Natural compounds targeting nuclear receptors for effective cancer therapy

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Abstract

Human nuclear receptors (NRs) are a family of forty-eight transcription factors that modulate gene expression both spatially and temporally. Numerous biochemical, physiological, and pathological processes including cell survival, proliferation, differentiation, metabolism, immune modulation, development, reproduction, and aging are extensively orchestrated by different NRs. The involvement of dysregulated NRs and NR-mediated signaling pathways in driving cancer cell hallmarks has been thoroughly investigated. Targeting NRs has been one of the major focuses of drug development strategies for cancer interventions. Interestingly, rapid progress in molecular biology and drug screening reveals that the naturally occurring compounds are promising modern oncology drugs which are free of potentially inevitable repercussions that are associated with synthetic compounds. Therefore, the purpose of this review is to draw our attention to the potential therapeutic effects of various classes of natural compounds that target NRs such as phytochemicals, dietary components, venom constituents, royal jelly–derived compounds, and microbial derivatives in the establishment of novel and safe medications for cancer treatment. This review also emphasizes molecular mechanisms and signaling pathways that are leveraged to promote the anti-cancer effects of these natural compounds. We have also critically reviewed and assessed the advantages and limitations of current preclinical and clinical studies on this subject for cancer prophylaxis. This might subsequently pave the way for new paradigms in the discovery of drugs that target specific cancer types.

Keywords Cancer · Nuclear receptors · Natural compounds · Signaling molecules · Metastasis

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1 Introduction

Neoplasms are multicellular and multifactorial pathological conditions that cause a massive public health burden across the world with an estimated 19.3 million newly diagnosed cases and 10.0 million deaths [1]. Drastic advancements in genomic, metabolomic, and proteomic research have revealed that neoplastic cell arises as a result of perturbations in multiple signaling pathways as well as pervasive genetic and epigenetic alterations in various genes that remain dormant for several years before developing the clinically diagnosable disease [2]. The heterotypic signaling machinery detailing the intercommunication between neoplastic cells and stromal cells within tumors to assemble and collaborate to develop various subtypes and to progress malignant stages of cancer was well documented [2, 3]. Extensive studies over the last few decades revealed that most cancers are exacerbated by dysregulation in several transcription factors (TFs) including nuclear factor-κB (NF-κB), signal transducers and activators of transcription (STATs), core-binding factor family TFs, ETS family TFs, runt-related TFs (RUNX1-RUNX3), and nuclear receptors (NRs) [4–7]. NRs have consistently been at the center of cancer research, where they have been shown to function as critical disease regulators. Several tumor types display a diverse set of NRs, whose interactions give different pathways for disease development and possibly exploitable therapeutic interventions [8–13]. Rapid advancement in genomic technologies has enabled more in-depth examination of the genome-wide impact of NRs on gene regulation emphasizing the vital role of coactivators and context [8, 14]. Therefore, NRs serve as biomarkers for tumor sub-classification and as therapeutic targets for developing novel drugs [8, 15]. To date, small molecules that bind to particular NRs have been one of the most effective and successful ways of targeting TFs in cancer [16, 17]. Drugs that directly influence the activity of the androgen receptor (AR), estrogen receptor (ER), glucocorticoid receptor (GR), and retinoic acid receptor (RAR) are currently employed to treat prostate cancer (PC), breast cancer (BC), acute lymphoblastic leukemia (ALL), and acute promyelocytic leukemia (APL), respectively [17–19]. The Food and Drug Administration (FDA) has approved more than ten chemotherapeutic drugs that target NRs for cancer treatment [16, 17]. However, few of these medications in log-term usage have shown inevitable adverse effects including deep vein thrombosis, pulmonary embolism, hypertension, severe hot flushes, epilepsy, depression, insomnia, cataracts, vaginal dryness, weight gain, fatigue, insomnia, seizures, and irritability affecting quality of life and survival of patients [17, 20]. As a result, establishing effective strategies to modify and reverse the neoplastic environment and significantly improve patient survival is imperative and is a key element of current pharmacological research. Interestingly, advanced *in vitro*, *in vivo*, *ex vivo*, and clinical studies have illustrated that natural compounds are safe, less toxic, economical, efficient multitargeting agents and have been a massive success for the treatment of various malignancies [21–23]. Natural products have a wide range of chemical scaffolds and have evolved to perform a variety of biological activities, giving them considerable drug-likeliness and making them a good source for finding novel drug leads [24–26]. These products accounted for approximately 25% of newly approved anti-cancer drugs during the period between 1981 and 2019 [27–29]. Concurrently, a plethora of compounds with anti-cancer potentials and/or distinct benefits in probing treatment modalities for neoplasms has been identified [30, 31]. Enormous research has established that NRs play a pivotal role in a wide range of metabolic and inflammatory illnesses, including diabetes, dyslipidemia, cirrhosis, fibrosis, and cancer. Numerous naturally occurring substances operate as NR ligands, controlling carbohydrate and lipid metabolism by modulating NR activity. Recent research has focused on potential NR modulating natural compounds derived from traditionally used medicinal plants or dietary sources for the prevention and treatment of various malignancies [8–11]. In this review, we provide an overview of natural compounds including phytochemicals, animal-derived agents, metabolites, and microbially derived substances that possess anti-cancer activities by targeting NRs. We have also presented the summary of ongoing clinical trials and patents on natural drugs that target NRs in cancer. Moreover, we have discussed the advantages and limitations of using natural compounds and highlighted future research regarding their potential as NR targets for the treatment of neoplasm.

2 NR superfamily and their mechanism of action

NRs are a family of ligand-dependent transcription factors that influence diverse physiological processes including embryonic development, cell growth, differentiation, systemic and cellular metabolism, homeostasis, immunity, and reproduction [16, 32–37]. In humans, a total of 48 members of this superfamily have been discovered to date [32]. Unlike other transcription factors, NRs directly bind to their lipophilic ligands such as steroid hormones and bile acids [38, 39]. NRs are divided into three distinct groups based on their interaction with the type of ligand as endocrine NRs, adopted NRs, and orphan NRs (Fig. 1A, B). Members of endocrine NRs are steroid hormone receptors including androgen (AR), estrogen (ER), glucocorticoid (GR),

Fig. 1 Classification of nuclear receptors and their physiological expression. **A** NRs are classified into endocrine receptors, adopted receptors, and orphan receptors based on whether their ligands and functions are known or unknown. The NRs along with their known physiological ligands have been shown. **B** NRs are widely expressed in almost all tissues. The predominantly expressed NRs in various organs are listed. The NRs in green color indicate tumor-inhibiting properties, red indicates tumor-promoting, and blue indicates dual nature. The figure was created in BioRender.com

mineralocorticoid (MR), and progesterone (PR) receptors [32, 40]. These receptors bind to DNA as homodimers to initiate target gene expression, and their ligands indeed are synthesized in the endocrine glands which are regulated by the hypothalamic-pituitary axis [41]. The circulating steroid hormones display a high affinity to their respective NRs with a dissociation constant of 0.01 to 10 nM [41]. This class of receptor systems controls a wide range of physiological processes including metabolism, sexual dimorphism, reproduction, and electrolyte balance [41]. Adopted NRs are those that were previously classified as orphans but were subsequently adopted as NRs once the physiological ligand was characterized and functions as heterodimers with the retinoid X receptor (RXR) [40]. The members of this

group include receptors for bile acids—farnesoid X receptor (FXR); fatty acids—peroxisome proliferator–activated receptors (PPARs); oxysterols—liver X receptors (LXR); xenobiotic receptors—steroid xenobiotic receptor or pregnane X receptor (SXR/PXR); and constitutive androstane receptor (CAR). These receptors possess lower affinities to their lipid ligands with the dissociation constant of > 1 to 10 μM [40]. A feedforward metabolic cascade is activated when a cognate ligand binds to each of these receptors, maintaining lipid homeostasis by regulating the transcription of genes involved in lipid metabolism, transport, storage, and clearance [40]. In addition to these adopted NRs, four RXR heterodimer receptors that do not fit precisely into either paradigm include ecdysone, retinoic acid receptor (RAR), thyroid hormone receptor (TR), and vitamin D receptor (VDR) [40, 42–45]. These receptors regulate morphogenesis, development, metabolism, and homeostasis [40, 41]. The third paradigm is represented by the large number of orphan NR members whose ligands, targets, and physiological functions are not well-known. Orphan NRs include photoreceptor-specific nuclear receptor (PNR/NR2E3), small heterodimer partner (SHP/NR0B2), steroidogenic factor-1 (SF-1/NR5A1), liver receptor homologue-1 (LRH-1/NR5A2), dosage-sensitive sex reversal, adrenal hypoplasia congenita critical region on the X chromosome gene 1 (DAX-1/NR0B1), tailless (TLX/NR2E1), germ cell nuclear factor (GCNF/NR6A1), RAR-related orphan receptor alpha (RORA/RORα/NR1F1), RAR-related orphan receptor beta (RORB/RORβ/NR1F2), RAR-related orphan receptor gamma (RORC/RORγ/NR1F3), estrogen-related receptor alpha (ERRα/ESRRA/NR3B1), estrogen-related receptor beta (ERRβ/ESRRB/NR3B2), estrogen-related receptor gamma (ERRγ/ESRRG/NR3B3), Rev-ErbA alpha (Rev-Erbα/NR1D1), Rev-ErbB beta (Rev-Erbβ/NR1D2), testicular receptor 2 (TR2/NR2C1), testicular receptor 4 (TR4/NR2C2), hepatocyte nuclear 4 (HNF4A/NR2A21), the chicken ovalbumin upstream promoter transcription factor I (COUP-TFI/COUPTF1/NR2F1), the chicken ovalbumin upstream promoter transcription factor II (COUP-TFII/COUPTFB/NR2F2), nerve growth factor–induced clone B (NGFIB/NUR77/NR4A1), Nur-related factor 1 (NURR1/NR4A2), and neuron-derived orphan receptor 1 (NOR1/NR4A3) [46]. The physiological functions of NRs are summarized in Fig. 2.

The structural arrangement of members of the NR superfamily has been remarkably evolutionarily conserved consisting of four major domains—the N-terminal domain (A/B region) activator function 1 region (AF1), deoxyribonucleic acid (DNA)–binding domain (DBD, C region) which possesses two zinc finger motifs that confer specificity for response elements binding, a hinge region (D) connecting DBD to ligand-binding domain (LBD, E/F region), and a ligand-dependent activator function 2 region (AF2)

that interacts with coactivators [47, 48]. NRs activate the transcription of their target genes by directly binding to response elements via the DBD domain [47–49]. Ligands allosterically govern the NR interaction with the coactivator or corepressor proteins by affecting either folding or dislodging the C-terminal helix (H12) in the AF2 domain [47, 48, 50]. Interaction with the coactivators facilitates the recruitment of transcriptosomes and chromatin remodeling [47, 48]. Conversely, the recently deduced structure of full-length AR by Yu et al. provided evidence that a coregulator protein can bind to AR independently of the AF2 region [51]. Whether AR is an exception or this is the rule for other NRs remains to be revealed. Genomic studies have revealed that NRs bind to the 5′-RGKTCA-3′ region which is organized as direct repeats with a variable-length spacer of 0–5 bp (DR0–DR5) [48, 52–54]. Studies on NR interaction with response elements using protein binding microarray have shown that the length of DR spacing is a key determinant of the DNA-binding specificity of NRs. For instance, PPAR/RXR prefers binding to DR1, whereas LXR/RXR prefers DR4. Recently, domain mutation followed by protein microarray analysis demonstrated that NR specificity to response elements does not solely depend on the DR spacing length; instead, it is the activity of the binding site that confers the specificity [54]. This study also demonstrated that all the type II NR heterodimers bind to DNA through half-site mode on both full- and half-sites which is a classic DNA-based allostery [54].

Considering the variety of regulatory strata that appear to tune receptor function, it is indeed easy to comprehend how the amazing context-dependent of NR transcriptional regulation would be jeopardized without the multitude of activators, repressors, and coregulators discovered to date. A plethora of studies demonstrated that coactivators, and/or corepressors, and/or regulators are primed for recruitment by NRs in response to appropriate triggers. The rapid development of molecular biology techniques and cloning of mammalian cDNAs encoding steroid receptor coactivator 1 (SRC-1)/nuclear receptor coactivator 1 (NCoA-1), glutamate receptor interacting protein 1 (GRIP-1)/transcriptional mediators/intermediatory factor 2 (TIF2)/steroid receptor coactivator 2 (SRC-2), and p300/CBP interacting protein (p/CIP)/RAC3/ACTR/AIB-1/TRAM-1/SRC-3 enabled to identify them as a family of ligand-recruited NR coactivators, SRC/p160 family [55–63]. The acetyltransferases CREB-binding protein (CBP) and p300; methylases coactivator-associated arginine methyltransferase 1 (CARM-1) and protein arginine methyltransferase 1 (PRMT-1); switch/sucrose non-fermentable (SWI/SNF) complex; serum resistance–associated protein (SRA); triiodothyronine captor auxiliary protein (TRAP)/vitamin D receptor–interacting protein (DRIP) complex; transcriptional machinery proteins — TATA-box binding protein (TBP), TBP-associated
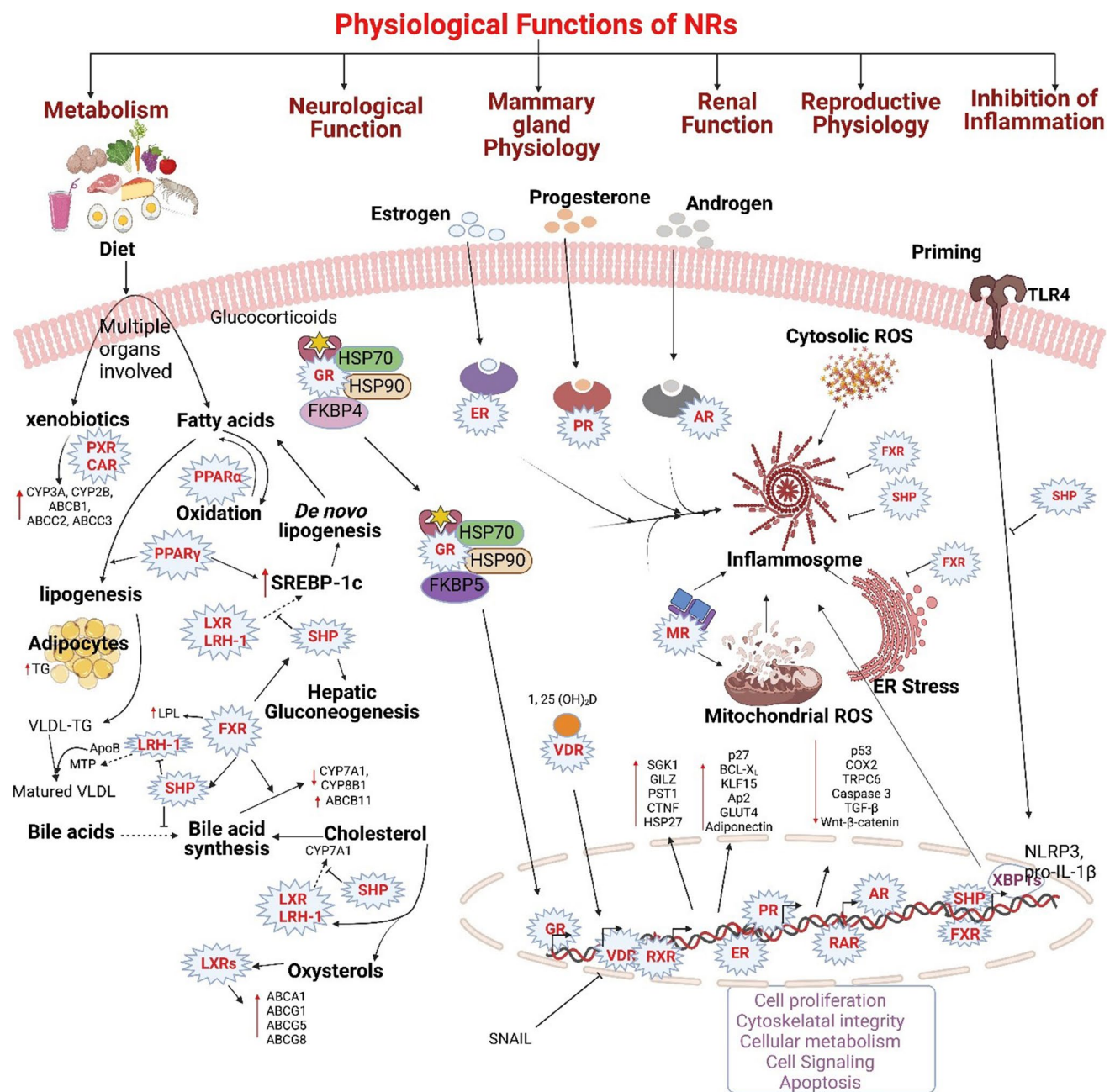
Fig. 2 Molecular insight into physiological functions of NRs. The figure was created in BioRender.com

factors (TAFs), and ubiquitin ligase E6–associated protein (E6-AP) are the additional proteins that met some or all the experimental criteria to be defined as NR coactivators [57, 62, 64–73]. A helical LXXLL motif or NR box is a common structural characteristic of NR coactivators [74]. In addition, various families of coactivators share several functional features, for instance, acetyltransferase activity is common among CBP, p300/CBP-associated factor (PCAF), and members of the SRC family [63, 75–77]. Corepressors of NRs (NCoR) and silencing mediators of thyroid and retinoid

receptors (SMRT) and repressor of estrogen activity (REA) are analogous to coactivators and are recruited by NRs in the presence or absence of ligands or by the antagonists such as tamoxifen and RU486 [62, 78, 79]. Moreover, amphipathic helical peptides known as "CoRNR boxes" are exploited by transcriptionally inert NRs to recognize corepressors [80]. Corepressors and coactivators are functionally similar, in addition to their structural similarities. Furthermore, coactivators of NRs are subjected to modulation by selective repressor molecules such as RIP140 [81, 82]. Perhaps more

crucially, several specific posttranslational changes have a great impact on how NRs, their coregulator complexes, and their cognate gene networks function. Phosphorylation of NRs aid in compartmentalization and methylation aid in coregulator recruitment, while ubiquitination reduces the half-life [, 62, 83].

