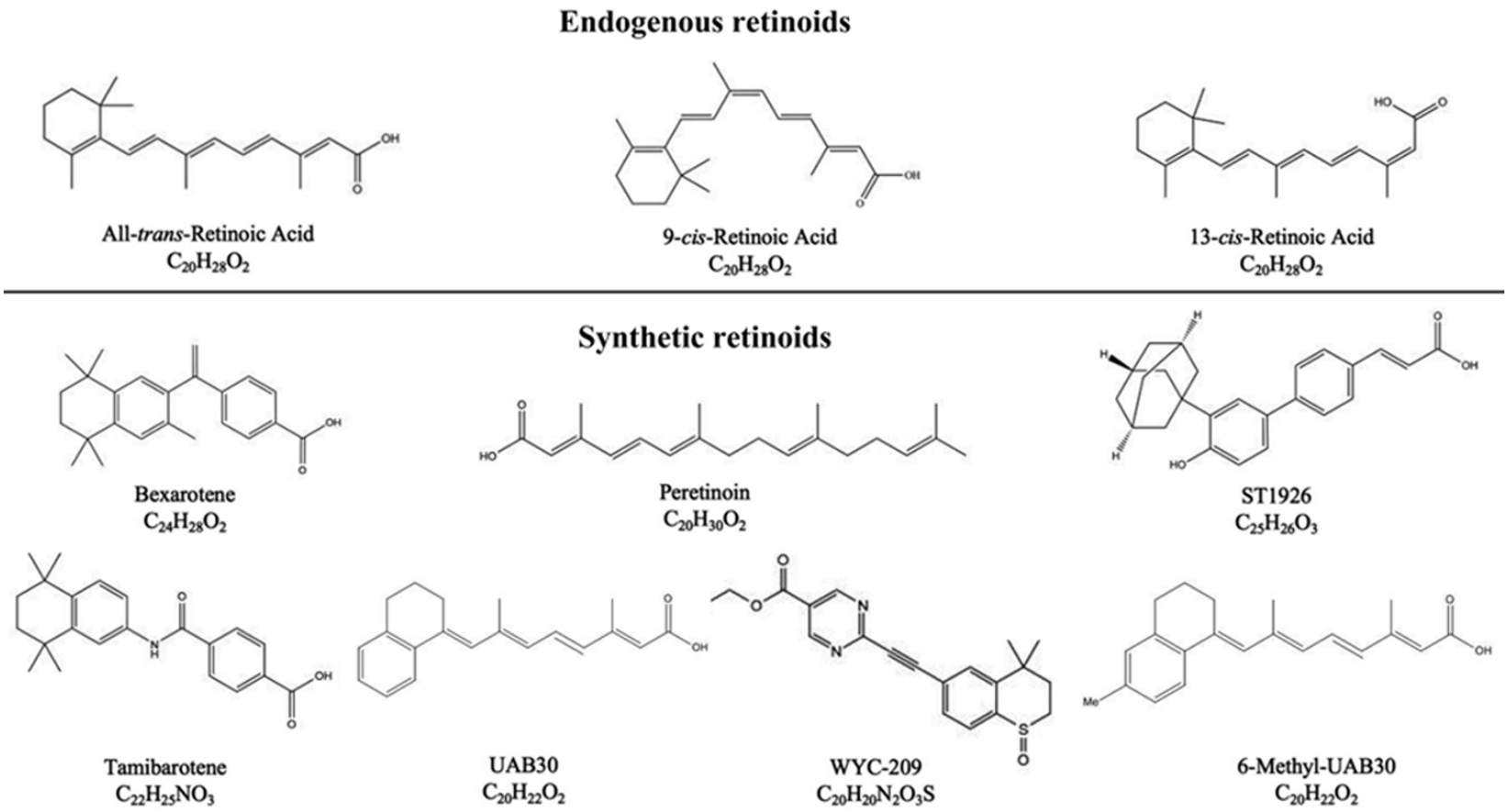

Figure 1. The chemical structures and molecular formula of endogenous and synthetic retinoids.

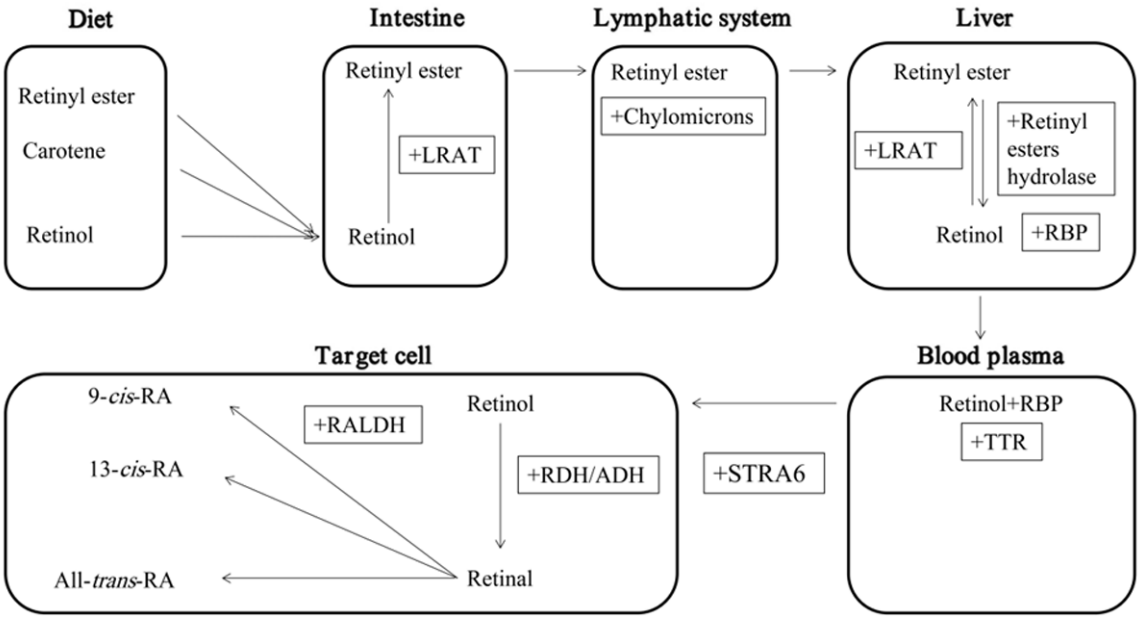

Figure 2. Retinoid metabolism pathway from the diet intake to intestine, lymphatic system, liver, blood plasma and target cell. LRAT: lecithin retinol acyltransferase; RBP: retinol-binding proteins; TTR: transthyretin; STRA6: stimulated by retinoic acid 6; RDH: retinol dehydrogenase; ADH: alcohol dehydrogenase; RALDH: retinol dehydrogenase.

tidrug resistance [11]. In the past 5 years, both endogenous and synthetic retinoids have been reported to act as chemotherapy agents through *in vitro* and *in vivo* studies, as well as some human clinical trials. Furthermore, the combination chemotherapy of retinoids with other drugs is used to overcome drug resistance and drug toxicity by decreasing the drug dosage [12, 13]. This review summarized the retinoids were used, either alone or in combination with other chemotherapy drugs, against breast cancer [14], melanoma [15], colorectal cancer [16], hepatocellular carcinoma [17], neuroblastoma [5], cutaneous T-cell lymphoma [18], glioma [19], lung cancer [20], prostate cancer [21], gastric cancer [22], thyroid cancer [23] and pancreatic cancer [24] both *in vitro and in vivo*, including human clinical trials. The mechanisms of action of retinoids in anticancer activities involving seventeen signaling pathways were also discussed in this review. Besides that, the anti-cancer effect of retinoids was found to associate with the regulation of mitochondrial function [14], microRNAs [17], and tumor stem cells [22].

Endogenous and synthetic retinoids

Endogenous retinoids

Natural endogenous retinoids have been isolated from plants or animals even though they can be found commercially available through the synthesis routes [25, 26]. The isolated retinoids exhibited different biological properties from the retinoids containing plants due to synergistic and antagonistic effects of the other components in the plants [25, 26]. As shown in **Figure 2**, all-*trans*-RA, 9-*cis*-RA, and 13-*cis*-RA are the retinoid derivatives produced from the retinoid-containing diets through the retinoid metabolism pathway. Retinyl ester, carotenoids, and retinol enter the small intestine through dietary intake are converted into retinol [27]. The retinol produced in the intestine will be re-esterified by lecithin retinol acyltransferase (LRAT) into retinyl ester [28], which binds to chylomicrons in the lymphatic system and is transferred into the liver [29]. The retinyl ester is subsequently hydrolyzed by retinyl ester hydrolase to form retinol [30]. The excessive retinol will be stored in hepatic stellate cells in the form of retinyl ester [27] and re-hydrolyzed to free retinol depending on its demand [30].