3 NRs in tumorigenesis and anti-cancer therapeutics

The importance of NRs in promoting the genesis and progression of cancer has been well recognized [16, 17, 84, 85]. Their roles in tumorigenesis are complex and paradoxical. The hormone receptors including ER, PR, and AR are required for homeostasis and contribute to tumorigenesis when aberrantly triggered in various cancer models. These receptors exert their effects via classical signaling milieu such as phosphatidylinositol 3 kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR), Notch, and Ras/mitogen-activated protein kinase (MAPK) pathways [9–11, 84, 85] (Figs. 3 and 4). Likewise, other nuclear receptors, such as GR and RARs, as well as adopted nuclear receptors, such as PPAR, RXR, ERRs, and LXR have been known to play a pivotal role in tumor progression, including the regulation of proliferative signaling, initiation of metastasis, interruption of apoptotic and autophagy signaling, angiogenesis, and metabolic reprogramming [9–11, 86–89]. A growing body of evidence shows that nuclear receptors fine-tune the effector functions of immune cells by regulating immuno-metabolic events [90, 91]. Indeed, several NRs are classified as metabolic receptors, including FXR, LXRs, PPARs, and PXR. These receptors were shown to regulate NLRP3-mediated inflammasome activation in various cancer models such
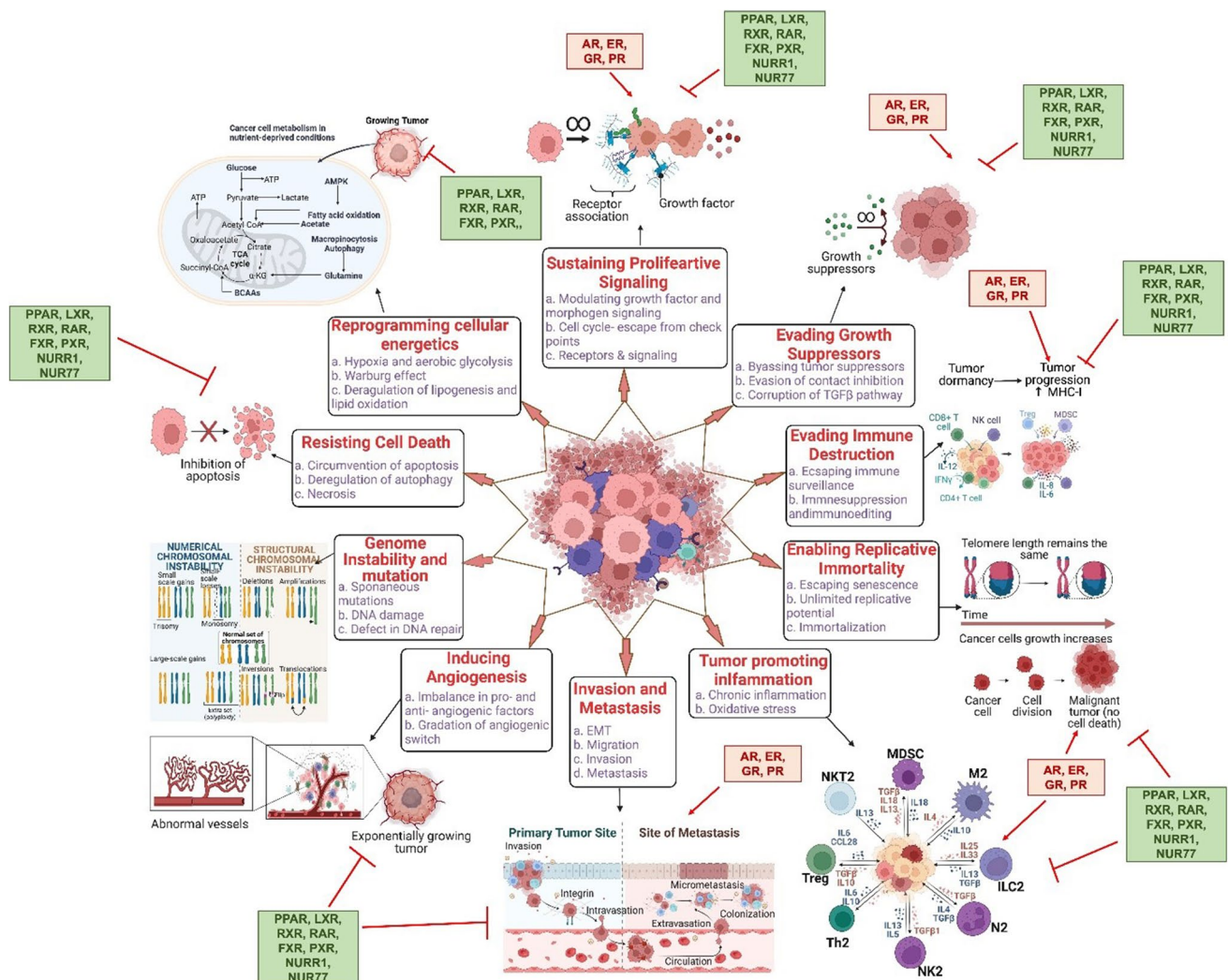
Fig. 3 Involvement of NRs in the regulation of cancer cell hallmarks. NRs regulate a wide range of cellular and molecular processes. The cancer cell hallmarks and the involvement of NRs in each process have been shown. The figure was created in BioRender.com
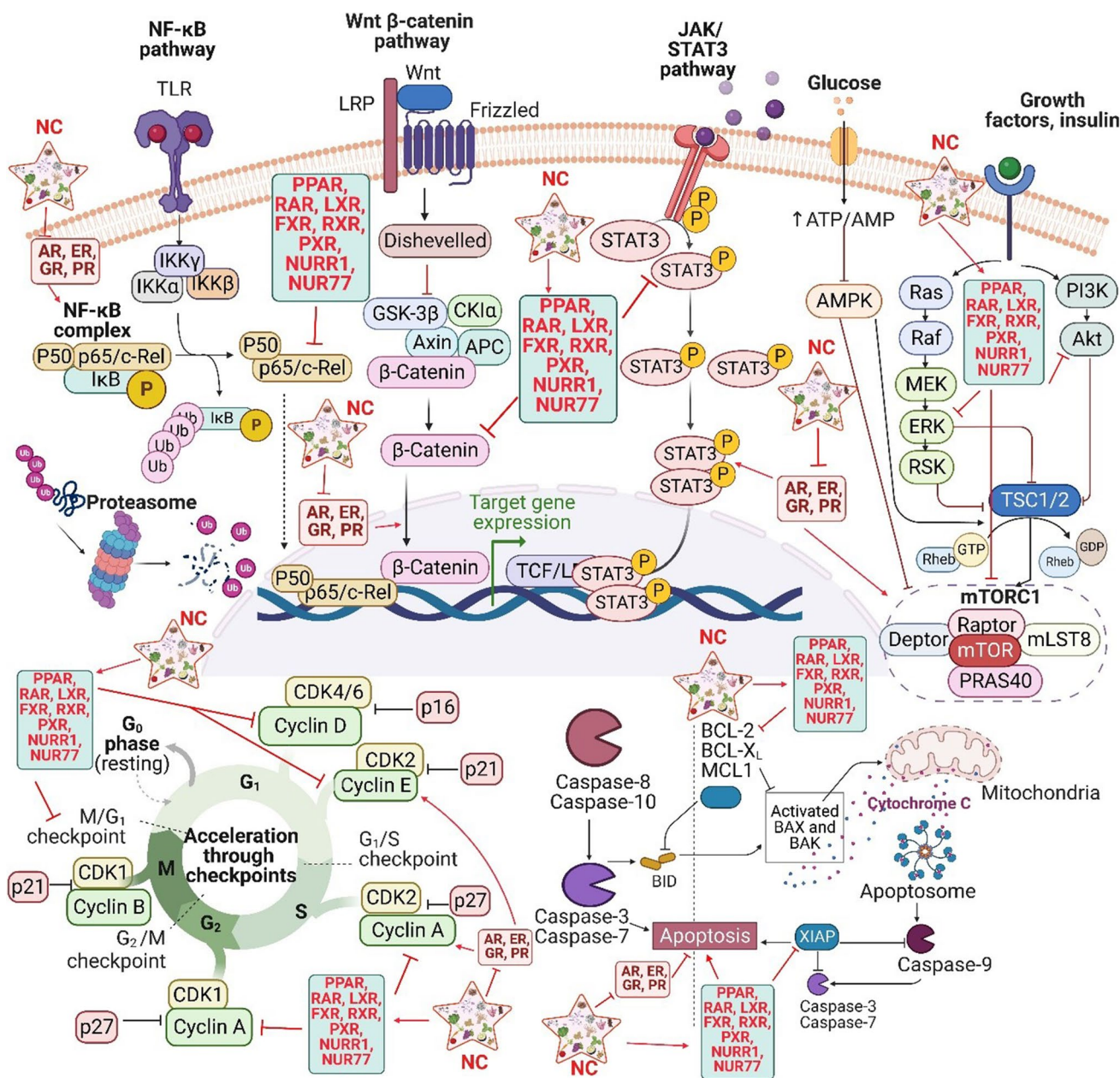
Fig. 4 Mechanism action of natural compounds through targeting NRs. NRs act upon several different pathways including NF-κB, STAT3, Akt, ERK, and Wnt signaling pathways to promote or inhibit cellular processes such as cell proliferation, cell cycle, and gene expression. The figure details the mechanism of action of NRs on different pathways and the role of natural compounds. The figure was created in BioRender.com

as breast, colon, leukemia, and lung [90, 91]. In addition, NRs have been demonstrated to modulate drug resistance via altering multidrug resistance protein 1 (MDR1) and breast cancer resistance protein (BCRP) expression [92–95]. For example, PXR and the CAR were shown to interact with the *MDR1* promoter and activate transcription [96–98]. Moreover, the BCRP promoter possesses response elements for both ER and PPARγ, indicating that NRs are involved in BCRP expression regulation [99, 100]. Interestingly, Geick

et al. discovered a distal enhancer region (at about −7.8 to −8 kilobase pairs) from the transcriptional start site (TSS) of the *MDR1* gene promoter that governs rifampicin-induced MDR1 expression in LS174T colon cancer cells. This study also validated that PXR/RXR binds to 3 DR4 (I, II, and III) and an ER6/DR4 complex by using an electrophoretic mobility shift assay (EMSA) (III). In addition, mutational investigations revealed that DR4(I) is required for rifampicin-mediated MDR1 induction [97]. Subsequently, Burk et al.

demonstrated that MDR1 is additionally controlled by CAR, through the DR4(I) and, to a lesser extent, the ER6/DR. Both DR4(I) and DR4(II) are required for the maximal induction of MDR1 by CAR [101]. In addition, PXR agonists including rifampicin, St. John's Wort, and carbamazepine can increase intestinal MDR1 expression while lowering the bioavailability and plasma concentrations of digoxin, talinolol, and fexofenadine that transported through MDR1 [96, 97]. Furthermore, SR12813 treatment stimulated PXR in the PC3 prostate cancer cell line and induced MDR1 expression and resistance to the anti-cancer medicines paclitaxel and vinblastine. PXR downregulation using siRNA in the endometrial cancer cell line HEC-1 reduced MDR1 expression and sensitized to paclitaxel and cisplatin [96]. Furthermore, elevated expression of RORC has been shown to promote cisplatin-induced apoptosis in bladder cancer both *in vitro* and *in vivo* through programmed cell death ligand 1 (PDL-1)/integrin subunit beta 6 (ITGB6)/signal transducer and activator of transcription factor 3 (STAT3) pathway [102]. More recently, Hu et al. demonstrated that suppression of TR4 by bexarotene resulted in increased sensitivity to docetaxel in prostatic cancer cell lines [103].

Innovative recent studies are providing enthralling support that targeting NRs by various approaches is a promising strategy against the progression and outcome of neoplastic diseases. Many anti-cancer drugs approved by FDA have been shown to target nuclear receptors (Table 1) [104–128]. However, these drugs have shown severe to moderate adverse side effects. This demands the screening of novel therapeutic agents that target NRs which possess low or no side effects and high efficacy.

4 Natural compounds as NR targets in cancer

Considering ligands play a critical role in modifying NR function, NR agonists and antagonists have been proposed for pharmacological development. Research over the past several years has showcased the cancer chemopreventive and therapeutic potential of natural products and their derivatives against various cancers [24–26, 129–138]. Biochemical, structural, and pharmacological screening and characterizations of natural product libraries have successfully discovered several unique compounds that modulate NRs [139]. A wide range of natural compounds from different sources including plants, animals, and microbially derived substances have been reported to possess anti-cancer activities by modulating NR expression [140–143]. In this section, we provide a detailed overview of these NR-targeting natural compounds and their anti-cancer mechanism with an emphasis on their therapeutic potential. The details about the natural compounds targeting

nuclear receptors in various cancers are summarized in Table 2.

5 Phytochemicals as NR modulators

Over the past several decades, numerous phytochemicals including alkaloids, carotenoids, coumarins, curcuminoids, flavonoids, indole derivatives, lignans, and terpenoids have been reported as anti-neoplastic agents by exhibiting agonistic or antagonistic properties against human NRs. The next section details some of the important phytochemicals that modulate the expression of NR and possesse anti-cancer properties. Figure 5 illustrates the various phytochemicals and their target NRs leading to reduced cancer hallmarks.

5.1 Alkaloids

Alkaloids are a broad collection of chemicals that possess cyclic structures with at least one basic nitrogen atom. These compounds are primarily found in plants belonging to the Leguminosae, Loganiaceae, Menispermaceae, Ranunculaceae, and Papaveraceae families. Numerous alkaloids are well-known as potent chemotherapeutic drugs, including berberine, camptothecin, evodiamine, matrine, vincristine, piperine, sanguinarine, tetrandrine, and vinblastine [144–147]. Alkaloids have also been shown to inhibit cancer progression through the modulation of NRs. For instance, treatment of KM12C colon cancer cells with berberine, a small molecule isoquinoline alkaloid isolated from rhizomes of *Coptis chinensis* and *Hydrastis canadensis*, at 25 µM attenuated proliferation and cell cycle by binding and activating RXRα, suppressing β-catenin signaling, and enhancing the expression of target genes including ATP binding cassette subfamily A member 1 (*ABCA1*), forkhead box O3 (*FOXO3A*), apolipoprotein E (*APOE*), cyclooxygenase 2 (*COX2*), and proliferating cell nuclear antigen (*PCNA*) [148, 149]. Similarly, another natural alkaloid, caffeine, found in a variety of plants including cocoa beans, coffee beans, cola nuts, and tea leaves, has been shown to limit cell proliferation, eliminate chemical or radiation-induced impediments in normal cell cycle, increase the cytotoxicity to radiation and anti-cancer drugs, and reduce ultraviolet B (UVB) radiation–induced malignant transformation [150–156]. Recently, Faudone et al. demonstrated that caffeine (30 µM) modulates orphan nuclear receptor TLX activity in T98G glioblastoma cell line. This study also showed that the derepression of TLX by caffeine diminished FXR, NURR1, RARα, and RXRα [157]. Another compound, capsaicin (N-vanillyl-8-methyl-nonenamide), a spicy

Table 1 FDA-approved drugs targeting NR and their adverse effects

Drug	Clinical trial number	Dose	Cancer	NR targeted	Adverse effects	Reference
Alitretinoin	NCT00002188 NCT00002439	0.1% gel	AIDS-related Kaposi sarcoma	RAR RXR	Diarrhea, leukopenia	[113]
Apalutamide	NCT01946204, NCT01171898	240 mg/d	Metastatic castration–resistant prostate cancer	AR	Grade 3 fatigue, diarrhea, nausea, hypertension, malignant melanoma, rash, hypothyroidism, fracture	[120, 122, 123]
Bexarotene	NCT01578499	150 mg/d	Cutaneous T-cell lymphoma	RXR	Fever, chills, myalgia, arthralgia, anorexia, weight loss, diarrhea, insomnia, impotence, confusion, depression, and changes in mood, memory, cognitive and motor function	[109, 114, 118]
Bicalutamide	NCT01809691, NCT02614859, NCT02058706, NCT00002874	50 mg/d	Metastatic prostate cancer	AR	Hypertension, fatigue, backache, dizziness, fall, decreased appetite, constipation, diarrhea, anemia, urinary tract infection	[105, 111]
Enzalutamide	NCT02495974, NCT02711956, NCT02987543, NCT03437941	160 mg/d	Metastatic castration–resistant prostate cancer	AR	Cardiovascular diseases, hypertension	[105–107, 119]
Flutamide	NCT00104741	250 mg/d	Metastatic prostate cancer	AR	Hepatic failure, cholestatic hepatitis, jaundice, diarrhea, abdominal pain, anorexia, nausea, vomiting	[108, 127]
Fulvestrant	NCT02913430, NCT03238196, NCT02738866	250 mg/d	Metastatic breast cancer	ER	Nausea, asthenia, pain, vasodilation, headache	[116, 117, 121]
Tamoxifen	NCT02913430, NCT02384239, NCT01196936	20 mg	Metastatic breast cancer	ER	Severe hot flushes, depression, insomnia, cataracts, vaginal dryness, weight gain and irritability, deep vein thrombosis, and pulmonary embolism	[110, 115]
Toremifene	NCT02506790	60 mg/d	Metastatic breast cancer	ER	Hot flushes, sweating, nausea and/or vomiting, dizziness, oedema, and vaginal discharge and/or bleeding	[124, 125]
Tretinoin	NCT01404949, NCT02339740	45 mg/ m², 0.1% cream	Acute promyelocytic leukemia	RAR	Skin rash, nasal congestion, and hypertriglyceridemia, headache, non-melanoma skin cancer	[112, 126, 128]

Table 2 The natural compounds that target NR and their anti-cancer effects

Name of the compound	Source	In vitro / In vivo	Cell line/model	Tumor type	Targeted NR	Effect on NR	Reference
Phytochemicals							
Carotenoids — β-carotene, astaxanthin, capsanthin, bixin		In vitro In vivo	K562	Leukemia	PPARγ	Activation	[167]
Fucoxanthin	Undaria pinnatifida (seaweed)	In vitro	Caco-2, HT-29, DLD-1	Colon cancer	PPARγ	Activation	[169]
		In vitro	LS174T	Colon cancer	PXR	Inhibition	[168]
		In vitro	HepG2	Liver cancer	PXR	Inhibition	[168]
β-cryptoxanthin	Citrus unshiu Marc	In vitro	A549, BEAS-2B	Lung cancer	RARβ	Transactivation	[170]
		In vivo	Male A/J mice	Lung cancer	RARβ	Activation	[171]
Apo-10′-lycopene	Lycopene derivative	In vitro	A549	Lung cancer	PPARγ	Activation	[172]
		In vitro	HuH7	Liver cancer	PPARγ	Activation	[172]
Curcumin	Curcuma longa	In vitro	MCF-7	Breast cancer	PPARγ	Activation	[227]
		In vitro	T47D	Breast cancer	ERα	Inhibition	[368]
		In vitro	MDA-MB-231, MDA-MB-468	Breast cancer	PPARβ/δ	Inhibition	[232]
		In vitro	MDA-MB-231, MDA-MB-468	Breast cancer	RARβ, RARγ	Activation	[231]
		In vitro	T47D	Breast cancer	ERα	Inhibition	[369]
		In vitro	KKU-M156	Cholangiocarcinoma	PPARγ	Activation	[223]
		In vitro	Moser cells	Colon cancer	PPARγ	Activation	[230]
		In vitro	HT-29	Colorectal cancer	PPARγ	Activation	[227]
		In vitro	HCT-116	Colorectal cancer	VDR RAR RXR	Activation	[228]
		In vitro	Caco-2	Colorectal cancer	VDR	Activation	[229]
		In vitro	Hepa 1-6	Liver cancer	ERα	Activation	[370]
		In vitro	HepG2	Liver cancer	LXRα	Activation	[224]
		In vitro	Huh7	Liver cancer	FXR	Activation	[225]
		In vitro	A549, H460	Lung cancer	RARβ	Promoter hypomethylation	[226]
		In vitro	BxPC-3	Pancreatic cancer	ERα	Inhibition	[371]
		In vitro	LNCaP, PC3	Prostate cancer	AR	Inhibition	[372]
		In vitro	LNCaP	Prostate cancer	AR	Inhibition	[373]
		In vitro	LNCaP	Prostate cancer	AR	Inhibition	[374]
		In vitro	LNCaP, PC3	Prostate cancer	AR	Inhibition	[375]
		In vitro	LNCaP	Prostate cancer	AR	Inhibition	[376]
		In vitro	LNCaP, C4-2B	Prostate cancer	AR	Inhibition	[377]

Table 2 (continued)

Name of the compound	Source	In vitro / In vivo	Cell line/model	Tumor type	Targeted NR	Effect on NR	Reference
Poly(lactic-co-glycolic acid)—curcumin nanoparticles	Curcuma longa	In vitro	C4-2, DU145, LNCaP	Prostate cancer	AR	Inhibition	[378]
		In vivo	C4-2 xenograft		AR	Inhibition	[378]
Curcumin, DHA		In vitro	SK-BR3, MDA-MB-231, MDA-MB-361, MCF7	Breast cancer	PPARγ	Activation	[233]
Curcumin, quercetin		In vitro	AR negative CaP cells, DU145, PC3	Prostate cancer	AR	Activation	[379]
Curcumin, resveratrol		In vitro	PTEN-CaP8	Prostate cancer	AR	Inhibition	[380]
Capsaicin	Pepper	In vitro	HT-29	Colon cancer	PPARγ	Activation	[159]
		In vitro	HepG2	Liver cancer	PPARγ	Activation	[160]
Thymoquinone	Nigella sativa	In vitro	MCF-7, MDA-MB-231 and BT-474	Breast cancer	PPARγ PPARβ/δ	Activation Activation	[347]
Honokiol	Magnolia officinalis	In vitro	U251-MG	Glioblastoma	RXRβ	Activation	[283]
Piceatannol	Grapes, white tea, passion fruit, and Japanese knotweed	In vitro	HepG2	Liver cancer	FXR, PPARα	Activation	[340]
Guggulsterone	Commiphora mukul	In vitro	A549, H1975, mouse LLC cell line	Lung cancer	FXR	Inhibition	[266]
		In vitro	SGKT-4, SGKT-5, TE-12	Esophageal cancer	FXR RARβ	Inhibition Activation	[260]
		In vitro	T24, J82, TSGH8301	Bladder cancer	FXR	Activation (E-isomer of guggulsterone)	[261]
		In vitro	GES-1	Gastric intestinal metaplasia	FXR	Inhibition	[262]
		In vitro	HepG2	Liver cancer	FXR SHP PPARα PXR	Inhibition Inhibition Inhibition Inhibition	[263]
		In vitro	MIA-PaCa2, PANC-1	Pancreatic cancer	FXR	Inhibition	[264]
Guggulsterone plus bexarotene		In vitro	MDA-MB-231	Breast cancer	FXR RXR	Inhibition Inhibition	[265]
Liquiritigenin	Glycyrrhizae uralensis	In vitro	MCF-7	Breast cancer	ERβ	Activation	[333]
Celastrol	Tripterygium wilfordii	In vitro	PC3, LNCaP	Prostate cancer	AR	Inhibition	[211]
		In vivo	PC3 cell bearing nude mice	Prostate cancer	AR	Inhibition	[211]
Triptolide	Tripterygium wilfordii	In vitro	PC3, LNCaP	Prostate cancer	AR	Inhibition	[348]
		In vivo	PC3 cell bearing nude mice	Prostate cancer	AR	Inhibition	[348]
		In vitro	MCF-7	Breast cancer	ERα	Inhibition	[349]

Table 2 (continued)

Name of the compound	Source	Tumor type	In vitro / In vivo	Cell line/model	Targeted NR	Effect on NR	Reference
Cryptotanshinone	Salvia miltiorrhiza	Prostate cancer	In vitro / In vivo	PC3, LNCaP and 22Rv1	AR	Transactivation	[215]
		Prostate cancer	In vitro	PC3, LNcaP, CWR22rv1	AR	Transactivation	[216]
		Prostate cancer	In vivo	CWR22rv1 xenograft model	AR	Transactivation	[216]
3β,7β-dihydroxy-25-methoxycucurbita-5,23-diene-19-al (DMC)	Momordica charantia	Breast cancer	In vitro	MCF-7, MDA-MB-231	PPARγ / ERα	Activation / Inhibition	[308]
Withaferin A	Withania somnifera	Hepatocellular carcinoma	In vitro	HepG, Hep3B, Huh-7 cells, QGY-7703	LXRα	Activation	[298]
Oridonin	Rabdosia rubescens	Osteosarcoma	In vitro	MG-63, HOS	PPARγ	Activation	[337]
Magnolol	Magnolia officinalis	Hepatocellular carcinoma	In vitro	HepG2	PPARα	Activation	[336]
Berberine	Coptis chinensis	Colon cancer	In vitro	KM12C	RXRα	Activation	[149]
		Colon cancer	In vivo	KM12C xenograft	RXRα	Activation	[149]
Hesperidin	Citrus fruits	Breast cancer	In vitro	MCF-7	ERα	Inhibition	[278]
		Breast cancer	In vitro	MCF-7	ERα	Inhibition	[279]
Chlorogenic acid		Breast cancer	In vitro	MCF-7	ERα	Inhibition	[279]
Piperine	Piper nigrum, Piper longum	Breast cancer	In vitro	MCF-7	ERα	Inhibition	[278]
				MCF-7, MDA-MB-231	PPARα	Inhibition	[163]
3-butoxy-1,8,9-trihydroxy-6H-benzofuro[3,2-c]-benzopyran-6-one (BTB)	Derivative of wedelolactone	Breast cancer	In vitro	MDA-MB-231	ERα, ERβ	Inhibition	[306]
		Endometrial carcinoma		Ishikawa, HEC-1-A	ERα, ERβ	Inhibition	
		Ovarian cancer		SKOV-3, OVCA429	ERα, ERβ	Inhibition	
Cabraleadiol, 24-epi-cabraleadiol, stigmast-22-en-3β-ol, cabraleahydroxylactone, cabraleahydroxylactone acetate	Dysoxylum tpongense Pierre	Hepatocellular carcinoma	In vitro	HepG2	LXR	Inhibition	[381]
Deoxyelephantopin	Elephantopus carolinianus	Cervical cancer	In vitro	HeLa	PPARγ	Transactivation	[312]
Isoprenols—farnesol, geranylgeraniol, and geraniol		Liver cancer	In vitro	HepG2	PPARα and PPARγ	Activation	[321]
Atraric acid	Pygeum africanum	Prostate cancer	In vitro	LNCaP, C4-2	AR	Inhibition	[301]
Atraric acid, n-butyl atraric acid, ethyl atraric acid, n-propyl atraric acid	Pygeum africanum	Prostate cancer	In vitro	Adenocarcinoma cells	AR	Inhibition	[382]

Table 2 (continued)

Name of the compound	Source	Tumor type	In vitro In vivo	Cell line/model	Targeted NR	Effect on NR	Reference
Indole-3-carbinol	Brassica vegetables	Breast cancer	In vitro	MCF-7	ERα	Proteasomal degradation	[323]
		Prostate cancer	In vitro	LNCaP	AR	Inhibition	[324]
7-(O)-carboxymethyl daidzein conjugated to N-t-boc-hexylenediamine		Thyroid cancer	In vitro	Human thyroid normal, goiter, and papillary thyroid carcinoma (PTC) cells	ERα and ERβ	Activation	[309]
Resveratrol	Natural polyphenol present in red wine, peanuts, grapes	Breast cancer	In vitro	MDA-MB-231	ERα	Inhibition	[383]
		Cervical cancer	In vitro	HeLa	AR	Inhibition	[179]
		Colon cancer	In vitro	HCT-116, Caco-2	PPARγ	Activation	[294]
		Oral cancer	In vitro	CA-9-22	PPARγ	Activation	[293]
		Prostate cancer	In vitro	LNCaP	AR	Inhibition	[384]
		Prostate cancer	In vitro	LNCaP, CWR22rv1 and DU145, C4-2	AR	Inhibition	[385]
		Prostate cancer	In vitro	LNCaP, PC3	AR	Inhibition	[386]
		Prostate cancer	In vitro	LNCaP, PC3	AR	Inhibition	[252]
		Prostate cancer	In vitro	LNCaP	AR	Inhibition	[104]
		Prostate cancer	In vitro	LNCaP	AR	Inhibition	[387]
		Prostate cancer	In vitro	LNCaP, LNCaP-B	AR	Inhibition	[388]
		Thyroid cancer (anaplastic)	In vitro	THJ-11T, THJ-16T, THJ-21T	RARβ PPARβ	Activation Inhibition	[295]
Phytol	Carbon side chain of chlorophyll	Liver cancer	In vitro	HepG2	PPARα	Activation	[339]
Sulforaphane	Cruciferous vegetables	Breast cancer	In vivo	August Copenhagen Irish (ACI) rats	ERα ERβ	Activation Inhibition	[328]
Isoalantolactone		Pancreatic cancer	In vitro	Mia-Pa-Ca-2	NUR77	Inhibition	[313]
n-butylidenephthalide	Angelica sinensis	Glioblastoma	In vitro	DBTRG-05MG, GBM 8401	NURR1 NUR77	Activation Activation	[205]
			In vivo	DBTRG-05MG xenograft mice	NUR77	Activation	[205]
3,3'-diindolylmethane	Derived from indole-3-carbinol Present in cruciferous vegetables	Liver cancer	In vitro	HepG2, J5	NUR77	Activation	[204]
		Skin cancer	In vitro	A431, NHEK	NURR1	Activation	[326]
Z-ligustilide	Angelica sinensis	Breast cancer	In vitro	Tamoxifen-resistant MCF-7	NUR77	Activation	[389]
Celastrol	Tripterygium wilfordii	Liver cancer	In vitro	HepG2	NUR77	Activation	[212]

Table 2 (continued)

Name of the compound	Source	In vitro In vivo	Cell line/model	Tumor type	Targeted NR	Effect on NR	Reference
Acetylshikonin	Lithospermum erythrorhizon	In vitro	Hepatitis B virus X protein-expressing Hep3B cells	Liver cancer	NUR77	Activation	[184]
		In vitro	HepG2	Liver cancer	NUR77	Activation	[183]
		In vitro	NIH-H460	Lung cancer	NUR77	Activation	[183]
		In vitro	HeLa	Cervical cancer	NUR77	Activation	[183]
1,1-bis (3'-indoly)-1-(p-hydroxyphenyl) methane	Bis-indole derivative	In vitro	Embryonic rhabdomyosarcoma cells	Rhabdomyosarcoma	NUR77	Inhibition	[390]
Baicalein	Scutellaria radix	In vitro	U266, ILKM2	Myeloma	PPARβ	Activation	[197]
	Garlic	In vitro	Huh7, HepG2	Liver cancer	CAR	Activation	[198]
	Scutellaria baicalensis	In vitro	LNCaP	Prostate cancer	AR	Inhibition	[199]
Chrysin	Garlic	In vitro	Huh7, HepG2	Liver cancer	CAR	Activation	[198]
Galangin	Garlic	In vitro	Huh7, HepG2	Liver cancer	CAR	Activation	[198]
Artemisinin	Artemisia annua	In vitro	PC3, LNCaP	Prostate cancer	AR	Inhibition	[186]
Artesunate	Artemisia annua	In vitro	PC3	Prostate cancer	AR	Inhibition	[188]
Dihydroartemisinin	Artemisia annua	In vitro	SW948	Colon cancer	PPARγ	Activation	[189]
Artemisinin derivatives		In vitro	PC3, LNCaP	Prostate cancer	AR	Inhibition	[187]
Auraptene	Citrus fruits	In vitro	HepG2	Liver cancer	PPARα	Activation	[192]
Bruceantin	Brucea species	In vitro	22RV1, C4-2B, CRPC	Prostate cancer	AR	Inhibition	[305]
Diterpenes including 6,12-dihydroxyabieta-5,8,11,13-tetraen-7-one, sugiol, ferruginol, and 5-epixanthoperol	Cryptomeria japonica	In vitro	22RV1 derived 103E cells	Prostate cancer	AR	Inhibition	[353]
Quercetin 3-glucuronide, quercetin 3-sulfate		In vitro	A549	Lung cancer	PPARγ	Activation	[391]
Emodin	Rheum palmatum	In vitro	LNCaP, PC3, DU145	Prostate cancer	AR	Inhibition	[245]
Embelin	Embelia ribes	In vitro	HCT116	Colon cancer	PPARγ	Activation	[85]
		In vivo	PPARγ+/+ PPARγ+/-/ PPARγ-/- mice	Colon cancer	PPARγ	Activation	[85]

Table 2 (continued)