In the liver, retinol will bind to the retinol-binding proteins (RBP), which will be released into the blood and bound to transthyretin (TTR) [28]. The TTR binding can reduce the RBP glomeruli filtration rate due to an increase in the molecular weight, resulting in a decrease in the urinary excretion of retinol [28]. Therefore, the retinol level in blood can be maintained by the RBP-

TTR-retinol complex. This complex circulates in the blood plasma until it comes into contact with the target cells where it binds to the vitamin A receptor, also known as stimulated by retinoic acid 6 (STRA6), in the membrane so that the retinol can be released into the cells [27]. Then, retinol dehydrogenase (RDH) or alcohol dehydrogenase (ADH) will oxidize the retinol to retinal, which is further transformed into all-*trans*-RA, 9-*cis*-RA, and 13-*cis*-RA by retinol dehydrogenase (RALDH) [31]. The all-*trans*-RA, 9-*cis*-RA, and 13-*cis*-RA are the endogenous retinoids that were found to regulate the transcription of targeted genes, revealing their potential in anti-cancer activities [32].

Synthetic retinoids

However, endogenous retinoids with poor water solubility [33], high toxicity [34], poor drug resistance [35], low affinity [36], and side effects [35] have limited usage in the clinical treatment of cancer. In comparison to endogenous retinoids, synthetic retinoids are chemically more stable [8]. The synthetic retinoids also revealed higher selectivity and effectiveness, as well as lower toxicity and side effects than endogenous retinoids [7, 8]. Some of the examples of synthetic retinoids are bexarotene, peretinoin, ST1926, tamibarotene, UAB30, WYC-209, and 6-methyl-UAB30. These retinoids act as the ligands of retinoid nuclear receptors and bind to RAR and/or RXR to regulate gene transcription of cancers.

Peretinoin is a synthetic oral acyclic retinoid that binds to both RXR and RAR and is mainly used in the treatment of liver cancer [37]. On the other hand, WYC-209 targets only RAR to inhibit the proliferation of malignant mouse and human melanoma cells with high efficacy and low toxicity [33]. Another synthetic retinoid ST1926 showed stable pharmacokinetic properties and bioavailability with minimal side effects against solid tumors [38], besides anticancer activities on colorectal, breast, and prostate cancers through its RAR binding ability [7, 34, 35]. Tamibarotene (Am80) is another selective agonist of RAR and is used in the treatment of recurrent acute promyelocytic leukemia [39]. It was proven for its anti-cancer effect in cutaneous T-cell lymphoma [39].

Conversely, bexarotene is selective to RXR binding [40] and an FDA-approved antineoplastic agent that is used in the clinical treatment of cutaneous T cell lymphoma [41]. Lastly, UAB30 is another non-toxic retinoid that selectively binds to RXR [42, 43] and possesses anti-cancer potential on cutaneous T-cell lymphoma with high efficacy [42]. Interestingly, its derivative, 6-methyl-UAB30 showed an enhanced potency on neuroblastoma cell proliferation inhibition [43].

Mechanisms of action of retinoids in cancer cells

The mechanisms of action for retinoids in anticancer were reported to involve several gene signaling pathways. Other mechanisms such as regulation of mitochondrial function [14], microRNAs [17], and tumor stem cells [22] were also reported. The overall mechanisms of actions in different types of cancers reported for retinoids were summarized in **Table 1**.

Regulation of gene signaling pathways

Both endogenous and synthetic retinoids could bind to selective receptor proteins in the nucleus of target cells such as RAR, RXR, EGFR, JAK2, and caspase-3 [26]. The retinoid receptor-complexes will be binding to a selective region of nuclear DNA and regulating the gene expression, which involves protein synthesis [26]. Therefore, modulating the relevant gene signaling pathways is able to inhibit the proliferation of cancer cells and the growth of tumors [26, 44]. These selective receptor proteins, also known as biomarkers or targeted genes, were summarized in **Table 1**. Each targeted gene has its corresponding signaling pathways and a total of seventeen gene signaling pathways were found to be involved in anticancer mechanisms of retinoids. These pathways include RAR/RXR [45], EGFR/MAPK [46], Wnt/β-catenin [20], JAK/STAT [19], caspase [47], DOK1/PPARγ [48], PI3K/AKT [49], ERK1/2 [49], Keap1/Nrf2/ARE [19], HER2 [50], FAK [50], MYCN [9], SPHK1-S1P [37], ERK1/MAPK [51], SKP2/$p27^{kip1}$ [42] and Src-YAP-IL6 [52].

Among the gene signaling pathways, RAR/RXR signaling pathway is one of the most reported signaling pathways for retinoids. It was reported to be involved in the treatment of neuroblastoma [53], gastric cancer [49], melanoma [54], and cutaneous T-cell lymphoma [39]. The absence of the RAR/RXR in epithelial adenomas

Table 1. The anti-cancer mechanisms of action of retinoids

Pathways	Cancer type	Biomarkers	References
Gene signaling pathways			
RAR/RXR	Melanoma	RAR	[54]
	Gastric cancer		[49]
	Neuroblastoma		[45, 53]
	Cutaneous T-cell Lymphoma	RAR	[39]
		RAR and RXR	[18]
	Prostate cancer	RAR and RXR	[21]
EGFR/MAPK	Breast cancer	MMP2 and MMP9	[46]
	Melanoma	EGFR, MAPK and MMP2	[15]
		MMP-9	[54]
	Lung cancer	EGFR	[20]
Wnt/β-catenin	Breast cancer	Cyclin D1, c-MYC and β-catenin	[8]
	Melanoma	Cyclin D1	[54]
	Colorectal cancer	MED28, cyclin D1, c-MYC, β-catenin, E-cadherin and HBP1	[66]
	Lung cancer	CTNNB1	[20]
JAK/STAT	Breast cancer	GRIM-19	[58]
	Hepatocellular carcinoma	JAK2 and STAT3	[69]
	Cutaneous T-cell lymphoma	JAK1, STAT3, STAT5, Bcl-xL and cyclin D1	[18]
Caspase	Melanoma	Caspase-3	[33]
	Lung cancer	BCL-2, survivin and BAX	[47]
MYCN	Hepatocellular carcinoma	MYCN and N-myc	[9]
	Neuroblastoma		[75]
DOK1/PPARγ	Breast cancer	DOK1 and PPARγ	[48]
Src-YAP-IL6		Src-YAP-IL6	[52]
HER2		HER2	[50]
FAK		FAK	
ERK/MAPK	Colorectal cancer	ERK1, MAPK and MLCK	
	Thyroid cancer	ERK2	[51]
SPHK1-S1P	Hepatocellular carcinoma	SPHK and S1P	[83]
SKP2/$p27^{kip1}$	Cutaneous T-cell lymphoma	SKP2 and $p27^{kip1}$	[37]
Keap1/Nrf2/ARE	Glioma	Keap1, Nrf2 and ARE	[42]
PI3K/AKT	Gastric cancer	AKT	[19]
ERK1/2		ERK1/2	
PAK	Pancreatic cancer	PAK	[49]
Other mechanisms			
Mitochondrial function	Breast cancer	Cardiolipins amount	[14]
	Neuroblastoma	mitochondrial stress response	[45]
	Glioma	ATP	[34]
MicroRNAs	Hepatocellular carcinoma	miR-200a-3p, miR-200c-3p and miR-141-3p	[17]
Tumor stem cells	Gastric cancer	CD44, ALDH, KLF4 and SOX2	[22]

and carcinomas leads to a loss of cellular ability in growth regulation and results in uncontrollable cell growth [55]. Thus, RXR and RAR have been identified as crucial biomarkers in this pathway [50, 54, 56]. As shown in **Figure 3**, retinoids bind to RAR or RXR and undergo conformational change [31]. These activated receptors could form RAR/RXR heterodimers or RXR-RXR/RAR-RAR homodimers that subsequently bind to the retinoic acid response element (RARE), which is a well-defined promoter region [31]. RARE will then recruit transcriptional repressors such as nuclear receptor corepressor (NCoR) to form transcription inhibitory factor complex [3, 44]. Subsequently, the complex will recruit histone deacetylase (HDAC), which facilitates the chromatin re-structuring in the cells, resulting in an inhibition of target

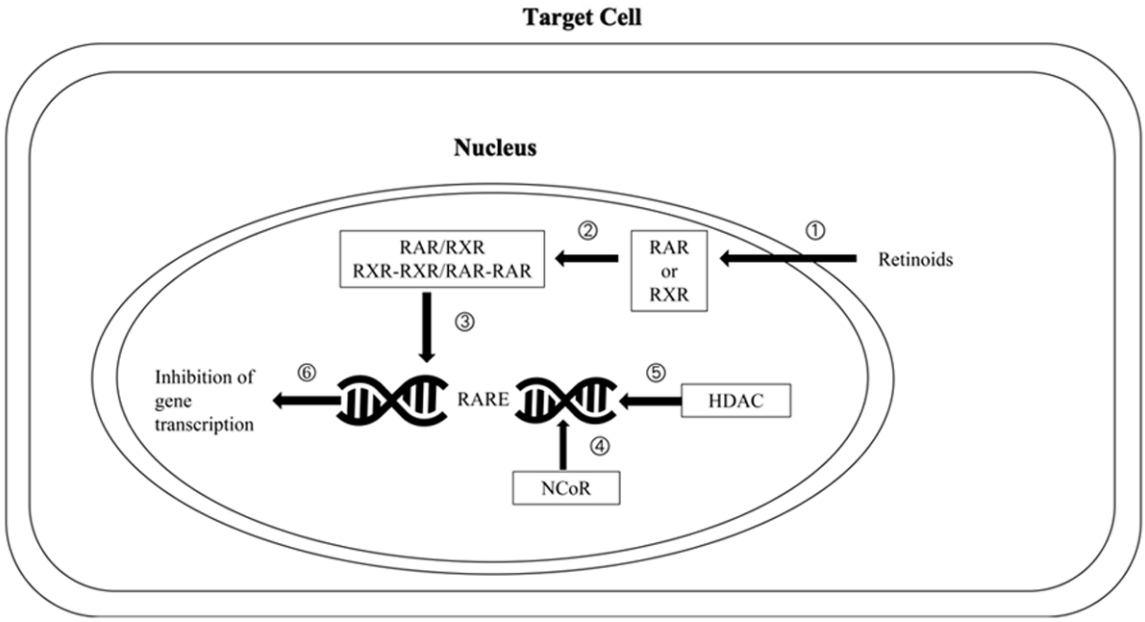

Figure 3. RAR/RXR signaling pathway within target cell. RARE: retinoic acid response element; NCoR: nuclear receptor corepressor; HDAC: histone deacetylase.

cancer gene transcription to generate an anti-cancer effect [3].