Name of the compound	Source	Tumor type	In vitro/In vivo	Cell line/model	Targeted NR	Effect on NR	Reference
Genistein	Soy food	Prostate cancer	In vitro / In vivo	LAPC-4	ERβ	Activation	[249]
			In vitro	LNCaP	AR	Inhibition	[250]
				LNCaP	AR	Inhibition	[251]
				LNCaP, PC3, DU145	AR	Inhibition	[248]
		Lung cancer	In vitro	EA.hy926 (HUVECs fused with A549)	PPARγ	Activation	[253]
		Ovarian cancer	In vitro	SKOV3	AR	Inhibition	[254]
		Cervical cancer	In vitro	HeLa	PPARα PPARγ	Activation Activation	[255]
		Prostate cancer	In vitro	LNCaP, PC3	AR	Inhibition	[252]
Formononetin	Astragalus membranaceus	Cervical cancer	In vitro	HeLa	PPARα PPARγ	Activation Activation	[255]
Calycosin	Astragalus membranaceus	Cervical cancer	In vitro	HeLa	PPARα PPARγ	Activation Activation	[255]
Daidzein	Pueraria thomsonii	Cervical cancer	In vitro	HeLa	PPARα PPARγ	Activation Activation	[255]
Biochanin A		Cervical cancer	In vitro	HeLa	PPARα PPARγ	Activation Activation	[255]
Metformin	Galega officinalis	Colon cancer	In vitro	LS174T	PXR SHP CAR VDR GR	Inhibition Inhibition Inhibition Inhibition Inhibition	[392]
		Liver cancer	In vitro	MZ-Hep-1	PXR SHP	Inhibition Inhibition	[392]
Ginkgolides A and B	Ginkgo biloba	Liver cancer	In vitro	HepG2	PXR	Activation	[350]
EGB 761					PXR	Activation	
Quercetin					PXR CAR	Activation Activation	
Kaempferol					PXR CAR	Activation	
Forskolin	Coleus forskohlii	Liver cancer	In vitro	HepaRG, HepG2	PXR FXR	Activation Activation	[317]
Allyl isothiocyanate	Brassica species	Liver cancer	In vitro	HepG2, HepaRG	PXR CAR	Inhibition Inhibition	[299]
Farrerol	Rhododendron dauricum	Ovarian cancer	In vitro	SKOV3	PPARγ	Activation	[315]

Table 2 (continued)

Name of the compound	Source	Tumor type	In vitro / In vivo	Cell line/model	Targeted NR	Effect on NR	Reference
Asaronic acid	Purple perilla	Leukemia	In vitro	J774.1, THP-1	PPARγ	Activation	[300]
N-butylbenzene-sulfonamide	*Pygeum africanum*	Prostate cancer	In vitro	LNCaP, PC3	AR PR GR THRB	Inhibition Inhibition Inhibition Inhibition	[303]
Neoruscogenin	*Rhei rhizoma*	Liver cancer	In vitro	HepG2	RORα	Activation	[393]
Ent-11alpha-hydroxy-15-oxo-kaur-16-en-19-oic-acid	*Pteris semipinnata*	Ovarian cancer	In vitro	HO-8910PM	Rev-Erbα	Activation	[341]
Gypenoside XLIX	*Gynostemma pentaphyllum*	Leukemia	In vitro	THP-1	PPARα	Activation	[273]
Lignans		Liver cancer	In vitro	HepG2, Huh7	PXR	Activation	[354]
Enterolactone		Liver cancer	In vitro	HepG2, Huh7	PXR	Activation	[354]
Organochlorine		Liver cancer	In vitro	HepG2, Huh7	PXR	Activation	[354]
Ellagic acid		Breast cancer	In vivo	Estrogen induced carcinogenesis in rats	ER	Inhibition	[239]
Tangeretin		Breast cancer	In vivo	7,12-dimethyl benz(a) anthracene (DMBA) induced mammary carcinoma in rats	ERα PR	Inhibition Inhibition	[351]
Cyanidin		Liver cancer	In vitro	HepG2	LXRα LXRβ	Activation	[352]
Compound b7	Adamantyl-substituted flavonoid derivatives	Lung cancer	In vitro	H460	NUR77	Activation	[394]
Fucosterol	Marine algae	Colon cancer	In vitro	Caco-2	LXRα LXRβ	Activation	[355]
Ethyl-2,4,6-trihydroxybenzoate	*Celtis biondii*	Liver cancer	In vitro	HepG2	LXRα LXRβ	Activation Activation	[356]
Iristectorigenin B	*Belamcanda chinensis*	Liver cancer	In vitro	HepG2, RAW264.7 (macrophage)	LXRα LXRβ	Activation Activation	[357]
Paeoniflorin	*Paeonia lactiflora*	Liver cancer	In vitro	HepG2	LXR	Activation	[358]
Octulosonic acid	*Chamaemelum nobile*	Liver cancer	In vitro	HepG2	PPARα PPARγ LXR	Activation Activation Activation	[395]
Riccardin C	liverworts	Leukemia	In vitro	THP-1	LXRα LXRβ	Activation Inhibition	[396]
Diosgenin	*Trigonella foenum-graecum*	Liver cancer	In vitro	HepG2	LXRα	Inhibition	[397]
Naringenin	*Grape fruit flavonoid*	Liver cancer	In vitro	Huh7	PPARα PPARγ LXRα	Activation Activation Inhibition	[398]

Table 2 (continued)

Name of the compound	Source	In vitro / In vivo	Cell line/model	Tumor type	Targeted NR	Effect on NR	Reference
Rhein	*Rheum palmatum*	*In vitro*	Hepa1-6	Liver cancer	LXR	Activation	[399]
		In vivo	LXR$^{-/-}$ mice	Hepatic steatosis	LXR	Activation	[399]
Phytosterols	Evening primrose oil	*In vitro*	HT-29	Colon cancer	LXR	Activation	[400]
Glycyrrhizic acid and 18β-glycyrrhetinic acid	Licorice	*In vitro*	Macrophages	Lung precancer	GR	Activation	[401]
		In vitro	THP-1	Leukemia	GR	Activation	[402]
		In vitro	HeLa	Cervical cancer	GR	Activation	[402]
Glycyrrhetinic acid	Licorice	*In vitro*	SW-480, HT-29	Colon cancer	PPARγ	Activation	[403]
Ginsenoside-Rg1	*Panax ginseng*	*In vitro*	FTO2B	Liver cancer	GR	Activation	[404]
Okadaic acid (OA) and dinophysistoxin-1 and dinophysistoxin-2 (DTX-1 and DTX-2), pectenotoxin-2 (PTX-2)	Phytoplankton	*In vitro*	HepG2, HepaRG	Liver cancer	PXR	Activation	[405]
Ferulic acid and p-coumaric acid	*Millet bran*	*In vitro*	HT-29, DLD1, HCT116, SW620, SW480	Colon cancer	GR	Inhibition	[406]
		In vivo	azoxymethane 96 (AOM)/dextran sodium sulfate (DSS)-induced colorectal cancer (CRC) mice model	Colon cancer	GR	Inhibition	[406]
Punicalagin	Pomegranate	*In vitro*	LNCaP	Prostate cancer	AR	Inhibition	[240]
Epigallocatechin gallate	Pomegranate	*In vitro*	LNCaP	Prostate cancer	AR	Inhibition	[407]
Delphinidin chloride							
Kaempferol							
Punicic acid							
Ellagic acid	Pomegranate	*In vitro*	LNCaP	Prostate cancer	AR	Inhibition	[240]
MF101	Herbal extract	*In vitro*	MCF-7	Breast cancer	ERβ	Activation	[408]
22 compounds	Si Wu Tang series decoctions	*In vitro*	MCF-7	Breast cancer	ERα	modulation	[409]
Caffeine		*In vitro*	T98G	Glioblastoma	TLX	Activation	[157]
Xanthine		*In vitro*	T98G	Glioblastoma	TLX	Activation	[157]
(20S)-2α, 3β, 12β, 24(S)-pentahydroxydammar-25-ene 20-O-β-D-glucopyranoside (TR1)	*Gynostemma pentaphyllum*	*In vitro*	THP-1	leukemia	LXRα LXRβ	Activation Activation	[410]
Wogonin	*Scutellaria baicalensis*	*In vitro*	LNCaP	Prostate cancer	AR	Inhibition	[199]
Neobaicalein	*Scutellaria baicalensis*	*In vitro*	LNCaP	Prostate cancer	AR	Inhibition	[199]
Skullcapflavone	*Scutellaria baicalensis*	In vitro	LNCaP	Prostate cancer	AR	Inhibition	[199]

Table 2 (continued)

Name of the compound	Source	Tumor type	In vitro In vivo	Cell line/model	Targeted NR	Effect on NR	Reference
Acetyl-11-keto-β-boswellic acid (AKBA)	*Boswellia carterii*	Prostate cancer	In vitro	PC3, LNCaP	AR	Inhibition	[411]
Perillyl alcohol	Fruits and vegetables	Prostate cancer	In vitro	LNCaP	AR	Inhibition	[412]
Morusin	*Morus australis and Ramulus Mori*	Breast cancer	In vitro	MCF-7, MDA-MB-231	PPARγ	Activation	[289]
		Breast cancer	In vivo	MCF-7 cells bearing nude mice	PPARγ	Activation	[289]
Emodin	*Rheum palmatum*	Liver cancer	In vitro	HepG2, Hep3B, Huh7	FXR	Inhibition	[246]
6-shogaol	*Zingiber officinale*	Breast cancer	In vitro	MCF-7	PPARγ	Activation	[342]
		Colon cancer	In vitro	HT29	PPARγ	Activation	[342]
(R)- and (S)-cyclocymopol monomethyl ether	*Cymopolia barbata*	Breast cancer	In vitro	T47D	PR	Inhibition	[413]
Diptoindonesin G	Tropical plants	Breast cancer	In vitro	T47D, MCF-7	ERα ERβ	Inhibition Activation	[414]
Neo-tanshinlactone	*Salvia miltiorrhiza*	Breast cancer	In vitro	MCF7, ZR-75-1, MDA-MB-231, BT-549, HCC1937	ERα	Inhibition	[415]
St. John's wort and hyperforin	*Hypericum perforatum*	Choriocarcinoma	In vitro	JEG-3	PXR	Activation	[360]
Blueberry diet		Breast cancer	In vivo	Female rats	ERα	Inhibition	[367]
Dietary flaxseeds		Breast cancer	In vivo	MCF-7 xenografts	ERα	Inhibition	[366]
Pomegranate juice	Pomegranate	Prostate cancer	In vitro	LNCaP	AR	Inhibition	[240]
Pomegranate extract	Pomegranate	Prostate cancer	In vitro	LNCaP	AR	Inhibition	[240]
Pomegranate emulsion		Breast cancer	In vivo	DMBA rat mammary carcinogenesis	ERα ERβ	Inhibition Inhibition	[364]
Extract	*Zanthoxyli fructus*	Prostate cancer	In vitro	PC3, LNCaP, DU145	AR	Inhibition	[361]
Extract	*Serenoa repens*	Prostate cancer	In vitro	LNCaP	AR	Inhibition	[362]
Hochu-ekki-to	Herbal medicine	Endometrial cancer	In vivo	Female mice	ERα ERβ	Inhibition Inhibition	[416]
Aqueous extract	*Psidium guajava L*	Prostate cancer	In vitro	LNCaP	AR	Inhibition	[363]
Ethanol extract	*Astragalus membranaceus*	Cervical cancer	In vitro	HeLa	PPARα	Activation	[255]
Ethanol extract	*Pueraria thomsonii*	Cervical cancer	In vitro	HeLa	PPARγ	Activation	[255]
BZL101	*Scutellaria barbata*	Breast cancer	In vitro	MCF-7, MDA_MB-231	ERα	Inhibition	[417]
		Prostate cancer	In vitro	PC3, LNCaP	AR	Inhibition	[417]
Dichloromethane extract	*Pygeum africanum*	Prostate cancer	In vitro	LNCaP	AR	Inhibition	[302]
Cornus alternifolia methanolic extract	*Cornus alternifolia*	Liver cancer	In vitro	HepG2	PPARα PPARγ LXR	Activation Activation Activation	[365]

Table 2 (continued)

Name of the compound	Source	In vitro In vivo	Cell line/model	Tumor type	Targeted NR	Effect on NR	Reference
Ethanolic extract Zootherapeutics	Scutellaria baicalensis	In vitro In vivo	LNCaP	Prostate cancer	AR	Inhibition	[199]
Psammaplin A	Pseudoceratina rhax	In vitro	MCF-7	Breast cancer	PPARγ	Activation	[418]
Sintokamide A	Dysidea sp.	In vitro	LNCaP	Prostate cancer	AR	Inhibition	[419]
Solomonsterols A and B	Theonella swinhoei	In vitro	HepG2	Liver cancer	PXR	Activation	[420]
Solomonsterol A	Theonella swinhoei	In vitro	HepG2	Liver cancer	PXR	Activation	[421]
Cholestan disulfate	Theonella swinhoei	In vitro	HepG2	Liver cancer	PXR	Activation	[422]
Theonellasterols B–H and conicasterol B	Theonella swinhoei	In vitro	HepG2	Liver cancer	PXR FXR	Activation Inhibition	[423]
Theonellasterols	Theonella swinhoei	In vitro	HepG2	Liver cancer	FXR SHP	Inhibition Inhibition	[424]
Theonellasterol,3-O-acetyl theonellasterol, theonellasterol methyl ether, 4-methyl diastereoisomers of theonellasterol	Theonella swinhoei	In vitro	HepG2	Liver cancer	FXR	Inhibition	[425]
Conicasterol E	Theonella swinhoei	In vitro	HepG2	Liver cancer	PXR	Activation	[426]
Conicasterol F	Theonella swinhoei	In vitro	HepG2	Liver cancer	PXR FXR	Activation Inhibition	[427]
Malaitasterol A	Theonella swinhoei	In vitro	HepG2	Liver cancer	PXR	Activation	[428]
4-Methylenesterols	Theonella swinhoei	In vitro	HepG2	Liver cancer	PXR FXR	Activation Inhibition	[429]
Compounds 3 and 8	Theonella swinhoei and T. conica	In vitro	HepG2	Liver cancer	PXR	Activation	[430]
Gracilioether B and plakilactone C	Plakinastrella mamillaris	In vitro	HepG2	Liver cancer	PPARγ	Activation	[431]
Gracilioether K, gracilioethers E–G, gracilioethers I and J	Plakinastrella mamillaris	In vitro	HepG2	Liver cancer	PXR	Activation	[432]
Incisterols A5 and A6	Plakortis cfr. lita	In vitro	HepG2	Liver cancer	PXR	Activation	[433]
Methanol extract	Niphates digitalis	In vitro	LNCaP	Prostate	AR	Inhibition	[434]
Niphatenone B	Niphates digitalis	In vitro	LNCaP	Prostate	AR	Inhibition	[434]
Luffariellolide	Marine sponges Luffariella sp. and Fascaplysinopsis	In vitro	THP-1 cells	Acute monocytic leukemia	RAR	Activation	[435]
		In vitro	MCF-7	Breast cancer cells	RAR	Activation	[435]
		In vitro	HCT-116, HCT-15	Colon cancer	RAR	Activation	[435]
		In vitro	HL-60, THP-1	Leukemia	RAR	Activation	[435]
Suvanine	Marine sponge	In vitro	HepG2	Liver cancer	FXR	Inhibition	[436]

Table 2 (continued)

Name of the compound	Source	In vitro In vivo	Cell line/model	Tumor type	Targeted NR	Effect on NR	Reference
12-deacetyl-12-*epi*-scalara-dial	*Hippospongia* sp.	*In vitro* *In vivo*	HeLa	Cervical cancer	Nur77	Activation	[437]
Phakefustatin A	*Phakellia fusca*	*In vitro*	HeLa	Cervical cancer	RXRα	Inhibition	[438]
Cinanthrenol A	*Cinachyrella* sp.	*In vitro*	MCF-7	Breast cancer	ER	Inhibition	[439]
		In vitro	HeLa	Cervical cancer	ER	Inhibition	[439]
Myrmenaphthol A	Hawaiian sponge of genus *Myrmekioderma*	*In vitro*	HeLa	Cervical cancer	ER	Inhibition	[440]
		In vivo	P388	Lymphoma	ER	Inhibition	[440]
Phallusiasterols A and B	*Phallusia fumigata*	*In vitro*	HepG2	Liver cancer	PXR	Activation	[441]
Phallusiasterol C	*Phallusia fumigata*	*In vitro*	HepG2	Liver cancer	PXR	Activation	[442]
Okadaic acid	*Ciona intestinalis*	*In vitro*	HepG2	Liver cancer	PXR	Activation	[443]
ET-743	*Ecteinascidia turbinata*	*In vitro*	Osteosarcoma cell line	Osteosarcoma	PXR	Inhibition	[444]
Ergost-5-en-3β-ol	*Sinularia kavarattiensis*	*In vitro*	HepG2	Liver cancer	PXR	Activation	[445]
Compounds 1 and 6	*Ophiocoma dentata*	*In vitro*	HepG2	Liver cancer	FXR	Inhibition	[446]
Compound 2	*Ophiarthrum elegans*	*In vitro*	HepG2	Liver cancer	FXR	Inhibition	[446]
Compound 3	*Ophioderma longicaudum*	*In vitro*	HepG2	Liver cancer	FXR	Inhibition	[446]
Compounds 4, 5, 7, 8	*Ophiolepis superba*	*In vitro*	HepG2	Liver cancer	FXR	Inhibition	[446]
Nemorosone	Bee	*In vitro*	MCF-7	Breast cancer	ERα	Inhibition	[447]
10-hydroxy-2-decenoic-10H2DA, 3,10-dihydroxydecanoic-3,10DDA, sebacic acid-SA	Bee	*In vitro*	MCF-7	Breast cancer	ERβ	Activation	[448]
Bee venom	Bee	*In vitro*	MCF-7	Breast cancer	ERα	Inhibition	[278]
Mucroporin-M1	Scorpion (*Lychas mucronatus*)	*In vitro*	HepG2.2.15	Hepatocellular carcinoma	HNF4α	Inhibition	[449]
Gly-Pro-Ala peptide	Fish skin	*In vitro*	THP-1	Leukemia	NUR77	Activation	[450]
Metabolite-derived compounds							
15d-PGJ2	Prostaglandin D2 metabolite	*In vitro*	U-937	Lymphoma	PPARγ	Activation	[451]
		In vitro	THP-1	Acute monocytic leukemia	PPARγ	Activation	[452]
15S-hydroxyeicosatetraenoic acid	Derived from arachidonic acid	*In vitro*	PC3	Prostate cancer	PPARγ	Activation	[453]
All-trans retinoic acid, 9-cis-retenoic acid	Dietary component	*In vitro*	T3M-4, AsPc-1, BxPc-3	Pancreatic cancer	RARγ	Activation	[454]
γ-tocopherol	Dietary component	*In vitro*	SW480	Colon cancer	PPARγ	Activation	[455]
Vitamin E	Dietary component	*In vitro*	SW480	Colon cancer	PPARγ	Activation	[455]

Table 2 (continued)

Name of the compound	Source	Tumor type	In vitro / In vivo	Cell line/model	Targeted NR	Effect on NR	Reference
Two glucuronides (49-O-, and 7-O-) and a glucuronyl (7-O-) sulfate (49-O-), genistein, two glucuronides (49-O-, and 7-O-) and a glucuronyl (7-O-) sulfate (49-O-) of daidzein, 7-O-glucuronides of glycitein, dihydrodaidzein and O-desmethylangolensin	Urine of human subjects fed tofu	Breast cancer	In vitro / In vivo	MCF-7	ERα / ERβ	Activation / Activation	[456]
Conjugated linoleic acid	Dietary component	Hepatoma cells	In vitro	HepG2, SK-HEP-1	PPARα	Activation	[457]
		Prostate cancer	In vitro	LNCaP, PC3	PPARδ	Inhibition	
		Glioblastoma	In vitro	ADF			
		Bladder cancer	In vitro	639 V, SG65			
		Breast cancer	In vitro	MDA-MB-231, MCF-7			
		Gastrointestinal cancer	In vitro	MKN28, Colo320	PPARγ	Activation	[458]
		Colon cancer	In vivo	Tissue specific PPARγ null mice	PPARγ	Activation	[459]
n-3 PUFA enriched LDL	Plasma of African green monkeys	Breast cancer	In vitro	MCF-7	PPARγ / PPARγ	Activation / Activation	[460] / [461]
n-3 PUFA-enriched LDL	Vervet monkeys	Prostate cancer	In vitro	PC3, DU145	PPARγ	Activation	[462]
Cis-9 (9Z), trans-11 (11E)-conjugated linoleic acid	Dietary component	Colon cancer	In vitro	Caco-2. HT-29	PPARδ	Inhibition	[463]
Sodium gluconate	Dietary bioactive compound	Carcinogen induced colon cancer	In vivo	Male Fischer-344 rats	RARα / RXRγ	Activation / Activation	[464]
Docosahexaenoic acid	Dietary component	Burkitt B-cell lymphoma	In vitro	Ramos and Reh	PPARγ	Activation	[465]
Tocopherols	Dietary component	Breast cancer	In vivo	Female Sprague Dawley rats	PPARγ	Activation	[466]
		Breast cancer	In vivo	N-methyl-N-nitrosourea (NMU)-treated female Sprague–Dawley rats	ERα / PPARγ	Inhibition / Activation	[467]
		Breast cancer	In vivo	Female ACI rats	ERα / ERβ / PPARγ	Inhibition / Activation / Activation	[468]
α-linolenic acid	Dietary component	Renal carcinoma	In vitro	OS-RC-2	PPARγ	Activation	[469]
Obeticholic acid (OCA)	Chenodeoxycholic acid derived	Liver cancer	In vitro	HepG2, Huh7, SNU-449	FXR	Activation	[470]
Compound 4 k	PUFA-alkanolamine	Lung cancer	In vitro	H460	NUR77	Activation	[471]

Table 2 (continued)

Name of the compound	Source	Tumor type	In vitro In vivo	Cell line/model	Targeted NR	Effect on NR	Reference
Sulforaphane	Dietary bioactive compound	Colorectal cancer	In vitro	LS180	PXR	Inhibition	[331]
		Breast cancer	In vitro	MCF-7	VDR	Activation (Increased expression)	[329]
		Colorectal cancer	In vitro	Caco-2	VDR	Activation (Increased expression)	[330]
Microbial-derived compounds							
Fungal metabolites	*Penicillium oblatum*	Breast cancer	In vitro	T47D	PR	Inhibition	[472]
					ER	Inhibition	
Equol	Action of gut microbiota on daidzein	Endometrial carcinoma	In vitro	HEC-1	ERα	Activation	[473]
					ER β	Activation	
		Prostate cancer	In vitro	PC3, DU145	ERα	Activation	[474]
Bacteroides thetaiotaomicron	Extract	Colon cancer	In vitro	Caco-2	PPARγ	Activation	[475]
Saccharomyces boulardii	Extract	Colon cancer	In vitro	HT-29	PPARγ	Activation	[476]
Cytosporone B	*Dothiorella* sp.	Gastric cancer	In vivo	BGS-823 nude mice xenografts	NUR77	Activation	[477]
Coprinus comatus	Ethanol and ethyl acetate extract	Prostate cancer	In vitro	LNCaP	AR	Inhibition	[478]
		Breast cancer	In vitro	MDA-kb2	AR	Inhibition	[478]
					GR	Inhibition	
Ganoderma lucidum	Ethanol and ethyl acetate extract	Prostate cancer	In vitro	LNCaP	AR	Inhibition	[478]
		Breast cancer	In vivo	MDA-kb2	AR	Inhibition	[478]
					GR	Inhibition	
Benzyldihydroxyoctenone	*Streptomyces* sp.	Prostate cancer	In vitro	LNCaP	AR	Inhibition	[479]
Indole and indole-3-propionic acid	Derived from symbiotic intestinal bacteria	Colon cancer	In vitro In vivo	Caco-2, LS174T $Nr1i2^{+/+}$ and $Nr1i2^{-/-}$ mice	PXR	Activation	[480]
White-line inducing principle, a lipodepsipeptide	*Lasiosphaera fenzlii* Reich	Leukemia	In vitro	K562	PPARα	Activation	[481]
					PPARγ	Activation	
Butyrate	Microbial fermentation product	Colon cancer	In vitro	Caco-2	PPARγ	Activation	[482]
Compounds 2 and 6	*Penicillium granulatum*	Lung cancer	In vitro	A549	RXRα	Activation	[483]
Mushroom polysaccharides and jiaogulan saponins	*Ganoderma lucidum* and *Gynostemma pentaphyllum*	Colorectal cancer	In vivo	$Apc^{Min/+}$ mice	PPARγ	Activation	[484]
Felix Kopp Kortager 5 and 6	Indole derivatives	Colon cancer	In vitro	Caco-2	PXR	Activation	[485]
β-glucan	*Lentinus edodes*	Breast cancer	In vitro	MCF-7, T47D	NUR77	Inhibition	[486]
Proteins	*Hericium erinaceus*	Colon cancer	In vivo	CT26 cells bearing xenograft mice	PPARα	Activation	[487]
					PPARγ	Activation	

Table 2 (continued)

Name of the compound	Source	In vitro / In vivo	Cell line/model	Tumor type	Targeted NR	Effect on NR	Reference
Fusarin	*Fusarium* sp.	In vitro	MCF-7	Breast cancer	ER	Activation	[488]
Bassiatin	*Fusarium oxysporum*	In vitro	MCF-7	Breast cancer	ERα	Inhibition	[489]
Bendigoles D–F	*Actinomadura* sp. *SBMs009*	In vitro	U2OS	Osteosarcoma	GR	Inhibition	[490]
		In vitro	SH-SY5Y	Neuroblastoma	GR	Inhibition	[490]
Commensal gut microbiota and derived metabolites—butyrate and propionate		In vitro	HT-29	Colon cancer	PPARγ	Activation	[491]
8-prenylnaringenin	*Fusarium* sp.	In vitro	Ishikawa cells	Endometrial cancer	ER	Inhibition	[492]
Xanthohumol	*Fusarium* sp.	In vitro	Ishikawa cells	Endometrial cancer	ER	Inhibition	[492]
1(2), 2(18)-diseco indole diterpenoid, drechmerin H	*Drechmeria* sp.	In vitro	HepG2	Liver cancer	PXR	Activation	[493]
Lithocholic acid	*Bacterial metabolite*	In vitro	4T1, MCF7, SKBR-3	Breast cancer	CAR	Activation	[494]
Indole propionic acid	*Microbial metabolite*	In vitro	4T1	Breast cancer	PXR	Activation	[495]
		In vivo	4T1 cells bearing mice		PXR	Activation	[495]
Sesterterpene MHO7	Mangrove fungus	In vitro	MCF-7	Breast cancer	ERα	Inhibition	[496]
5-hydroxy-3-methoxy-5-methyl-4-butylfuran-2(5H)-one	*Setosphaeria* sp. SCSIO41009	In vitro	HepG2	Liver cancer	PPARα	Activation	[497]
Pestalotiochromenoic acids A–D and pestalotiochromones A and B	*Pestalotiopsis neglecta* SCSIO41403	In vitro	HepG2	Liver cancer	LXRα LXRβ	Activation Activation	[498]

component of pepper, preferentially promotes apoptosis in specific cancer cells and has a putative role in cancer chemoprevention [158]. In another study, Kim and colleagues demonstrated that capsaicin-induced PPARγ both at mRNA and protein levels led to apoptotic cell death of HT-29 cells and this effect was abrogated by the addition of PPARγ inhibitor [159]. In addition, capsaicin at 200 μM has been shown to enhance transient receptor potential cation channel subfamily V member 1 (TRPV1), adenosine mono phosphate (AMP)–activated protein kinase (AMPK), calcium/calmodulin-dependent kinase kinase beta (CaMKKβ), phospho-sterol regulatory element binding protein 1c (p-SREBP1c), p62, PPARα, PPARγ, and autophagy and reduce phosphorylation of Akt, mTOR, and lipid accumulation in HepG2 cells [160]. Likewise, a major dietary alkaloid found in the extracts of *Piper longum* and *P. nigrum*, piperine, has been earlier attributed to anti-cancer, anti-inflammatory, anti-microbial, chemopreventive, and immunosuppressive activities and was also shown to modulate NRs [161–163]. It was shown that piperine of 100 μM concentration elevated miR-181c-3p levels and suppressed leptin-induced proliferation, colony formation, and migration of breast cancer cells via PPARα inhibition [163].

5.2 Carotenoids

Carotenoids are membrane-stabilizing chemicals recruited as photoprotective pigments during photosynthesis. According to their chemical structure, carotenoids are classified as isoprenoid polyenes, which are lipid-soluble, yellowish-orange pigments and are biosynthesized by algae, plants, and certain microbes [164, 165]. Carotenoids including astaxanthin, β-carotene, β-cryptoxanthin, crocin, fucoxanthin, lutein, and lycopene are the most common plant pigments that play key roles in the prevention and treatment of several diseases, including cancer [166]. Zhang et al. explored the anti-proliferative activities of four different carotenoids β-carotene, astaxanthin, capsanthin, and bixin on K652 leukemia cancer cells. It was observed that these carotenoids attenuated cancer cell growth and cell cycle by upregulating PPARγ in a dose-dependent manner ranging from 0.5 to 50 μM. This study also showed the upregulation of p21 and nuclear factor erythroid–related factor 2 (NRF2), and inhibition of cyclin D1 expression was PPARγ dependent [167]. In another study, Liu and coworkers demonstrated that fucoxanthin extracted from *Undaria pinnatifida* inhibited the proliferation and expression of cytochrome P450 3A4 (CYP3A4) and MDR1 in colon and hepatocarcinoma cell lines by blocking the interaction of PXR with SRC1 [168]. Moreover, this compound was shown to induce apoptosis

and enhance the anti-proliferative effect of troglitazone in colon cancer cell lines by activating PPARγ [169]. Another carotenoid, β-cryptoxanthin, purified from *Citrus unshiu* has been shown to arrest the cell cycle and reduce proliferation by upregulating RARβ in lung cancer cells [170]. In addition, β-cryptoxanthin hampered nicotine-induced lung cancers in male A/J mice by transactivating RARβ resulting in decreased interleukin 6 (IL-6), increased sirtuin 1 (SIRT1), and survival probability [171]. Furthermore, apo-10′-lycopene, a lycopene derivative, has been shown to reduce migration, invasion, and angiogenesis dose-dependently (2.5–40 μM) in the liver and lung cancer *in vitro* models through the activation of PPARγ [172].

5.3 Polyphenols

Polyphenols are substances with one or more hydroxyl group(s) linked to at least one aromatic ring. They are the broad collection of secondary metabolites found in plants that range in size from small molecules to highly polymerized substances. They are widely distributed in plant-based foods and beverages including fruits, nuts, soy, spices, tea, vegetables, and wine [173]. Natural polyphenols are categorized into five types based on their chemical structures: flavonoids, phenolic acids, lignans, stilbenes, and other polyphenols [174, 175]. A plethora of research has documented the anti-cancer properties of polyphenols. Anthocyanins from blueberries, curcuminoids from turmeric, epigallocatechin gallate (EGCG) from green tea, isoflavones from soy, and resveratrol from red wine are a few noteworthy examples [175–180]. This section summarizes the NR-targeting activities of different polyphenols in various cancers.

5.3.1 Acetylshikonin

Acetylshikonin is a physiologically active biochemical commonly obtained from the roots of *Lithospermum erythrorhizon*, with anti-tumor and anti-inflammatory properties [181, 182]. Several reports have demonstrated that acetylshikonin induces apoptosis and endoplasmic reticulum stress through the activation and cytoplasmic localization of NUR77 in cervical, liver, and lung cancer cells [183, 184].