Regulation of mitochondrial function, microRNAs, and tumor stem cells

The mechanisms of action for retinoids in anti-cancer activities are also associated with the regulation of mitochondrial function [14], microRNAs [17], and tumor stem cells [22]. The regulations of mitochondrial function reported include breast cancer [14], glioma [34], and neuroblastoma [45]. Retinoids reduced the amount of cardiolipin located in the mitochondrial inner membrane and led to mitochondrial dysfunction of cancer cells [14, 34]. Besides that, retinoids were found to be involved in the regulation of microRNAs in hepatocellular carcinoma [17]. MicroRNAs include miR-141-3p, miR-200a-3p, and miR-200c-3p are endogenous non-coding small RNA molecules. The down-regulation of these microRNAs could inhibit cancer cell growth and differentiation, as well as tumor formation [17]. Lastly, the regulation of tumor stem cells was claimed to contribute to the anti-cancer activities of retinoids in gastric cancer [22]. CD44 and ALDH are the biomarkers of cancer stem cells while KLF4 and SOX2 are the cancer stem cells transcription factors [22]. The down-regulation expression of these biomarkers could inhibit the differentiation and formation of tumors [22].

Role of retinoids in anti-cancer activities

The *in vitro* and *in vivo* studies reported in the past five years revealed that retinoids are potential anti-cancer agents. The following sections summarized the anti-cancer activities of endogenous and synthetic retinoids (**Table 2**), in addition to the combination treatment of retinoids with other chemotherapy drugs (**Table 3**).

Breast cancer

According to the World Health Organization (WHO), breast cancer is the most prevalent cancer in the world by the end of 2020 and arises from the glandular tissue of the breast in the epithelial cells [56]. Thus, breast cancer was the most studied cancer for retinoids in recent years. The anti-cancer activity of an endogenous retinoid, all-*trans*-RA was found to be correlated to a decrease in the number of mitochondria, causing deficits in the respiration and energy balance in the breast cancer cells of HCC1419, HCC1599, HCC202, MDA-MB-361, and SKBR3 at a concentration of 10 μM [14]. Moreover, it inhibited cell proliferation of MCF7 and regulated the DOK1/PPARγ signaling pathway by enhancing the expression of DOK1 and inhibiting the expression of PPARγ at 3.33 μM [48]. In addition, the treatments of all-*trans*-RA [52] and 9-*cis*-RA [46] showed a reduction in the cell migration and invasion of

Table 2. The anti-cancer effects of endogenous and synthetic retinoids

Cancer type	Retinoids		Study Model	Concentration	Findings	References
Breast cancer	Endogenous retinoid	All-*trans*-RA	HCC1419, HCC1599, HCC202, MDA-MB-361 and SKBR3 cells (*In vitro*)	10 μM	● Decreased mitochondria amounts	[14]
			MCF7 cells (*In vitro*)	3.33 μM	● Inhibited cell proliferation ● Up-regulated DOK1 and down-regulated PPARγ in the DOK1/PPARγ signaling pathway	[48]
			MDA-MB-468 cells (*In vitro*)	5 μM	● Inhibited cell migration and invasion ● Inhibited Src-YAP-IL6 signaling pathway	[52]
		9-*cis*-RA	MDA-MB-231 cells (*In vitro*)	50 and 200 μM	● Inhibited cell migration and invasion ● Down-regulated MMP2 and MMP9 in the EGFR/MAPK signaling pathway	[46]
	Synthetic retinoid	ST1926	MCF7 and MDA-MB-231 cells (*In vitro*)	0.5 μM	● Inhibited cell proliferation (stronger than all-*trans*-RA) ● Inhibited Wnt/β-catenin signaling pathway	[8]
Melanoma	Endogenous retinoid	All-*trans*-RA	B16F10 cells (*In vitro*)	20 μM	● Down-regulated EGFR, MAPK, and MMP2 in the EGFR/MAPK signaling pathway	[15]
	Synthetic retinoid	WYC-209	B16-F1 cells (*In vitro*)	0.1 and 1 μM	● Inhibited cell proliferation ● Up-regulated RAR in the RAR/RXR signaling pathway and caspase-3 in the caspase signaling pathway	[33]
			C57BL/6 mice (*In vivo*)	0.22 mg/kg (body weight)	● Suppressed tumor development	
Colorectal cancer	Endogenous retinoid	All-*trans*-RA	HCT116 cells (*In vitro*)	1 μM	● Inhibited cell proliferation	[66]
			SW480 cells (*In vitro*)	0.5 μM	● Down-regulated MED28, cyclin D1, c-MYC, and β-catenin, and up-regulated E-cadherin and HBP1 in the Wnt/β-catenin signaling pathway	
			RKO cells (*In vitro*)	80 μM	● Inhibited cell migration ● Down-regulated MLCK in the ERK/MAPK signaling pathway	[51]
			APCMin/+ mice (*In vivo*)	4 IU/g (diet)	● Suppressed tumor development	[16]
			Colitis-associated colorectal cancer mice (*In vivo*)	4 IU/g (diet)	● Suppressed tumor development	[68]
	Synthetic retinoid	ST1926	Xenograft tumor mice (*In vivo*)	15 mg/kg (body weight)	● Suppressed tumor development	[35]
Hepatocellular carcinoma	Endogenous retinoid	All-*trans*-RA	Hepal-6 cells (*In vitro*)	10 μM	● Inhibited cell proliferation and migration ● Induced apoptosis ● Down-regulated miR-141-3p, miR-200a-3p, and miR-200c-3p	[17]
	Synthetic retinoid	Peretinoin	HH7 and HC cells (*In vitro*)	10 μM	● Down-regulated MYCN in the MYCN signaling pathway	[9]
			Huh7 cells (*In vitro*)	10 μM	● Down-regulated SPHK1 in the SPHK1-S1P signaling pathway	[37]
			Hepatocellular carcinoma mice (*In vivo*)	0.03% (diet)	● Improved tumor histology	[71]
Neuroblastoma	Endogenous retinoid	All-*trans*-RA	Human clinical trial	2240 mg/m^2	● Achieved 59% survival rate for 5 years compared to control (41%)	[73]
		13-*cis*-RA	SK-N-SH cells (*In vitro*)	10 μM	● Inhibited cell proliferation	[5]
	Synthetic retinoid	6-methyl-UAB30	SH-EP, SK-N-AS, SK-N-BE and WAC cells (*In vitro*)	10 and 25 μM	● Inhibited cell proliferation (stronger than UAB3)	[43]
			Xenograft tumor mice (*In vivo*)	50 mg/kg (body weight)	● Suppressed tumor development ● Prolonged survival rate	

Cutaneous T-cell lymphoma	Endogenous retinoid	9-*cis*-RA	HUT78 and MyLa cells (*In vitro*)	0.1, 1, and 10 μM	● Inhibited cell proliferation ● Induced apoptosis ● Inhibited JAK/STAT pathway and induced RAR/RXR signaling pathway	[18]
	Synthetic retinoid	UAB30	HH, HUT78 and MyLa cells (*In vitro*)	25 μM	● Inhibited cell proliferation (stronger than bexarotene) ● Induced apoptosis ● Down-regulated SKP2 and up-regulated $p27^{kip1}$ in the SKP2/$p27^{kip1}$ signaling pathway	[42]
		Bexarotene	Phase I/II human clinical trial	300 mg/m^2	● Tolerated dose	[77]
Glioma	Synthetic retinoid	ST1926	LN229, T98G, U251, U373 and U8 cells (*In vitro*)	2.5, 5, and 10 μM	● Inhibited cell proliferation ● Mitochondrial dysfunction	[34]
			BALB/c nude mice (*In vivo*)	10 and 20 mg/kg (body weight)	● Suppressed tumor development	
Lung cancer	Endogenous retinoid	All-*trans*-RA	H1975 cells (*In vitro*)	1 and 10 μM	● Inhibited cell proliferation ● Induced apoptosis ● Down-regulated EGFR in the EGFR signaling pathway and CTNNB1 in the Wnt/β-catenin signaling pathway	[20]
			Immunodeficient athymic nude mice (*In vivo*)	1 and 10 μM	● Suppressed tumor development	
Prostate carcinoma	Endogenous retinoid	9-*cis*-RA	LNCaP and PC3 cells (*In vitro*)	0.1 μM	● Inhibited cell proliferation ● Induced apoptosis ● Up-regulated RAR and RXR in the RAR/RXR signaling pathway	[21]
	Synthetic retinoid	ST1926	DU145 and PC3 cells (*In vitro*)	1 μM	● Inhibited cell proliferation (stronger than all-*trans*-RA)	[7]
			Xenograft tumor mice (*In vivo*)	20 mg/kg (body weight)	● Suppressed tumor development	
Gastric cancer	Endogenous retinoid	All-*trans*-RA	MKN45 and MKN74 cells (*In vitro*)	5 μM	● Inhibited cell proliferation ● Down-regulated CD44, ALDH, KLF4 and SOX2 stem cells	[22]
			Xenograft tumor mice (*In vivo*)	9.9 mg/kg (body weight)	● Suppressed tumor development	
Thyroid cancer	Endogenous retinoid	All-*trans*-RA	CD133 stem cells (*In vitro*)	40 μM	● Inhibited cell proliferation	[23]
			BCPAP and FRO cells (*In vitro*)	0.01, 0.1, 1, and 10 μM	● Inhibited cell proliferation	[81]

Table 3. The anti-cancer effects of combination treatment of retinoids and other drugs

Cancer type	Retinoids (concentration)	Combined drug (concentration)	Study Model	Findings	References
Breast cancer	All-*trans*-RA (10 μM)	Epirubicin (20 μM)	MCF7 cells (*In vitro*)	● Inhibited cell migration and invasion (stronger than epirubicin) ● Up-regulated GRIM-19 and down-regulated STAT3 in the JAK/STAT signaling pathway	[57]
	All-*trans*-RA (5 μM)	Docosahexaenoic acid (30 μM)		● Induced apoptosis (stronger than all-trans-RA)	[59]
	All-*trans*-RA (0.75 μM)	Interferon-β (1.87 μM) Curcumin (40 μM)		● Inhibited cell proliferation and migration ● Induced apoptosis	[58]
	All-*trans*-RA (20 μM)	ω-3 free fatty acids (80 μM)	ER + MCF7 and HER2 + SKBR3 cells (*In vitro*)	● Inhibited cell proliferation (stronger than all-trans-RA) ● Induced apoptosis	[60]
	All-*trans*-RA (10 μM)	Trastuzumab (0.0687 μM)	BT474 and SKBR3 cells (*In vitro*)	● Inhibited cell proliferation, invasion, and migration (stronger than all-trans-RA) ● Down-regulated FAK and HER2 in their respective signaling pathways	[50]
Melanoma	All-*trans*-RA (17.53 μM)	Allicin (30.81 μM)	CD44+ cells (*In vitro*)	● Inhibited cell proliferation (stronger than all-trans-RA) ● Up-regulated MMP-9 in the EGFR/MAPK signaling pathway, cyclin D1 in the Wnt/β-catenin signaling pathway, and RAR in the RAR/RXR signaling pathway	[54]
	All-*trans*-RA (12.65 μM)	CD20 antibody (1 μg/mL)	CD20 + cells (*In vitro*)	● Inhibited cell proliferation (stronger than all-trans-RA)	[64]
	All-*trans*-RA (5 μM)	Paclitaxel (0.005 and 0.01 μM)	A375 cells (*In vitro*)	● Inhibited cell proliferation (stronger than paclitaxel)	[62]
	All-*trans*-RA (In combination: 12.5 and 25 μM)	Vorinostat	A375, HL60, LN229, L929, SH-SY5Y and U-118 MG cells (*In vitro*)	● Inhibited cell proliferation (stronger than all-trans-RA) ● Induced apoptosis	[63]
	All-*trans*-RA (In combination: 10 mmol/kg (body weight))	Vorinostat	Xenograft tumor mice (*In vivo*)	● Suppressed tumor development	
	All-*trans*-RA (150 mg/m^2)	Ipilimumab (10 mg/kg)	Phase II human clinical trial	● Decreased the frequency of circulating myeloid-derived suppressor cells ● Suppressed the frequency of occurrence for Grade 3 or 4 adverse effects	[65]
Colorectal cancer	All-*trans*-RA (Nanoparticles: 5 μg/mL)	Oxaliplatin	SW-480 cells (*In vitro*)	● Inhibited cell proliferation ● Induced apoptosis	[67]
Hepatocellular carcinoma	All-*trans*-RA (10 μM)	Interferon-β (4.99 μM)	HepG2 cells (*In vitro*)	● Inhibited cell proliferation (stronger than all-trans-RA and interferon-β) ● Induced apoptosis ● Down-regulated JAK2 and STAT3 in the JAK/STAT signaling pathway	[69]
	All-*trans*-RA (In combination: 25.7 μM)	Paclitaxel	A549 cells (*In vitro*)	● Inhibited cell proliferation (stronger than all-trans-RA)	[70]
	All-*trans*-RA (0.35 mg/kg (body weight))	Paclitaxel (2 mg/kg (body weight))	Xenograft tumor mice (*In vivo*)	● Suppressed tumor development ● Prolonged survival rate	
Neuroblastoma	All-*trans*-RA (5 μM)	Estradiol (0.001 μM) Cholesterol (12.93 μM)	SH-SY5Y cells (*In vitro*)	● Inhibited cell proliferation (stronger than all-*trans*-RA)	[74]
	All-*trans*-RA (0.1 μM)	NaB (1000 μM) 5-Aza (1 μM)	SH-SY5Y and SK-N-BE cells (*In vitro*)	● Inhibited cell proliferation (stronger than all-*trans*-RA) ● Up-regulated RAR in the RAR/RXR signaling pathway	[53]
	All-*trans*-RA (0.1 μM)	TNIIIA2 (3 μg/mL)	IMR-32 and Kelly cells (*In vitro*)	● Accelerated cell differentiation (stronger than all-*trans*-RA and TNIIIA2) ● Down-regulated N-Myc in the MYCN signaling pathway	[75]
	All-*trans*-RA (6.67 mg/kg (body weight))	TNIIIA2 (8.34 mg/kg (body weight))	Xenograft tumor mice (*In vivo*)	● Suppressed tumor development (stronger than all-*trans*-RA)	

	13-*cis*-RA (50 μM)	Poly (I:C) (50 μg/ml)	SK-N-DZ cells (*In vitro*)	● Inhibited cell proliferation (stronger than 13-*cis*-RA) ● Induced apoptosis ● Up-regulated mitochondrial stress response	[45]
	13-*cis*-RA (5 mg/kg (body weight))	Poly (I:C) (10 mg/kg (body weight))	Xenograft tumor mice (*In vivo*)	● Suppressed tumor development through acceleration in neural differentiation and inhibition of vessel formation	
Cutaneous T-cell lymphoma	Tamibarotene (25 μM)	MS-275 (1 μM)	SeAx cells (*In vitro*)	● Inhibited cell proliferation (stronger than tamibarotene) ● Up-regulated RAR in the RAR/RXR signaling pathway	[39]
	Tamibarotene (2 mg/kg (body weight))	MS-275 (5 mg/kg (body weight))	Xenograft tumor mice (*In vivo*)	● Suppressed tumor development (stronger than tamibarotene) ● Prolonged survival rate	
Glioma	All-*trans*-RA (10 μM)	Temozolomide (400 μM)	U251 cells (*In vitro*)	● Inhibited cell proliferation (stronger than temozolomide) ● Induced apoptosis ● Inhibited the Keap1/Nrf2/ARE signaling pathway	[19]
	9-*cis*-RA (600 μM)	Metformin (20000 μM)	C6 cells (*In vitro*)	● Induced apoptosis (stronger than 9-*cis*-RA or metformin) ● Up-regulated caspase-3 in the caspase signal pathway	[78]
Lung cancer	All-*trans*-RA (10 μM)	Gefitinib (15 μM)	A549 and H1650 cells (*In vitro*)	● Inhibited cell proliferation (stronger than gefitinib)	[79]
	All-*trans*-RA (0.01 μM)	CIK cells Effector: Target ratio of CIK cells (20:1)	A549 and NCI-H520 cells (*In vitro*)	● Inhibited cell proliferation ● Down-regulated BCL-2 and surviving, and up-regulated BAX in the caspase signaling pathway	[47]
Gastric cancer	All-*trans*-RA (25 μM)	DAPT (5 μM)	AGS and MKN45 cells (*In vitro*)	● Inhibited cell proliferation (stronger than all-*trans*-RA) ● Up-regulated caspase-3 in the caspase signaling pathway	[80]
	All-*trans*-RA (Conjugate: 0.5 μM)	Podophyllotoxin	MKN45 and BGC-823 cells (*In vitro*)	● Inhibited cell proliferation (stronger than all-*trans*-RA) ● Induced apoptosis ● Up-regulated RAR in the RAR/RXR signaling pathway and down-regulated ERK1/2 and AKT in the PI3K/AKT signaling pathway	[49]
Thyroid cancer	All-*trans*-RA (70 μM)	Sorafenib (18 μM)	FTC-133 cells (*In vitro*)	● Inhibited cell proliferation ● Down-regulated ERK2 in the ERK/MAPK signaling pathway	[83]
	All-*trans*-RA (Polymer micelles: 10 mg/kg (body weight))	Sorafenib	BALB/c nude mice (*In vivo*)	● Induced apoptosis ● Induced re-differentiation of cells in tumor tissue	
	13-*cis*-RA (1.5 mg/kg)	Iodine-131 (60 μg)	Human clinal trial	● Reduced or stabilized tumor size after 2.5 years	[82]
Pancreatic cancer	All-*trans*-RA (50 μM)	Gemcitabine (10 μM)	AsPC-1 cells (*In vitro*)	● Inhibited cell proliferation (stronger than gemcitabine)	[24]
	All-*trans*-RA (30 μM)	Gemcitabine 0.6 μM	MiaPaCa-2 and TB33117 cells (*In vitro*)	● Inhibited cell proliferation and migration (stronger than gemcitabine) ● Down-regulated PAK in the PAK signaling pathway	[84]
	All-*trans*-RA (45 mg/m^2)	Paclitaxel (125 mg/m^2)	Phase I human clinical trial	● Grade 4 of Dose-Limiting Toxicity ● Achieved survival duration of 11.7 months	[85]