5.3.2 Artemisinin

It is a bioactive sesquiterpene lactone isolated initially from the *Artemisia annua* and is a potent anti-malarial drug. Artemisinin has long been recognized for its anti-cancer activity due to its preference for cytotoxic effects in cancer cells than normal cells [185]. Studies have reported that artemisinin exerts its effects through modulating NF-κB, vascular endothelia growth factor (VEGF), MAPK, hypoxia-inducible factor 1 alpha (HIF-1α), survivin, and
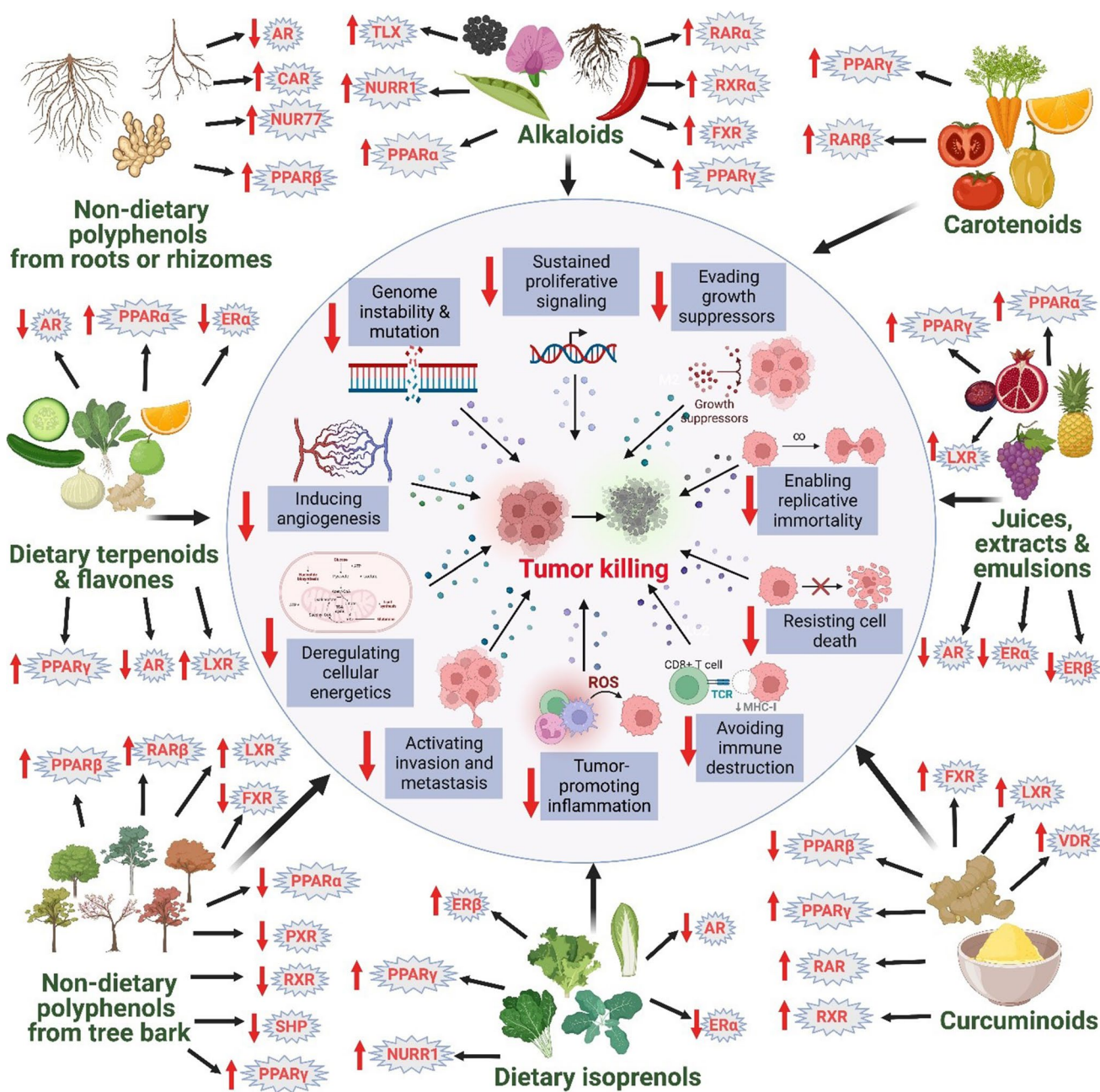
Fig. 5 Phytochemicals that target various NRs lead to reduced hallmarks of cancer cells. The extracts, juices, and emulsions of plants and the phytochemicals including alkaloids, carotenoids, curcuminoids, dietary and non-dietary terpenoids, isoflavones, and isoprenols have been shown to possess anti-cancer and anti-inflammatory activities through the modulation of various NRs. The figure was created in BioRender

Wnt signaling [185]. It has also been shown to inhibit AR activities and enhance AR binding to MDM2 leading to reduced proliferation of prostate cancer cells [186]. Artesunate, a derivative of *Artemisia annua*, and artemisinin derivatives also showed the suppression of prostate cancer cell growth through the degradation of AR [187, 188]. In addition, another derivative of artemisinin, dihydroartemisinin has been demonstrated to induce cell death and inhibit migration of colon cancer cells via the induction of PPARγ [189].

5.3.3 Auraptene

Auraptene is a monoterpene isolated from *Citrus* fruits. Auraptene is known to possess anti-bacterial, anti-diabetic, anti-fungal, anti-genotoxic, anti-inflammatory, and

anti-protozoal effects [190]. It exerts anti-cancer effects by modulating the expression of matrix metalloproteinases (MMPs), VEGF receptor 1 (VEGFR1), VEGF receptor 2 (VEGFR2), IL-6, IL-2, STAT3, NF-κB, and PPARα in various cancers including breast, cervical, colon, liver, and ovarian cancer cells [191–194].

5.3.4 Baicalein

Baicalein is a major active ingredient extracted from the root of *Scutellariae radix*. Its anti-tumor actions are mediated by numerous molecular pathways, including blocking multiple cyclins or cyclin-dependent kinases (CDKs) that control the cell cycle, scavenging free radicals, and limiting MAPK, Akt, and mTOR activities [195, 196]. Baicalein also has been demonstrated to suppress the growth of meyeloma cells through the activation of PPARβ [197]. Baicalein, chrysin, and galangin derived from garlic have been shown to retard the growth of liver cancer cells through the upregulation of CAR [198]. In addition, baicalein attenuated cell cycle arrest in prostate cancer cells by alleviating AR activity [199].

5.3.5 N-butylidenephthalide

N-butylidenephthalide, a compound derived from *Angelica sinensis*, has been shown to suppress the growth of several human cancer cell lines, including breast, brain, lung, and liver cancer cells [200–204]. In liver cancer cells, n-butylidenephthalide reduced cell proliferation via activating NUR77 [204]. In another study, Lin et al. examined that n-butylidenephthalide impeded cell proliferation and induced cell death through the activation of NUR1 and NUR77 in both *in vitro* and *in vivo* models of glioblastoma [205].

5.3.6 Celastrol

A polyphenol, celastrol, is a quinine methide triterpenoid isolated from the *Tripterygium wilfordii* and has evolved as a potential anti-cancer agent during the last few years [206–208]. Celastrol inhibited constitutively active STAT3 and liver cancer cell migration in pre-clinical studies [209]. Addition of celastrol inhibited expression of STAT3, Akt, p38, p65, c-Jun N-terminal kinase (JNK), and IL-6 through the suppression of peptide-prolyl cis–trans isomerase NIMA-interacting 1 (Pin1) resulting in reduced proliferation, migration, and stemness of ovarian cancer cells [210]. Another study showed celastrol prevents prostate cancer cell growth both *in vitro* and *in vivo* by targeting AR to proteasomal degradation [211]. Recently, Hu et al. investigated the role of celastrol on liver cancer cells and found that celastrol reduced inflammation by fostering mitochondrial ubiquitination and autophagy through the activation of NUR77 [212].

5.3.7 Cryptotanshinone

Cryptotanshinone, a principal tanshinone extracted from *Salvia miltiorrhiza* roots, is commonly used in herbal medicine to treat diabetes, cardiovascular diseases, cancer, chronic renal failure, hepatitis, and menstrual disorders [213, 214]. It is shown to suppress the castration-resistant prostate cancer cells both *in vitro* and *in vivo* by reducing the transactivation of AR and by profound inhibition of AR binding to lysine-specific demethylase 1 (LSD1) [215, 216].

5.3.8 Curcumin

It is a naturally occurring polyphenol found in the rhizomes of *Curcuma longa* and has piqued the interest of scientists across the world due to its various biological properties including anti-oxidant, anti-microbial, anti-viral, anti-inflammatory, and anti-cancer effects [217–220]. Curcumin has been shown to exert anti-cancer effects by modulating several pathways including NF-κB signaling, Akt/mTOR signaling, STAT signaling, epidermal growth factor receptor (EGFR) signaling, interleukin pathways, cyclins, CDKs, MMPs, and NRs [221, 222]. Prakobwong et al. illustrated that curcumin mediates anti-proliferative and apoptotic effects through the inhibition of NF-κB nuclear translocation, STAT3 phosphorylation (Y703 and Y705), Akt phosphorylation, and activation of PPARγ at the concentration of 50 μM in KKU100, KKU-M156, and KKU-M214 cholangiocarcinoma cell lines [223]. This study also showed that curcumin downregulated B-cell lymphoma 2 (Bcl-2), X-linked inhibitor of apoptosis (XIAP), cellular FLICE inhibitory protein (c-FLIP), a cellular inhibitor of apoptosis protein 1 (cIAP-1), a cellular inhibitor of apoptosis protein 2 (c-IAP-2), survivin, cyclin D1, c-Myc, and upregulated death receptors DR4 and DR5 resulting in enhanced apoptosis of biliary cancer *in vitro* [223]. Moreover, curcumin has been revealed to induce LXRα and FXR expression in hepatoma cell lines HepG2 and Huh7 leading to reduced inflammation, cell viability, and enhanced expression of ATP-binding cassette subfamily G member 1 (ABCG1), cytochrome P450 family 7 subfamily A member 1 (CYP7A1), cytochrome P450 family 8 subfamily B member 1 (CYP8B1), organic anion transporting polypeptide 1A1 (OATP1A1), ileal bile acid transporter gene (IBAT), and organic solute transporter beta subunit (OSTβ) [224, 225]. In another study, Jiang et al. showed that curcumin reactivated silenced RARβ by reducing promoter DNA methylation in lung cancer *in vitro* and *in vivo* resulting in reduced tumor growth [226]. In two independent studies, curcumin was shown to activate PPARγ, VDR, RAR, and RXR expressions in various colon cancer cell lines causing increased AMPK and decreased COX2 expression [227, 228]. Besides, curcumin activated VDR resulting in the upregulation of CYP3A4,

CYP24, p21, and TRPV6 and enhanced chemoprevention in Caco-2 cells [229]. In Moser cells (human colon cancer–derived cell line), curcumin induced cell cycle arrest at the G2/M phase, suppressed cell survival/proliferation, and reduced EGFR phosphorylation by activating PPARγ [230]. In various breast cancer *in vitro* models, curcumin showed apoptotic effects via upregulating PPARγ, RARβ, and RARγ and downregulating PPARβ leading to increased cleaved-PARP, cleaved caspase-9 levels and reduced COX2, phospho-extracellular signal-regulated kinase (p-ERK), p38, VEGF, pyruvate dehydrogenase kinase 1 (PDK1), and p65 [227, 231, 232]. In another study, curcumin (12 μM) treatment along with docosahexaenoic acid (18 μM) showed synergistic effects on inhibiting apoptosis and metastasis *in vitro* through PPARγ activation in breast cancer cells [233].

5.3.9 Ellagic acid

Ellagic acid is a plant-derived polyphenol abundant in pomegranates, raspberries, and walnuts [234]. In experimental cancer models, ellagic acid was reported to decrease the incidence of chemically induced colon, lung, mammary, oral, and intestinal tumors [235–239]. Furthermore, Munagala and coworkers demonstrated that this compound reverses the micro-RNA signatures including miR-182, miR-375, miR-183, miR-122, miR-127, and miR-206 and modulates the expression of cyclin D1 (CCND1), cyclin G1 (CCNG1), Bcl-w, FOXO1, FOXO3A, and Ras-related dexamethasone-induced 1 (RASD1) in estrogen-mediated mammary tumors [239]. In addition, ellagic acid derived from pomegranates has been found to inhibit AR expression in prostate cancer cells [240].

5.3.10 Embelin

Embelin (2,5-dihydroxy-3-undecyl-1,4-benzoquinone) is a major active component isolated from the fruits of *Embelia ribes*, and it has been studied for the treatment of a wide range of cancers [241, 242]. Dai and co-workers demonstrated that embelin impedes the cell proliferation and tumor growth of colon cancer cells via the reduction of CCND1, PCNA, survivin, and COX2 in both *in vitro* and *in vivo* colon cancer models. This study also showed that embelin exerts its anti-cancer mechanism through the activation of PPARγ and failed to induce cancer cell death in PPARγ$^{-/-}$ mice [85].

5.3.11 Emodin

Emodin (1,2,8-trihydroxy-6-methylanthraquinone), a bioactive chemical isolated from *Rheum palmatum*, is more effective than genistein and curcumin on prostate cancer cells [243, 244]. It has been demonstrated to be a potent AR antagonist and downregulates prostate cancer cell proliferation [245]. Additionally, emodin has been revealed to inhibit cell growth and division of liver cancer cells through the activation of FXR and modulating gene expression of such as Cdc25c, cyclin B, Chk2, CDK2, p27, p21, CDK1, palmdelphin (PALMD), insulin-like growth factor binding protein 3 (IGFBP3), thioredoxin-interacting protein (TXNIP), Chac cation transport regulator-like 1 (CHAC1), CYP1B1, CYP1A1, TCDD-inducible poly (ADP-ribose) polymerase (TIPARP), growth differentiation factor 15 (GDF15), serpin peptidase inhibitor clade E member 1 (SERPINE1), son of sevenless homolog 1 (SOS1), RASD1, solute carrier family 7A member 11 (SLC7A11), cysteine-rich angiogenic inducer 61 (CYR61), and muscle RAS oncogene homolog (MRAS) [246].

5.3.12 Genistein

Genistein [5,7-dihydroxy-3-(4-hydroxyphenyl)-4H-1-benzopyran-4-one] is a predominant isoflavone found in soy and soy-based food products consumed by Asians daily. The principal molecular targets of genistein include Akt, Bax, Bcl-2, caspases, ERK, MAPK, NF-κB, and Wnt signaling pathway [247]. This phytochemical was shown to inhibit the prostate cancer cells by exerting an inhibitory effect on nuclear receptor AR at the physiological concentration [248]. It also induced prostate cancer cell death by activating ERβ [249]. Genistein-mediated reduction of cholesterol accumulation, an increase of apoptosis, and alleviation of prostate-specific antigen (PSA) levels were attributed to AR degradation in prostate cancer cells [250, 251]. Besides, genistein together with resveratrol was found to be the potent antagonist of AR in prostate cancer cells [252]. In addition, genistein treatment was shown to reduce hydrogen peroxide–induced oxidative stress and overexpression of Nrf2 in lung cancer hybrid cells through the activation of PPARγ [253]. Another study showed that genistein-induced reduction of AR resulted in induction of cleaved poly(ADP-ribose) polymerase (PARP), cleaved-caspase 3, and downregulation of ABI family member 3–binding protein (ABI3BP), A-kinase anchoring protein 12 (AKAP12), annexin A3 (ANXA3), amyloid beta precursor protein–binding family B ember 1–interacting protein (APBB1IP), bone morphogenic protein receptor type 1B (BMPR1B), F-box leucine–rich repeat protein 7 (FBXL7), gastrulation brain homeobox 2 (GBX2), general transcription factor IIA subunit 1 (GTF2A1), high mobility group AT hook 2 (HMGA2), muscleblind-like splicing regulator 1 (MBNL), MYB-binding protein 1A (MYBBP1A), neural EGFL-like 2 (NELL2), phosphofructokinase subunit M (PFKM), phosphoserine aminotransferase 1 (PSAT1), pseudouridine synthase 1 (PUS1), serum glucocorticoid regulated kinase 2 (SGK2), and T-box transcription factor 19 (TBX19) in ovarian cancer

cells resistant to taxol [254]. Furthermore, it was shown that isoflavones genistein, formononetin, calycosin, daidzein, and biochanin A isolated from *Astragalus membranaceus* and *Astragalus membranaceus* activate both PPARα and PPARγ in HeLa cervical cancer cells [255].

5.3.13 Guggulsterone

Guggulsterone is a sterol isolated from the gum resins of the *Commiphora* sp. tree and is widely used in Indian traditional medicine for the treatment of various diseases [131, 256–258]. Recently, guggulsterone has been proven to be a potential anti-tumorigenic agent in several cancers such as head and neck, lymphoma, and pancreatic and prostate malignancies [259]. For example, guggulsterone has been shown to reduce cell viability and induce apoptosis in TE-3 and TE-12 esophageal cancer cells [260]. In addition, E- and Z-guggulsterone isomers at 40 μM concentration have been demonstrated to induce apoptosis through caspase 3 and PARP cascade, induce cell cycle arrest by upregulating p21, and reduce bladder cancer cell viability via inducing FXR activation [261]. Another study revealed that Z-guggulsterone attenuates bile acid–induced FXR expression and NF-κB signaling in *in vitro* models of gastric intestinal metaplasia [262]. In hepatocarcinoma cells, guggulsterone has been shown to lower cholesterol accumulation by inhibiting FXR, PPARα, PXR, and SHP expressions [263]. Furthermore, guggulsterone suppressed FXR expression dose-dependently which resulted in reduced cell viability, cell migration, and invasion of PANC-1 and MIA-PaCa2 cell lines [264]. In another study, guggulsterone combined with bexarotene reduced resistance to doxorubicin and induced apoptosis in breast cancer cells through the inhibition of FXR and RXR [265]. More recently, Tian et al. examined that Z-guggulsterone inhibited cell cycle progression of non-small cell lung cancer cells and hampered tumor growth in Lewis lung carcinoma xenografts in a dose and time-dependent manner. The mechanistic experiments demonstrated that Z-guggulsterone at a concentration of 40 μM mediated the upregulation of PD-L1 partly by inhibiting FXR in these cells [266].

5.3.14 Gypenoside XLIX

Gypenosides are the major components in *Gynostemma pentaphyllum* and have shown high anti-cancer efficacy in different experimental settings [267]. A clinical study conducted in 1993 revealed that *Gynostemma pentaphyllum* soup reduced cancer relapse rate and metastasis rate to 11.9% and 8.5% compared to 72.4% and 55.2% in the control group respectively in advanced metastatic cancer patients [268]. A plethora of studies has shown that gypenosides induce apoptosis of cancer cells by generating ROS and reducing

mitochondrial membrane potential [269–272]. In line with these studies, Huang et al. illustrated that the gypenoside XLIX isolated from the *Gynostemma pentaphyllum* abolished the LPS-induced inflammation and reduced tissue factor in leukemia cells through the activation of PPARα [273].