MDA-MB-468 cells (5 μM) and MDA-MB-231 cells (50 and 200 μM), respectively, through the wound healing assay and Corning Matrigel invasion chamber method. The mechanisms of action involved are the inhibition of the Src-YAP-IL6 signaling pathway [52] and inhibition of MMP2 and MMP9 expression in the EGFR/MAPK signaling pathway [46]. A synthetic retinoid, ST1926 was reported to exhibit stronger cytotoxic effects towards MCF7 and MDA-MB-231 cells than all-*trans*-RA. At a concentration of 0.5 μM, ST1926 was bound to cyclin D1, c-MYC, and β-catenin to down-regulate the Wnt/β-catenin signaling pathway [8].

Interestingly, several studies were conducted on the anti-cancer effects of the combination treatment of all-*trans*-RA with other compounds and have shown stronger anti-cancer activities. For instance, combination treatments on MCF7 cells by using 10 μM all-*trans*-RA + 20 μM epirubicin [57], 0.75 μM all-*trans*-RA + 1.87 μM IFN-β + 40 μM curcumin [58] and 5 μM all-*trans*-RA + 30 μM docosahexaenoic acid [59] exhibited higher effectiveness in the inhibition of cell proliferation, migration, and invasion, as well as promotion of cell apoptosis. Among these treatments, 0.75 μM all-*trans*-RA + 1.87 μM IFN-β + 40 μM curcumin has shown up-regulation of GRIM-19 and inhibition of the STAT3 expression in the JAK/STAT signaling pathway [58]. Furthermore, a co-administration of 0.0687 μM trastuzumab (monoclonal antibody drug) and 10 μM all-*trans*-RA was found to decrease cell proliferation, invasion, and migration in BT474 and SKBR3 cells at a higher degree compared to all-*trans*-RA alone [50]. Its anti-cancer activity was regulated by reducing the expression of FAK and the HER2 in their respective signaling pathways [50]. Moreover, Lin *et al*. (2017) found that a combination of 20 μM all-*trans*-RA and 80 μM ω-3 free fatty acids resulted in stronger effects in the inhibition of cell viability and promotion of cell apoptosis in ER + MCF7 and HER2 + SKBR3 cells examined by CCK-8 assay and annexin V-FITC/PI staining assay, respectively [60].

The recent findings above highlighted both endogenous and synthetic retinoids have potential anti-cancer effects on breast cancer. The comparison of treatment concentration showed that synthetic retinoid ST1926 is more effective against breast cancer than endogenous retinoids. However, the combination therapies of endogenous retinoid all-*trans*-RA with other compounds include epirubicin, Trastuzumab, ω-3 free fatty acids, curcumin, docosahexaenoic acid could enhance its anti-cancer effects. The anti-cancer activities of retinoids in breast cancer involve the regulation of EGFR/MAPK, Wnt/β-catenin, JAK/STAT, DOK1/PPARγ, Src-YAP-IL6, HER2 and FAK signaling pathways, as well as mitochondrial function.

Melanoma

Melanoma is the most aggressive type of skin cancer according to the World Cancer Report 2020 and originates from melanocytes-pigment-producing cells in the skin [61]. This is the second most studied cancer for retinoids in the past 5 years. The anti-cancer activity of an endogenous retinoid all-*trans*-RA was proven at a concentration of 20 μM by reducing the expression of EGFR, MAPK, and MMP2 in the EGFR/MAPK signaling pathway in B16F10 cells [15]. On the other hand, a synthetic retinoid WYC-209 showed an anti-cancer activity at lower concentrations of 0.1 and 1 μM through activation of RAR in the RAR/RXR signaling pathway and enhancement of caspase-3 expression in the caspase signaling pathway in B16-F1 cells [33]. Its cell proliferative effects were measured through MTT assay and an IC_{50} value of 0.19 μM was obtained [33]. Furthermore, WYC-209 abrogated 87.5% of melanoma tumor-repopulating cells in wild-type C57BL/6 mice at a dosage of 0.22 mg/kg (body weight) [33].

Similar to the anti-cancer effects of endogenous retinoid towards breast cancer, all-*trans*-RA showed an enhancement effect towards melanoma if it was used in the treatments together with other drugs. Jobani *et al*. (2018) reported a combination treatment of all-*trans*-RA and an organic sulfur compound allicin exerted approximately 2 times stronger anti-proliferative activities in CD44+ cells than all-*trans*-RA [54]. The expressions of MMP-9 in the EGFR/MAPK signaling pathway, cyclin D1 in the Wnt/β-catenin signaling pathway, and RAR in the RAR/RXR signaling pathway were observed to be enhanced by a combination treatment of 17.53 μM all-*trans*-RA and 30.81 μM allicin [54]. Another chemotherapeutic therapy of 5 μM all-*trans*-RA and paclitaxel (0.005 and 0.01

μM) showed a significant improvement in the anti-cancer effect of paclitaxel by inhibiting the proliferation of A375 cells [62].

The retinoic hydroxamic acid nanoparticles made up of all-*trans*-RA and an HDAC inhibitor drug, vorinostat could inhibit cell proliferation and promote cell apoptosis of A375, HL60, LN229, L929, SH-SY5Y, and U-118 MG cells at a higher level than all-*trans*-RA when examined at the same concentrations of 12.5 or 25 μM [63]. Furthermore, the nanoparticles of retinoic hydroxamic acid have been shown to hinder the development of xenograft tumors at a dosage of 10 mmol/kg (body weight) in the mice model [63]. Besides that, the conjugated nanoparticles composed of all-*trans*-RA and CD20 antibody exhibited approximately 5 times stronger inhibitory effects on CD20+ cell viability than all-*trans*-RA through CCK-8 assay [64]. A randomized phase II clinical trial involving 10 advanced melanoma patients was conducted with an oral treatment comprised of a combination of 10 mg/kg ipilimumab and 150 mg/m^2 all-*trans*-RA. The combination has significantly decreased the frequency of circulating myeloid-derived suppressor cells and suppressed the frequency of occurrence for Grade 3 or 4 adverse events if compared to ipilimumab in advanced-stage melanoma patients. The outcomes revealed that this combination is effective in the treatment of melanoma [65].

A higher concentration of retinoids used is likely to restrict their applications in the clinical treatment of cancers due to an increase in their cytotoxicity. The treatment concentration of endogenous and synthesis retinoids reported lately does not differ in a huge range but the combination treatments of retinoids with other chemotherapeutic drugs such as allicin, CD20 antibody, paclitaxel, vorinostat, and ipilimumab, is a beneficial approach in anti-cancer treatment on melanoma. In summary, the anti-cancer mechanisms of action in melanoma include the regulation of RAR/RXR, EGFR/MAPK, Wnt/β-catenin, and caspase signaling pathways.

Colorectal cancer

Colorectal cancer is s a highly preventable disease with the third morbidity and the second leading cause of cancer death in 2020 in accordance with WHO [56] and World Cancer Report 2020 [61]. In recent years, an endogenous retinoid all-*trans*-RA was well studied and showed potential anti-cancer activities towards colorectal cancer. Lee *et al*. (2016) reported that all-*trans*-RA could reduce the cell viabilities of HCT116 (1 μM) and SW480 (0.5 μM), and further studies on the mechanisms of action resulted in a reduction of the expression of MED28, cyclin D1, c-MYC, and β-catenin and an increment of E-cadherin and HBP1 in the Wnt/β-catenin signaling pathway [66]. The same retinoid also inhibited the migration ability of RKO cells at a concentration of 80 μM measured by wound healing assay. The authors also reported that its anti-cancer activity was regulated by reducing MLCK expression in the ERK1/MAPK signaling pathway [51].