5.3.15 Hesperidin

Hesperidin, also known as hesperetin 7-rutinoside, a flavonoid present naturally in citrus fruits, is recognized to have broad-spectrum applicability in the prevention and treatment of cancer [274, 275]. Hesperidin is shown to induce cell cycle arrest by downregulating cyclin D1 and upregulating wild-type p53 levels. It is also known to stimulate the autophagy pathway through Aurora-A-mediated PI3K/Akt/glycogen synthase kinase 3 beta (GSK-3β) pathway in the colon cancer model [274, 276, 277]. Moreover, hesperidin is shown to attenuate cell cycle, proliferation, ATP synthesis, and mitochondrial DNA replication synergistically either with piperine and bee venom or with chlorogenic acid in breast cancer *in vitro* models through the inhibition of ERα [278, 279].

5.3.16 Honokiol

Recent studies have enumerated the anti-angiogenic, anti-cancer, anti-inflammatory, and anti-oxidant mechanisms of another polyphenol, honokiol (3′,5-di-(2-propenyl)-1,1′-biphenyl-2,4′-diol), isolated from the bark of *Magnolia* spp. [280]. It has been shown to target multiple signaling pathways including NF-κB, STAT3, EGFR, and Akt/mTOR [281, 282]. Additionally, Jung and coworkers showed that honokiol induced apoptosis of glioblastoma cells by activating RXRβ [283].

5.3.17 Morusin

Morusin, a flavonoid isolated from the root bark of *Morus australis* and the branch of *Ramulus mori*, has been shown to exhibit cytotoxicity against breast cancer, cervical cancer, colorectal cancer, liver cancer, and prostate cancer [284–288]. Li et al. showed that the inclusion of 4 μg/mL and 6 μg/mL morusin enhanced the expression of PPARγ in MCF-7 and MDA-MB-231 cells *in vitro* and inhibited colony formation and induced apoptosis in these cells [289]. This study also demonstrated that treatment of mice with 5 mg/kg and 10 mg/kg body weight of this compound significantly increased the expression of PPARγ in tumor tissues and inhibited the further growth of tumors in nude mice bearing MCF-7 cells [289].

5.3.18 Resveratrol

Resveratrol (3,4′,5-trihydroxy-trans-stilbene), first purified from the roots of *Veratrum album*, has been proved as a potential anti-cancer agent by many studies during the last couple of decades [290–292]. Extensive preclinical and clinical studies have enumerated an inexhaustible list of therapeutic benefits of resveratrol ranging from boosting immunity, slowing aging, and anti-obesity effects, to alleviating the diseases such as diabetes, cancer, cardiovascular diseases, and neurodegenerative diseases [291]. In cancer cells, resveratrol has been shown to regulate several pathways including suppression of STAT3, Akt, HIF1α, MAPK, β-catenin, TGF-β, SMAD, Snail, IKK, FOXO3A, and NF-κB [291]. Resveratrol has been shown to inhibit cell proliferation and cell division in cancer cells through the activation of PPARγ in oral cancer cells [293]. In addition, Ulrich et al. demonstrated that resveratrol ameliorates spermine/spermidine acetyltransferase, cell growth, and induces PPARγ coactivator 1 alpha (PGC-1α), SIRT1, and p-38 in HCT116 and CaCo-2 cells through the activation of PPARγ [294]. In the anaplastic thyroid cancer cells, THJ-11 T, THJ-16 T, and THJ-21 T, resveratrol induced cell cycle arrest and apoptosis via the induction of RARβ and reduction of PPARβ [295].

5.3.19 Withaferin A

Withaferin A is a steroidal lactone purified from the leaves of *Withania somnifera*. It is a well-known phytochemical which has significant anti-inflammatory, pro-apoptotic, anti-angiogenic, anti-invasive, and anti-metastatic properties [296]. The direct cellular targets of withaferin A include cytoskeletal and structural remodeling proteins such as vimentin and desmin, transcription factors such as NF-κB and heat shock transcription factor 1 (HSF1), and kinases such as MAPK, Akt, JNK, ERK, and p38 [296, 297]. Recently, Shiragannavar and co-workers found that withaferin A (2.5 µM) inhibits hallmarks of hepatic neoplastic cells including proliferation, migration, and invasion by activating LXRα expression [298]. Furthermore, this study showed that treatment of HepG2 cells with withaferin A enhances the expression of LXRα targets ABCA1 and ABCG1. Withaferin A also inhibited angiogenesis by downregulating angiogenin, endothelin-1, macrophage migration inhibitory factor (MIF), plasminogen activator inhibitor-1 (PAI-1), monocyte chemoattractant protein 1 (MCP-1), intercellular adhesion molecule 1 (ICAM-1), serpin F1(PEDF), plasminogen activator urokinase (uPA), and platelet-derived growth factor (PDGF)-AA in an LXRα-dependent manner [298].

5.4 Other polyphenols

Several additional natural polyphenols have been shown to suppress various cancer hallmarks by targeting NRs. For instance, allyl isothiocyanate, found in *Brassica* species, was found to downregulate the expression of CYP3A4 and CYP2B6 by inhibiting PXR and CAR significantly at the concentration of 20 µM and 40 µM [299]. Another compound, asaronic acid, isolated from the purple perilla and its anti-inflammatory activities are confined to the PPARγ mediated activation of IL-4α, arginase-1, CD163, IL-10, p-STAT6, and TGF-β in a dose-dependent manner in J774.1 macrophages and THP-1 leukemia cells [300]. Also, atraric acid, isolated from the bark of *Pygeum africanum* and its derivatives, is shown to downregulate AR expression, thereby attenuating migration and invasion of prostate cancer cells [301, 302]. Another compound isolated from the bark of *Pygeum africanum*, N-butyl sulfonamide, was also revealed to reduce PSA and prostate cancer cell growth by inhibiting AR, PR, GR, and THRB [303]. Besides, a triterpene derived from *Brucea* species, bruceantin, was shown to attenuate cell growth and disrupt the interaction of AR with heat shock proteins such as HSP70, HSP90, and HSP40 [304, 305]. Moreover, a wedelolactone derivative, 3-butoxy-1,8,9-trihydroxy-6H-benzofuro[3,2-c]-benzo-pyran-6-one (BTB), belongs to the furanocoumarin family of compounds shown to regulate activation of ER [306]. This study also showed that the BTB retarded estrogen-induced growth of breast, endometrial, and ovarian cancer cells by reducing the expression of cyclin D1, E2F1, TERT, and c-Myc and inhibiting ERα and ERβ expression [306].

Recently, thirteen cucurbitanes isolated from the *Momordica charantia* plant were shown to possess inhibitory effects of Epstein-Barr virus antigen in Raji cells and reduced cell viability [307]. A compound isolated from the same extract, 3β,7β-dihydroxy-25-methoxycucurbita-5,23-diene-19-al (DMC), was revealed to induce PPARγ and ERα in breast cancer cells leading to increased expression of caspase-9, LC3-II, autophagosomes, and reduced cell proliferation [308]. In another study, 7-(O)-carboxymethyl daidzein, a soy isoflavone conjugated to N-t-boc-hexylenediamine, was examined for its anti-proliferative activities against thyroid carcinoma cells by activating ERα and ERβ [309]. Another study conducted by Ichikawa et al. reported that deoxyelephantopin, a sesquiterpene lactone obtained from leaf extract of *Elephantopus carolinianus*, exhibited inhibitory effects on NF-κB and modulated gene expression by repressing IKK [310, 311]. It was also demonstrated that deoxyelephantopin significantly inhibited cell cycle progression by upregulating PPARγ in HeLa cells [312]. Another sesquiterpene lactone, isoalantolactone, purified first from *Inula helenium*, has been shown to ameliorate the body fat and impede adipogenesis through the inhibition of NUR77 in MiaPaCa-2 cell lines

[313]. In addition, farrerol (FA), a flavanone extracted from "Man-shan-hong," a Chinese herbal medication (*Rhododendron dauricum* L.) inhibited the proliferation of SKOV3 cells and induced caspases through the activation of PPARγ [314, 315]. Recently, a natural cyclic AMP activator found in the roots of *Coleus forskohlii*, forskolin, has also been described to upregulate the expression of CYP3A4, NTCP, OATP2B1, and BSEP in liver cancer cells at a concentration of 50 µM and downregulated BCR/ABL expression at 40 µM concentration in leukemia cells [316, 317].

Another group of polyphenols, the dietary isoprenols, is known to perform multifunction such as cation channel regulation, suppression of tumor cell proliferation, and induction of tumor cell death [318–320]. Takahashi et al. demonstrated that isoprenols — farnesol (28 µM), geranylgeraniol (60 µM), and geraniol (135 µM) — aid in clearing the cellular lipid through the activation of PPARγ in HepG2 cells [321]. Another major bioactive dietary component in cruciferous vegetables, indole-3-carbinol, a potent anti-carcinogenic and anti-tumorigenic agent, was shown to degrade ERα in breast cancer cells [322, 323]. In another study, it was shown to downregulate AR expression leading to reduced PSA and proliferation in LNCaP cells [324]. Another compound, 3,3′-diindolylmethane derived from the cruciferous vegetable, was also shown to elicit NURR1 and thereby prevented UVB-induced DNA damage and cell proliferation in skin cancer cells [325, 326]. Another compound, sulforaphane, majorly found in cruciferous vegetables, has been proven to evoke anti-cancer activity partially through a Nrf2–dependent pathway, which was triggered by changes in estrogen metabolism in breast epithelial cells [327]. Furthermore, Palliyaguru et al. demonstrated that sulforaphane prevents estrogen-induced mammary tumor formation, and DNA damage by eliciting ERβ, while inhibiting the ERα at the same time in rats [328]. Furthermore, several studies have shown that sulforaphane, a dietary component, downregulates HDAC and CYP27B1 via activating VDR in breast and colorectal cancer cell lines [329, 330]. It has also been shown to downregulate CYP3A4 through the inhibition of PXR in colorectal cancer cells [331].

Additionally, liquiritigenin, a plant-derived flavone with strong estrogenic activity, was demonstrated to inhibit tumor vascularization and growth by down-regulating VEGF in cervical cancer cells and xenografts [332]. Liquiritigenin in a low concentration (36 nM) acted as ERβ agonist and inhibited MCF-7 cell growth [333]. Likewise, recently, a study by Tian and their team explained that magnolol (5,5′-diallyl-2,2′-dihydroxybiphenyl), a polyphenolic compound purified from the *Magnolia officinalis*, plays a key role in suppressing steatosis, dyslipidemia, through the activation of PPARγ [334–336]. Furthermore, oridonin, a diterpenoid derived from the medicinal plant *Rabdosia rubescens*, was demonstrated to inhibit NF-κB signaling by activating PPARγ in

MG-63 and HOS osteosarcoma cells [337]. In another study, Goto and coworkers showed that phytol, a side chain of chlorophylls, at 50 µM concentration activates both PPARα, PPARγ, and PPARδ and their target genes CPT1A, acyl-coA synthase (ACS), acyl-coA oxidase (ACO) expression in HepG2 carcinoma cells [338, 339].

Recently, Yang et al. explored that piceatannol, a stilbenoid, remarkably suppressed the intracellular fatty acid and lipid accumulation by reducing SREBP1 and CD36 in HepG2 cells. Furthermore, this study showed that piceatannol induced β-oxidation of fatty acids is FXR and PPARα dependent [340]. Another study demonstrated that PsL5F (ent-11alpha-hydroxy-15-oxo-kaur-16-en-19-oic-acid) derived from *Pteris semipinnata* showed an agonistic effect on Rev-Erbα in ovarian cancer cells in *vitro* [341]. Furthermore, 6-shogoal, a major pungent bioactive constituent of rhizomes of *Zingiber officinale* (ginger), was shown to arrest the cell cycle and induce apoptosis in breast and colon cancer cell lines through the activation of PPARγ at 10 µM concentration [342]. This study also illustrated that the percentage of cells undergoing apoptosis was reduced to 50% upon 6-shogoal treatment (10 µM) in PPARγ depleted MCF-7 and HT-29 *in vitro* which shows that PPARγ is one of the most important mechanisms of 6-shagoal induced apoptosis [342]. Another biologically active compound from the seeds of *Nigella sativa*, thymoquinone, has shown anti-tumorigenic effects against colorectal cancer, fibrosarcoma, leukemia, osteosarcoma, squamous cell carcinoma, and prostate cancer in various *in vitro* and *in vivo* experimental models [343–346]. Woo et al. demonstrated that thymoquinone (40 µM) mediates anti-proliferative and apoptotic effects via the activation of PPARγ and PPARβ/δ in MCF-7, MDA-MB-231, and BT-474 breast cancer cell lines [347]. In another study, Huang et al. illustrated that inclusion of a 5-µM concentration of triptolide, a bioactive component extracted from the root bark of *Tripterygium wilfordii*, suppressed the growth of prostate cancer cells LNCaP and PC3 and xenografts by inhibiting c-Jun and AR activities [348]. In addition, the treatment of breast cancer cells with 40 nM triptolide enhanced wild-type p53 expression, reduced cell viability, and cell cycle arrest by downregulating ERα expression [349]. Furthermore, bioactive terpenoids and isoflavones such as ginkgolide A and B, EGB 761, quercetin, and kaempferol have been shown to induce MDR1, CYP2B6, CYP3A4, UDP glucuronosyltransferase family 1 member A1 (UGT1A1), multidrug-resistant protein 2 (MRP2), and aryl hydrocarbon receptor (AhR) through activation of PXR and CAR in liver cancer cells [350]. Another isoflavone tangeretin, derived from citrus fruits, reduced CA-15–3 and breast tumor growth *in vivo* by the inhibition of ERα and PR [351]. In another study, cyanidin, a flavonoid abundantly found in fruits and vegetables, was shown to inhibit the lipid accumulation in hepatocarcinoma

cells via the activation of LXRα and LXRβ [352]. Furthermore, diterpenes including 6,12-dihydroxyabieta-5,8,11,13-tetraen-7-one, sugiol, ferruginol, and 5-epixanthoperol derived from *Cryptomeria japonica* reduced prostate cancer cell growth through the inhibition of AR [353]. In another study, lignans, enterolactone, and organochlorine have been shown to induce PXR in liver cancer cells [354]. In another study, fucosterol derived from marine algae has been demonstrated to be effective against colon cancer cells through the activation of both LXRα and LXRβ [355]. Another phytochemical ethyl 2,4,6-trihydroxybenzoate purified from *Celtis biondii* reduced the cellular lipid accumulation in HepG2 cells through the upregulation of LXRα and LXRβ [356]. Also, iristectorigenin B, a product from *Belamcanda chinensis*, displayed significant agonistic activity for LXRα and LXRβ and induced the expression of ABCA1 and ABCG1 leading to cholesterol efflux in macrophages without lipid accumulation in HepG2 cells [357]. Another compound, paeoniflorin from *Paeonia lactiflora*, was shown to activate LXR and its targets ABCA1 and GAL4 in HepG2 cells [358]. These studies demonstrate the remarkable potential of phytochemicals in modulating the expression of NRs and exerting anti-cancer properties.

6 Effect of whole plant extracts or juice or emulsions on NR in cancer

A plethora of studies has reported that whole plant extracts and juices can be used to treat cancer and are proposed to be having better therapeutic potential compared to isolated compounds [359]. A decade of research has demonstrated that whole plant extracts also exert their anti-cancer effects through modulating NRs. For example, Wentworth et al. treated choriocarcinoma cells with St John's wort extract and hyperforin from *Hypericum perforatum* and found that the extract activates PXR in these cells [360]. In another study, a whole plant extract from *Zanthoxyli fructus* was shown to inhibit AR activation in prostate cancer cells leading to decreased PSA, cyclin D1, Akt, and increased apoptosis [361]. Similarly, extracts of *Serenoa repens* have also been found to arrest the cell cycle and induce apoptosis by inactivating the AR signaling pathway [362]. In line with these studies, an aqueous extract from *Psidium guajava* L. remarkably inhibited PSA, cell proliferation, cell cycle, phospho-Akt, and ERK in prostate cancer cells by inhibiting AR expression [363]. In addition, dichloromethane extract of *Pygeum africanum*, ethanolic extract of *Scutellaria baicalensis*, and pomegranate juice and its extract have also been found to inhibit AR thereby reducing the proliferation of LNCaP prostate cancer cells [199, 240, 302]. Furthermore, an emulsion of pomegranate was found to inhibit ERα and ERβ in breast cancer *in vivo* leading to reduced

β-catenin and cyclin D1 [364]. In another study, He et al. showed that the methanolic extract of *Cornus alternifolia* was a potent agonist of PPARα, PPARγ, and LXR in HepG2 cells [365]. In addition, two independent studies have demonstrated that dietary inclusion of blue berries and flaxseeds delayed tumor latency and induceed chemoprevention in breast cancer cells *in vivo* through the inhibition of ERα [366, 367]. Taken together, these studies suggest that plant-derived compounds and extracts that exert effects through one or more NRs could be potential anti-cancer drugs.