A combination treatment in SW480 cells by using all-*trans*-RA and oxaliplatin loaded in the cholesterol-coated poly-nanoparticle was studied [67]. The outcomes showed that 5 μg/mL poly-nanoparticle can inhibit the CT-26 cells viability and promote cell apoptosis through MTS assay and annexin V-FITC/PI staining assay, respectively [67]. In colorectal mice models, Bhattacharya *et al*. (2016) and Penny *et al*. (2016) found that supplementation of all-*trans*-RA of 6.6 mg/kg (body weight) [68] and 4 IU/g (diet) [16], respectively, decreased the tumor burden. On the other hand, synthetic retinoid ST1926 was reported to reduce tumor volume significantly in xenograft cancer mice at a dosage of 15 mg/kg (body weight) [35]. Again, the recent findings above revealed that all-*trans*-RA exhibited anti-cancer in colorectal cancer both *in vitro* and *in vivo*, and its potential in combination treatment with other chemotherapeutic drugs is worth to be further explored, especially through the regulation of Wnt/β-catenin and ERK1/MAPK signaling pathways.

Hepatocellular carcinoma

Liver cancer is the third leading cause of cancer death worldwide in 2020 [56] with hepatocellular carcinoma as a major subtype of liver cancer according to World Cancer Report 2020 [61]. The retinoids that have been reported lately to give positive effects towards anti-hepatocellular carcinoma include all-*trans*-RA and peretinoin. Once again, all-*trans*-RA, a well-studied endogenous retinoid in anti-cancer, has been confirmed to inhibit the proliferation

and migration of Hepal-6 cells, besides inducing apoptosis at a concentration of 10 μM in MTT assay, wound healing assay, and annexin V-FITC/PI staining assay, respectively. The down-regulation of miR-141-3p, miR-200a-3p and miR-200c-3p in the same cells were captured at 10 μM [17].

Due to the anti-cancer activities of all-*trans*-RA, its potential in combination therapy with drugs such as interferon-β and paclitaxel were attempted by researchers. Zhao *et al*. (2016) studied a combination treatment of 10 μM all-*trans*-RA and 4.99 μM interferon-β in the HepG2 cell proliferation and apoptosis [69]. The outcomes showed that this combination could inhibit the cells and promote apoptosis at a higher level than all-*trans*-RA or interferon-β [69]. Its anti-cancer activity regulation was observed through the inhibitions of JAK2 and STAT3 expressions in the JAK/STAT signaling pathway [69]. Another study conducted by Nair *et al*. (2018) used a combination of all-*trans*-RA and paclitaxel to inhibit the A549 cells in MTT assay and obtained an IC_{50} value of 25.7 μM, which is almost 3 times more cytotoxic than all-*trans*-RA (IC_{50}=72 μM) [70]. The authors further assessed the combination in solid tumor mice by using 0.35 mg/kg (body weight) all-*trans*-RA and 2 mg/kg (body weight) paclitaxel. The outcomes supported the *in vitro* study where the combination of all-*trans*-RA and paclitaxel could prevent tumor growing effectively and prolong the survival rate of the mice [70].

For synthetic retinoid, peretinoin has been studied *in vitro* on the mechanism of action against hepatocellular carcinoma by using HH7, HC, and Huh7 cells at 10 μM in two different recent studies. The signaling pathways involved are the MYCN [9] and SPHK1-S1P [37], signaling pathways respectively. In addition, this retinoid was examined *in vivo* and proven to improve the liver tumors histology significantly by a diet of 0.03% peretinoin in the hepatocellular carcinoma mouse model [71].

The recent findings on the anti-cancer effect of retinoids towards hepatocellular carcinoma showed that synthetic retinoid peretinoin is more cytotoxic than the endogenous retinoid all-*trans*-RA. However, all-*trans*-RA could enhance its cytotoxicity through combination treatment with drugs such as interferon-β and paclitaxel. The anti-cancer activities of retinoids in hepatocellular carcinoma involve the regulation of microRNAs, as well as the signaling pathways of JAK/STAT, MYCN, and SPHK1-S1P.

Neuroblastoma

Neuroblastoma is a neuroendocrine tumor type that accounts for 7%-9% of all tumors detected in children [72]. The recent studies on endogenous retinoids for their anti-cancer activities related to neuroblastoma are mainly focused on the combination treatment with other compounds instead of individual retinoids. 13-*cis*-RA and all-*trans*-RA are the two endogenous retinoids that were assessed *in vitro* and *in vivo* as one of the components in combination treatments. 13-*cis*-RA has been confirmed to reduce the SK-N-SH cells proliferation and viability at 10 μM in the CellTox Green cytotoxicity assay and CellTiter-Blue cell viability assay, respectively [5]. Chuang *et al*. (2020) evaluated the combined effect of 50 μM 13-*cis*-RA and 50 μg/mL polyinosinic: polycytidylic acid (poly I:C), a synthetic agonist drug, on cell proliferation and apoptosis in SK-N-DZ cells [45]. The results showed an improved anti-proliferative activity and apoptotic induced response from 13-*cis*-RA through WST-1 assay and annexin V-FITC/PI staining assay, respectively [45]. The mechanism of action involves an up-regulation of the mitochondrial stress response [45]. In addition, an upscale combination treatment of 5 mg/kg (body weight) 13-*cis*-RA and 10 mg/kg (body weight) poly (I:C) was used in a xenograft mice model [45]. The outcomes showed that this combination could induce neural differentiation and subsequently slow down the growth of tumors, as well as inhibition of vessel formation [45].

For all-*trans*-RA, a clinical trial was conducted with 98 neuroblastoma patients treated with 2240 mg/m^2 of all-*trans*-RA after high-dose chemotherapy, followed by autologous hematopoietic stem cell transplantation. The survival rate for 5 years was reported to be 59%, which is higher than the control group (41%), indicating that all-*trans*-RA has improved the survival rate of neuroblastoma patients [73]. On the other hand, the *in vitro* and *in vivo* studies on the combination drugs in recent years include HDAC inhibitor, DNA methyltransferase inhibi-

tor, estradiol, and TNIIIA2. All the combination treatments showed enhanced anti-cancer effects towards neuroblastoma. For instance, Teppola *et al*. (2016) combined 5 μM all-*trans*-RA with a steroid sex hormone drug estradiol (0.001 μM) and examined its cell growth effect in SH-SY5Y cells by using Hoechst 33258 counting assay [74]. The results were as expected with the combination treatment showed better effects. Another combination of all-*trans*-RA with cholesterol (12.93 μM) also displayed the same outcome [74].

In addition, Almeida *et al*. (2017) reported that the combination of 0.1 μM all-*trans*-RA with either 1000 μM HDACi (NaB) or 1 μM DNA methyltransferase inhibitor (5-Aza) demonstrated greater inhibition effects in the proliferation of neuroblastoma cells of SH-SY5Y and SK-N-BE and activated the transcription of RAR in the RAR/RXR signaling pathway [53]. Another study reported the same concentration of all-*trans*-RA used in a combination with 3 μg/mL TNIIIA2, a chemotherapeutic drug, accelerated cell differentiation of malignant properties in IMR-32 and Kelly cells through counting assay [73]. It showed down-regulation of N-Myc expression in the MYCN signaling pathway and was further assessed *in vivo* by the same researchers [73]. Furthermore, an administration of 6.67 mg/kg (body weight) all-*trans*-RA and 8.34 mg/kg (body weight) TNIIIA2 was found to inhibit the growth and progression of tumors more effectively in the neuroblastoma xenograft mice [73].

On the other hand, 6-methyl-UAB30 is a synthetic retinoid that has been studied lately in the cell proliferation of SH-EP, SK-N-AS, SK-N-BE, and WAC by colorimetric cell proliferation assay [43]. The results have shown that it exhibited stronger anti-proliferative activities than its counterpart UAB30 when examined at a range of concentration of 49-60 μM [43]. An animal study supported its anti-cancer effect by inhibiting tumor growth and improving animal survival after the treatment of 6-methyl-UAB30 in xenograft mice with a dosage of 50 mg/kg (body weight) [43]. This finding revealed that 6-methyl-UAB30 is a stronger anti-cancer agent towards neuroblastoma. In short, the research on the combinations of endogenous retinoids with chemotherapeutic drugs is gaining popularity due to many studies reported on enhanced effects on anti-cancer activities. The anti-cancer activities of retinoids in neuroblastoma are mainly targeting the RAR/RXR and MYCN signaling pathways, as well as the mitochondrial function.

Cutaneous T-cell lymphoma

Cutaneous T-cell lymphomas are a group of irregular heterogeneous lymphomas characterized by the proliferation of cutaneous T-cell clones [74]. More recent studies were focused on synthetic retinoids and their combination effects with other drugs for their effectiveness against cutaneous T-cell lymphoma. UAB30 and bexarotene were examined in the HH, HUT78, and MyLa 2973 cells on their anti-proliferative effects [42]. These positive results suggested that UAB30 showed stronger anti-proliferative effects than bexarotene, especially against HuT 78 cells with the respective IC_{50} values of 5.1 and 24.5 μM [42]. Furthermore, UAB30 has shown down-regulation of SKP2 in the SKP2/$p27^{Kip1}$ signaling pathway at a concentration of 25 μM and increased $p27^{Kip1}$ protein stability, subsequently inhibiting G1 to S cell cycle transition to achieve the anti-cancer effects [42]. In a phase I/II clinical trial, 13 cutaneous T-cell lymphomas patients were administrated orally with bexarotene at a dose of 300 mg/m^2 daily for 24 weeks. The results showed that bexarotene is well tolerated with the dose [77].

Another synthetic retinoid tamibarotene was examined *in vitro* and *in vivo* as a combination with an HDAC inhibitor drug MS275. The anti-proliferative activity of SeAx cells was measured with a combination of 25 μM tamibarotene and 1 μM MS-275 and its activity is approximately 3 times stronger than tamibarotene after 72 h [39]. The activation of the RAR transcription in the RAR/RXR signaling pathway was found to be associated with its anti-cancer effect towards cutaneous T-cell lymphomas [39]. The same authors took the extra mile to examine this combination in a tumor-bearing NOD-SCID mice model. The dosage of 2 mg/kg (body weight) tamibarotene and 5 mg/kg (body weight) MS-275 had shown significant suppression on subcutaneously transplanted cutaneous T-cell lymphoma growth (14-fold) and prolonged the survival rate (6-fold) of the mice if compared to the control [39].

The only endogenous retinoid was studied in recent years is 9-*cis*-RA, which has shown to involve the common signaling pathways of cancer, RAR/RXR, and JAK/STAT pathways [18]. Besides its ability to inhibit the cell proliferation and promote the cell apoptosis of HUT78 and MyLa cells at a concentration as low as 0.1 μM, it managed to activate both RAR and RXR transcriptions in the RAR/RXR signaling pathway, as well as decrease the phosphorylation of JAK1, STAT3, and STAT5 and down-regulate Bcl-xL and cyclin D1 in the JAK/STAT signaling pathway [18].

Overall, an endogenous retinoid 9-*cis*-RA unveiled the anti-cancer potential of endogenous retinoids in cutaneous T-cell lymphoma without any enhancement required through the combination treatment approach, which is commonly used for endogenous retinoids. Conversely, synthetic retinoids, which attracted more researchers in recent years, exhibited activity at a higher concentration even though used in a combination treatment. The anti-cancer activities of these retinoids on cutaneous T-cell lymphoma involve the regulation of RAR/RXR, JAK/STAT, and Skp2/$p27^{Kip1}$ signaling pathways.

Glioma

Glioma is a common brain tumor occurs in more males than females and more whites than blacks in accordance with World Cancer Report 2020 [61]. Similar to the studies of endogenous retinoids against other types of cancer, these retinoids have been examined in the form of combination treatment rather than individual retinoids. Temozolomide and metformin were mixed with all-*trans*-RA and 9-*cis*-RA, respectively, for their *in vitro* anti-cancer effects on glioma. The treatment of 10 μM all-*trans*-RA + 400 μM temozolomide inhibited proliferation and induced apoptosis of U251 cells [19] while 600 μM 9-*cis*-RA + 20000 μM metformin-induced early and late apoptosis of C6 cells [78]. Both combination treatments that used endogenous retinoids have enhanced the anti-cancer effects of the drugs temozolomide and metformin [19, 78]. The anti-cancer activities were regulated by suppressing the Keap1/Nrf2/ARE signaling pathway (U251 cells) and increasing the expression of caspase-3 in the caspase signal pathway (C6 cells) [19, 78].

For synthetic retinoid, ST1926 was the only retinoid being studied in recent years but both *in vitro* and *in vivo* experiments were conducted. It was found to be cytotoxic to many cell lines, including LN229, T98G, U251, U373, and U8 cells at the concentrations of 2.5, 5, and 10 μM through the MTT assay [34]. The activities were related to the mitochondrial dysfunction of the cells to reduce the ATP production for cell energy [34]. The animal study further confirmed the anti-cancer effect of ST1926 through the suppression of xenograft tumor growth in the male BALB/c nude mice with the dosage of 10 and 20 mg/kg (body weight) [34].

The recent findings showed that the synthetic retinoid ST1926 has a higher potential in anti-glioma activities than the endogenous retinoids. Unlike the other cancers, the concentrations of both endogenous retinoids and drugs used in the combination treatment are much higher, as well as when compared to synthetic retinoids. The mechanisms of action reported for anti-glioma activities of retinoids are the regulation of Keap1/Nrf2/ARE signaling pathway and mitochondrial function.

Lung cancer

Lung cancer mainly consists of adenocarcinoma and squamous cell carcinoma with the second morbidity and highest mortality in 2020 based on WHO (2021) [56] and World Cancer Report 2020 [61]. In recent years, only endogenous retinoid was focused on the anti-cancer related to lung. All-*trans*-RA is the only endogenous retinoid being studied, either as an individual retinoid or in combination with other drugs. Zito *et al.* (2017) used all-*trans*-RA to reduce the cell viability of H1975 cells at 1 and 10 μM by using MTT assay. The apoptosis of the same cell line was observed through Annexin V-FITC/PI staining assay and its anti-cancer activity was proven by down-regulating the expression of EGFR and CTNNB1 in the respective signaling pathways of EGFR and Wnt/β-catenin [20]. After injecting 1 uM of all-*trans*-RA into the xenografted tumor of immunodeficient athymic nude mice for 21 days, the inhibition of tumor growth was observed to be 2 times stronger than control [20].

For the combination treatments, chemotherapeutic drug gefitinib (15 μM) was used together with all-*trans*-RA (10 μM) in an *in vitro* lung can-

cer cells anti-proliferative assay. This combination treatment in both H1650 and A549 cells showed 2-folds stronger cell growth inhibition effects than gefitinib [76]. Besides that, the combination of 0.01 μM all-*trans*-RA and cytokine-induced killer (CIK) cells at an effector to target ratio of 20:1 showed beneficial synergistic effects by inhibiting the proliferation of A549 and NCI-H520 cells if compared to that of all-*trans*-RA [47]. The authors reported that the anti-cancer activity was controlled by a significant decrease in the expression of BCL-2 and survivin, as well as an increase in the expression of BAX in the caspase signaling pathway [47].

These findings revealed that an endogenous retinoid all-*trans*-RA is a potent anti-cancer agent towards lung cancer that targeted the EGFR/MAPK, Wnt/β-catenin, and caspase signaling pathways. The lung cancer treatment using all-*trans*-RA individually or in combination treatment is worthwhile.

Prostate cancer

Prostate cancer is the fourth most common cancer in 2020 [56] and showed the greatest racial disparity of any major cancer type according to World Cancer Report 2020, particularly prevalent among older men [61]. An endogenous retinoid, 9-*cis*-RA [21], and a synthetic retinoid, ST1926 [7] were evaluated for their cell viability against PC3 cells at a concentration of 1 μM in two different studies. These studies revealed that both 9-*cis*-RA and ST1926 showed anti-proliferative effect on PC3 cells [7, 21]. In addition, 9-*cis*-RA was found to inhibit cell proliferation of LNCaP cells [21] while ST1926 is cytotoxic towards DU145 cells [7], at the same concentration. On the other hand, the cell viability of DU145 and PC3 cells was not affected by all-*trans*-RA at 10 μM but a significant decrease was detected at as low as 0.1 μM when ST1926 was treated, indicating that ST1926 is more cytotoxic than all-*trans*-RA [7].

The regulation of RAR/RXR signaling pathway by 9-*cis*-RA through activation of RAR and RXR receptors was detected at a concentration as low as 0.1 μM [21]. On the other hand, ST1926 was evaluated further in an animal model by using prostate cancer xenograft mice. The tumor volume in the mice treated with 20 mg/kg (body weight) of ST1926 was reported to be 30 mm^2 after 6 weeks, which is 4 times smaller if compared to the control, suggesting that ST1926 inhibited the growth and progression of prostate cancer tumors [7]. These recent findings showed that the anti-cancer effects of endogenous and synthetic retinoids on prostate cancer are comparable. Thus, more studies will need to be conducted on the potency of the retinoids and combination therapy could be explored by imitating studies reported for the other types of cancers.

Gastric cancer

Gastric cancer is the sixth most frequently diagnosed cancer in the world and the fourth most common cause of cancer-related death in 2020 based on WHO data (2021) [56]. Gastric adenocarcinoma is the most common type of gastric cancer and *Helicobacter pylori* infection is the principal cause of gastric cancer [61]. Similar to the recent reports on the anti-cancer effects of lung cancer, all-*trans*-RA is the only retinoid being studied against gastric cancer. A study was conducted to evaluate its cytotoxic effects on MKN45 and MKN74 cells at the concentrations of 1, 5, 10 μM through MTT assay and the positive results were obtained with the cell viability being suppressed by all-*trans*-RA [22]. The anti-cancer activities were regulated by suppressing the expression of the cancer stem cells markers CD44 and ALDH, as well as the transcription factors include KLF4 and SOX2, at 5 μM in both cells [22]. Furthermore, a daily treatment of 9.9 mg/kg (body weight) all-*trans*-RA for two weeks resulted in a suppression of tumorsphere initiation and growth in the xenograft mice [22].

The combination treatment approach was also used for all-*trans*-RA to examine their effectiveness against gastric cancer. A stronger cytotoxic effect was found in a combination of 25 μM all-*trans*-RA and 5 μM γ-secretase inhibitor (DAPT) than all-*trans*-RA in AGS and MKN45 cells with a huge decline in cell viability as observed in the MTT assay [80]. The cytotoxicity was linked to an up-regulation of caspase-3 expression in the caspase signaling pathway [80]. Once again, combination treatment showed that a conjugate of all-*trans*-RA and an anticancer drug podophyllotoxin is more effective than all-*trans*-RA. The conjugate was treated and proven to inhibit the cell viability of

MKN45 and BGC-823 cells in the CCK-8 assay [49]. The IC_{50} values obtained are 0.419 and 0.202 μM, respectively, which are much lower than that of all-*trans*-RA with IC_{50} values >80 μM [49]. This conjugate induced the apoptosis of both cells through annexin V-FITC/PI staining assay at a concentration of 0.5 μM, besides increased RAR in the RAR/RXR signaling pathway and decreased ERK1/2 and AKT in the PI3K/AKT signaling pathway [49].

Thyroid cancer

Papillary and follicular thyroid cancers are the most common subtypes of thyroid cancer with papillary thyroid carcinoma having the lowest mortality rate as stated in World Cancer Report 2020 [61]. All-*trans*-RA was found again as the main endogenous retinoid studied for anti-cancer effect on thyroid cancer in recent years. This retinoid has shown anti-proliferative effects on CD133+ stem cells, as well as BCPAP and FRO cancer cells in different studies. In the CCK-8 assay, all-*trans*-RA showed cytotoxicity with an IC_{50} value of 40 μM against CD133+ stem cells [23]. Cristiano *et al.* (2017) also found that all-*trans*-RA decreased the cell viability of BCPAP and FRO significantly to approximately 60%-65% after 72 h treatment in MTT assay [81].

Moreover, Li *et al.* (2020) composed a polymer micelle of all-*trans*-RA and a kinase inhibitor drug sorafenib and examined its cytotoxicity in MTT assay [83]. The combination of 18 μM Sorafenib and 70 μM all-*trans*-RA showed the most potent cytotoxic effects in FTC-133 cells and its mechanism of action involved an inhibition of ERK2 in the MAPK/ERK signaling pathway [83]. Furthermore, immunofluorescence and histological analysis of the BALB/c nude mice model revealed that this polymer micelle could induce cell apoptosis and re-differentiation of the tumor tissue section [83].

Another endogenous retinoid 13-*cis*-RA was studied in a clinical trial involving 13 thyroid cancer patients. A daily oral dose of 1.5 mg/kg (body weight) 13-*cis*-RA was given for 65 days, followed by a daily dose of 60 μg iodine-131 for 6 weeks. The results showed that 7 out of the 13 patients have experienced a reduced or stable tumor size after 2.5 years, indicating that 3-*cis*-RA is a potential anti-cancer agent in the treatment of thyroid cancer [82]. Even though a clinical study was reported recently, overall studies on the thyroid cancer suppression effects of retinoids are not as common as the other cancers thus more studies are recommended to be conducted to investigate their mechanisms of action.

Pancreatic cancer

Pancreatic cancer is the seventh leading cause of cancer-related deaths with an overall five-year survival rate of less than 9% according to World Cancer Report 2020 [61]. The infiltrating pancreatic ductal adenocarcinoma is the most prevalent form of pancreatic cancer [61]. A pancreatic cancer chemotherapy drug, gemcitabine was combined with all-*trans*-RA and found to inhibit the AsPC-1 cells proliferation by 2.8-fold if compared to gemcitabine [24]. Subsequently, this combination treatment has shown inhibition towards the cell proliferation and migration in both MiaPaCa-2 and TB33117 cells through sulforhodamine B assay and Boyden Chamber assay, respectively [84]. The IC_{50} values obtained were approximately 1.2-fold higher than gemcitabine for both cells, indicating weaker cytotoxicity of gemcitabine [84]. Moreover, the combination treatment downregulated the expression of PAK in the PAK signaling pathway [84].

Furthermore, a phase I clinical trial was conducted with 27 pancreatic cancer patients who were treated orally with 45 mg/m^2 all-*trans*-RA in combination with 1000 mg/m^2 gemcitabine and 125 mg/m^2 paclitaxel. The outcomes revealed that the combination falls under Grade 4 of Dose-Limiting Toxicity and survival duration of 11.7 months. Thus, it is safe to be used in pancreatic cancer therapy [85]. The findings indicated that all-*trans*-RA in combination with gemcitabine and paclitaxel increased the effectiveness of gemcitabine in the treatment of pancreatic cancer. The anti-cancer activities of retinoids in gastric cancer involve the regulation of PAK signaling pathway. The endogenous retinoid, all-*trans*-RA has been the only potential candidate being studied lately for its anti-cancer effects on pancreatic cancer.

Conclusion and future perspectives

This review summarized recent reports on the anti-cancer potential of retinoids and their mechanisms of action. These studies were con-

ducted through both *in vitro, in vivo* and human clinical studies using endogenous and synthetic retinoids, as well as in a combination with other drugs. The overall review found that the most studied anti-cancer effect on retinoids is breast cancer and followed by melanoma, colorectal cancer, hepatocellular carcinoma, neuroblastoma, and cutaneous T-cell lymphoma. The reports on glioma, lung cancer, prostate cancer, gastric cancer, thyroid cancer, and pancreatic cancer were also spotted but to a lesser extent.

Among the retinoids, all-*trans*-RA is the most well-studied endogenous retinoids and followed by 9-*cis*-RA and 13-*cis*-RA, which are inactive minor metabolites present in the body. The endogenous retinoids were reported to induce adverse effects, including poor water solubility, teratogenicity, cytotoxicity, tumor resistance and relapse. Thus, synthetic retinoids, especially ST1926 were widely studied recently. ST1926 has been proven on its low toxicity and high affinity towards retinoic acid receptors. It exhibited stronger anti-cancer activity than the endogenous retinoids, all-*trans*-RA and 9-*cis*-RA. Another synthetic retinoid WYC-209 also showed stronger anti-cancer activity than endogenous retinoids. The other synthetic retinoids that showed anti-cancer activities are 6-methyl-UAB30, UAB30, peretinoin, and bexarotene. The potential of synthetic retinoids as anti-cancer agents unveils an anti-cancer research direction in drug discovery and development on synthetic retinoids. Novel structures with a retinoid main skeleton could be designed and synthesized to target the cancer regulatory genes in the signaling pathways summarized in this review.

In recent years, many studies were focused on the anti-cancer enhancement effect by using combination treatment of retinoids with chemotherapy drugs. The outcomes from these studies are positive with the combination approach having stronger anti-cancer effects. This review provides an important insight to the researchers on the chemotherapy drugs combination strategy with their estimated effective doses. Moreover, recent combination treatments using retinoids are focused more on endogenous retinoids rather than synthetic retinoids. Thus, synthetic retinoids, which showed stronger anti-cancer effects are highly recommended to be used in the drug combination strategy and their effective doses can likely be further reduced, as observed in the past drug combination studies using endogenous retinoids.

The retinoids are selective receptor-ligands that involve the transcription and regulation of the promoter region of tumor-targeted genes in the respective signaling pathways, subsequently activating the genes to inhibit cancer cells proliferation, migration, vitality, and induce apoptosis. Besides that, the mechanisms of action of retinoids are linked to mitochondrial function, microRNA, tumor stem cells, and immunity function. RAR/RXR signaling pathway is the most reported pathway for anti-cancer effects of retinoids due to the high-affinity binding receptors, RAR and RXR.

Although the signaling pathways were reported to be involved in the mechanisms of action of retinoids on their anti-cancer activities, there is no definitive study on the connections or interactions among these signaling pathways. This review speculates that the RAR/RXR signaling pathway is an upstream pathway of all other reported pathways. Therefore, molecular biology studies on the connection between RAR/RXR pathway and the other signaling pathways reported in this review are recommended to provide a deeper insight to the researchers on the selection of targeted genes for retinoids as anti-cancer agents.

Although the anti-cancer potential of retinoids has been extended to animal and human clinical trial studies, most of the reports were focused on the *in vitro* bioassay model in recent years. An extremely limited number of human clinical trials were reported in the past 5 years covering only melanoma, neuroblastoma, cutaneous T-cell lymphoma, thyroid cancer, and pancreatic cancer. Therefore, more animal studies and clinical studies should be anticipated to be conducted in the near future, especially on synthetic retinoids as one of the ingredients in the combination drug approaches.

Acknowledgements

Fundamental Research Grant Scheme (FRGS) (FRGS/1/2020/STG03/TAYLOR/01/1) from the Ministry of Education (MOE) is acknowledged.

Disclosure of conflict of interest

None.

Address correspondence to: Siau Hui Mah, School of Biosciences, Faculty of Health and Medical Sciences, Taylor's University (Lakeside Campus), 1, Jalan Taylors, Subang Jaya, Selangor, Malaysia. E-mail: SiauHui.Mah@taylors.edu.my

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