7 Zootherapeutics that modulate NRs

Zootherapy is a branch of ethnozoology concerned with the treatment of human illnesses using animal and animal-derived compounds. Since ancient times, a wide range of animals and products derived from various parts and organs of their bodies have been a reservoir of therapeutic substances used in diverse cultures. Bones, feathers, hooves, skins, toxins, tusks, venom, and other by-products of wild and domestic animals are crucial components in the formulation of curative and preventive medicines [499–501]. Zootherapy is an essential alternative among several other established therapies practiced in modern society. Several investigations on the anti-tumoral activities of animal-derived by-products have been conducted to combat lethal diseases such as cancer [502]. A study conducted by Jang et al. reported that the four peptides — DFHING, FHG, GFHI, and GLSDGEWQ — derived from beef hydrolysate possess strong anti-cancer activities against breast cancer (MCF-7) and stomach adenocarcinoma (AGS) cell lines [503]. ACBP-3, a bioactive peptide derived from the spleen and liver of goats, exhibited gastric and colon cancer both *in vitro* and *in vivo* [504, 505]. Moreover, numerous studies have reported the anti-cancer activities of compounds derived from cows, birds, reptiles, mollusks, and crustaceans [506–513]. In this section, we focus on the active components derived from various animal sources that exhibit agonistic and antagonistic activity against NRs and their implication in cancer prevention and treatment. Figure 6 shows the various zootherapeutic and their target NRs leading to reduced cancer hallmarks.

Natural compounds derived from marine organisms have been valued for over half a century, but growing interest in this promising novel natural medication has only recently emerged. Numerous unique compounds that modulate NRs have been discovered by chemical, structural, and pharmacological characterizations of marine natural resources [514]. Marine sponges and tunicates have been proven to be an outstanding source of novel chemical entities with anti-infectious, anti-inflammatory anti-oxidant, and anti-cancer activities [514, 515]. Mora et al. demonstrated that marine

sponge *Pseudoceratina rhax* metabolite psammaplin A of 10 µM concentration induces apoptosis in MCF-7 breast cancer cell lines by activating PPARγ within 10 h of treatment [418]. A bioactive compound sintokamide A extracted from *Dysidea* species of marine sponge showed potent AR inhibitory activity when treated for one hour at a concentration of 5 µg/mL in LNCaP prostate cancer cell lines [419]. Two novel compounds, solomonsterol A and B isolated from *Theonella swinhoei*, were demonstrated to inhibit IL-1β expression in RAW264.7 macrophage cells *in vitro*. This study also showed that these solomonsterols transactivated PXR and its target genes CYP3A4 and MDR1 in HepG2 cells [420]. Moreover, *in vitro* studies using HepG2 cell lines showed that cholestan disulfate (10 µM), a modified solomonsterol A, isolated from *Theonella swinhoei*, was a potent PXR agonist [422]. Another study isolated theonellasterols B-H and conicasterols B from *Theonella swinhoei* methanolic extract and examined the potential role in modulating nuclear receptors [423]. This study illustrated that theonellasterols B-F and theonellasterol H antagonize the effects of FXR and act as PXR agonists when treated with hepatocarcinoma cell line (HepG2 cells) at 10 µM concentration for 18 h post-transfection stimulation in luciferase assay [423]. Theonellasterol G, however, antagonized the effects of chenodeoxycholic acid on FXR and transactivated FXR in the absence of this natural ligand indicating that theonellasterol-G is a modulator of FXR [423]. Another compound, 10 and 50 µM of conicasterol B acted as an antagonist of FXR and agonist of PXR in HepG2 cells [423]. In addition, Renga et al. revealed that theonellasterol of 50 µM concentration antagonized the effect of both natural and synthetic FXR agonists and induced the expression of SHP in HepG2 cells [424]. Another study showed that theonellasterol and its esters (10 µM) antagonized the agonist effect of chenodeoxycholic acid on FXR in HepG2 cells [425]. Another compound, conicasterol E isolated from the *Theonella swinhoei* showed PXR agonistic activity when treated with HepG2 cells at 10 µM concentration [426]. Similarly, another polyhydroxylated sterol, conicasterol F, derived from *Theonella swinhoei* showed potential PXR agonistic activity and FXR antagonistic activity in HepG2 cells at 10 µM concentration [427]. In another study, treatment of 10 µM malaitasterol A derived from *Theonella swinhoei* was shown to induce the transactivation of PXR in HepG2 cells [428]. In addition, 4-methylenesterols including conicasterol, conicasterol H, conicasterol J, and swinhosterol isolated from methanolic extract of *Theonella swinhoei* showed inhibitory activity against CDCA induced transactivation of FXR and effectively induced PXR expression in HepG2 cells when treated at 50 µM concentration[428]. Furthermore, Sepe et al. isolated conicasterol (compound 1), theonellasterol (compound 2), and preconicasterol (compound 3) from *Theonella swinhoei* and *Theonella conica* and further chemically modified

preconicasterol to obtain around 25 derivatives. This study showed that compound 3 (preconicasterol) and its derivative compound 8 remarkably transactivated PXR in HepG2 cells at both 10 and 50 µM concentrations with EC_{50} of 21 and 18 µM, respectively [445].

Festa et al. isolated thirteen new plakilactones from the marine sponge *Plakinastrella mamillaris* and showed that among these compounds, gracilioether B, gracilioether C, and plakilactone C act as potent non-covalent PPARγ agonists in HepG2 cells with EC_{50} of 5, 10, and 2 µM, respectively [431]. Moreover, gracilioethers E, I, J, and K isolated from an apolar extract of *Plakinastrella mamillaris* sponge showed potent PXR agonistic activity when treated with HepG2 cells with 10 µM concentration [432]. Chianese et al. demonstrated that incisterols A5 (10 µM) and A6 (10 µM) derived from *Plakortis* cfr. *lita* were potent trans activators of PXR and induced the target genes *CYP3A4* and *MDR1* expression in HepG2 liver cancer cells [433]. In another study, Meimetis et al. showed that the methanolic extract of whole sponge *Niphates digitalis* and its active component niphatenone B inhibited the proliferation of LNCaP prostate cancer cells through the suppression of AR gene expression. This study also showed that niphatenone B covalently binds to the AF-1 region of NTD of AR [434]. Additionally, a sesterterpene, luffariellolide, isolated from the hexane extract of marine sponges *Luffariella* sp. and *Fascaplysinopsis* sp. was shown to inhibit the growth of breast cancer cells (MCF-7), colon cancer cells (HCT-15, HCT-116), and leukemia cells (HL-60, THP-1) at 5 µM concentration through the induction of RARα and RARβ expressions [435]. Another marine sponge-derived compound suvanine ($EC_{50} = 24$ µM) and 13α-hydroxyl derivative of suvanine ($EC_{50} = 25$ µM) were shown to possess excellent antagonistic activity against FXR in HepG2 cells [436]. Another novel compound, 12-deacetyl-12-*epi*-scalaradial, a sesterterpene isolated from *Hippospongia* sp., was shown to inhibit the cell proliferation of MCF-7 breast cancer cells ($IC_{50} = 36$ µM), HeLa cervical cancer cells ($IC_{50} = 13.74$ µM), HCT-116 colon cancer cells ($IC_{50} = 27.1$ µM), and HepG2 liver cancer cells ($IC_{50} = 23.4$ µM) [437]. Mechanistic studies revealed that 12-deacetyl-12-*epi*-scalaradial significantly inhibits phosphorylation of ERK and induces the PARP cleavage and phosphorylation of NUR77 by interacting with its LBD leading to apoptosis in HeLa cells [437].

Recently, Wu et al. demonstrated that phakefustatins A-C (kynurenine-bearing cycloheptapeptides) isolated from marine sponge *Phakellia fusca* suppressed the cell proliferation and induced G2/M cell cycle arrest and apoptosis in HeLa cells by inhibiting p85α (catalytic subunit of PI3K), Akt phosphorylation, and cyclin B1 and inducing PARP cleavage in RXRα-dependent manner [438]. Another novel estrogenic steroid, cinanthrenol A, isolated from *Cinachyrella* sp. was shown to effectively inhibit ERα and cell
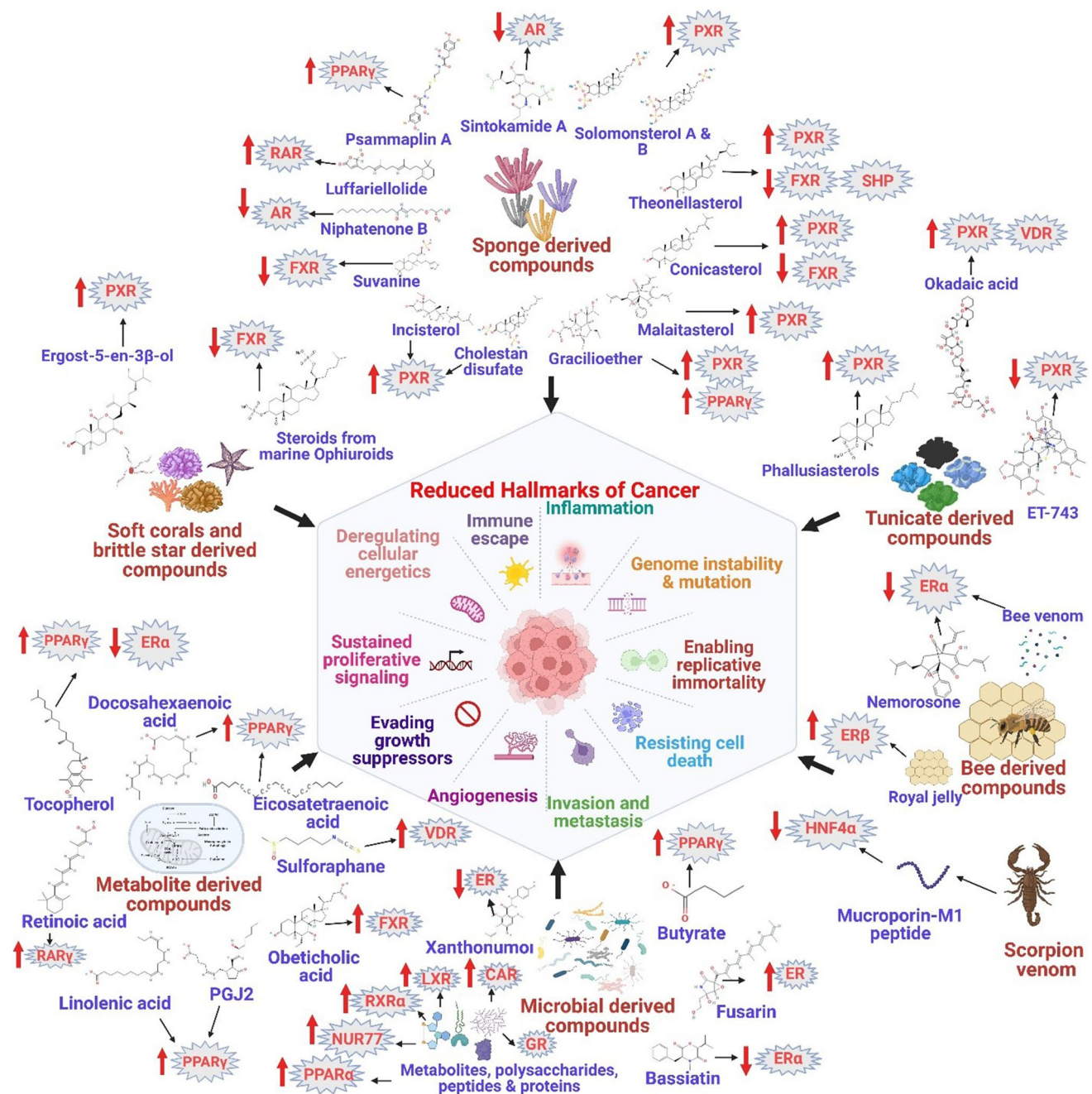
Fig. 6 Summary of natural compounds derived from various origins that target NRs in cancers. Zootherapeutic and microbially derived compounds markedly inhibited various hallmarks of cancer cells through the regulation of NRs. Various compounds derived from animals such as bees, corals, scorpions, sponges, and tunicates were shown to be potential agonists or antagonists of different NRs. In addition, animal metabolite–derived compounds and microbially derived compounds including gut microbes were also shown to inhibit cancer cell growth and progression through the regulation of NRs. The figure was created in BioRender.com

proliferation (IC$_{50}$ = 10 nM) in the cervical (HeLa) and breast cancer (MCF-7) cells [439]. This study also showed that cinanthrenol modulated the expression of ER-responsive genes including *A-MYB* and *SMAD3* in MCF-7 cells [439]. Recently, Parrish et al. demonstrated that a novel compound, myrmenaphthol A, isolated from a Hawaiian sponge of

genus *Myrmekioderma* inhibits ERα in the cervical (HeLa) and lymphoma (P388) cells [440].

Apart from sponges, tunicates are the potential source of numerous marine natural products. Tunicate-derived compounds such as ET-743 (FDA approved), aplidine, PM01183, and vitilevuamide have shown significant

anti-cancer properties under various clinical and pre-clinical trials [514, 515]. Several studies have shown that tunicate-derived compounds modulate nuclear receptors at the molecular level in cancer cells. For instance, Imperatore et al. showed that phallusiasterols A (10 µM) and B (10 µM) isolated from the tunicate, *Phallusia fumigata*, transactivate PXR and induce the downstream target genes *CYP3A4* and *MDR1* in hepatocellular carcinoma cell lines [441]. The same group later demonstrated that another novel compound phallusiasterol C from *Phallusia fumigata* also transactivated PXR and induced the expression of CYP3A4 and MDR1 when treated with 50 µM in the same cells [442]. In another study, 15 marine natural compounds isolated from a tunicate, *Ciona intestinalis*, including bensulfuron-methyl, butafenacil, β-cyfluthrin, α-cypermethrin, diethylhexylphthalate, esfenvalerate, fenpyroximate, mancozeb, mesosulfuron-methyl, permethrin, foramsulfuron, gymnodimine, okadaic acid, pectenotoxin-2, and yessotoxin, were explored for their effect on xenobiotic receptors. It was observed that okadaic acid showed the highest PXR activation capacity with an EC_{50} of 7.2 ± 1.1 nM in HepG2 cancer cells. The other compounds which activated PXR in these cells include bensulfuron-methyl ($EC_{50} = 89.4 \pm 5.5$ µM), butafenacil ($EC_{50} = 6.0 \pm 0.5$ µM), β-cyfluthrin ($EC_{50} = 2.5 \pm 0.3$ µM), α-cypermethrin ($EC_{50} = 1.6 \pm 0.2$ µM), diethylhexylphthalate ($EC_{50} = 1.8 \pm 0.2$ µM), esfenvalerate ($EC_{50} = 1.5 \pm 0.2$ µM), and permethrin ($EC_{50} = 5.6 \pm 0.6$ µM) [443].

Increasing lines of evidence showed that bee-derived compounds including honey and venom possess potential anti-cancer activities such as cell cycle arrest, apoptotic induction, mitochondrial permeabilization, anti-inflammatory effect, and immunomodulation [516, 517]. Mechanistic studies have shown that the anti-cancer activities of these substances are attributed to NR modulation. For instance, nemorosone derived from Cuban propolis of bee inhibits the proliferation of MCF-7 breast cancer cells through the downregulation of ERα [447]. Khamis et al. demonstrated that treatment of MCF-7 cells with bee venom, piperine, and hesperidin combination effectively inhibits ERα [278]. Another study by Moutsasou et al. showed that 10-hydroxy-2-decenoic-3,10-dihydroxydecanoic-3 sebacic acid derived from royal jelly exerts anti-cancer effects by activating ERβ in MCF-7 cells [448].

Moreover, a plethora of studies has shown that scorpion venom, a complex mixture of biogenic amines, mucoproteins, nucleotides, neurotoxins, organic salts, peptides, and proteins, possesses immense anti-cancer potential due to its cytotoxic, immunosuppressive, anti-proliferative, and pro-apoptotic properties [518, 519]. Zhao et al. demonstrated that scorpion venom–derived peptide, mucroporin-M1, inhibited hepatitis B virus (HBV) capsid DNA, intracellular HBV RNA replication intermediates, and HBV core protein in the cytoplasm and reduced the amount of extracellular HBsAg, HBeAg, and HBV DNA productions in HepG2.2.15 hepatocellular carcinoma cells. This study also showed that the mucroporin-M1 inhibited HBV replication through MAPK pathway–mediated down-regulation of HNF4α [449].

These studies suggested that animal-derived products possess anti-cancer effects by markedly modulating numerous nuclear receptors including AR, ER, FXR, HNF4α, and PXR. However, further preclinical and clinical studies need to be conducted to validate their potentiality as anti-cancer drugs.

8 Metabolite-derived compounds targeting nuclear receptors in cancer

Increasing lines of research have proved that numerous metabolites regularly generated as byproducts of cellular metabolisms, such as those containing reactive groups or those that operate as competitive analogs against other metabolites, are highly cytotoxic [520]. Hence, by tackling the downstream enzymes in a metabolic pathway that produces a toxic byproduct or by treating the cancer cells with these compounds, we might be able to provoke the accumulation of this cytotoxic metabolite and destroy cancer cells [520]. Attia et al. demonstrated that obeticholic acid, derived from chenodeoxycholic acid, inhibits the cell cycle, invasion, and migration of HepG2, Huh7, and SNU-449 hepatocarcinoma cells by activating FXR resulting in reduced IL-6, phospho-STAT3, IL-1β, and upregulation of SOCS3 expression [470]. In another study, 5-oxo-6,8,11,14-(E,Z,Z,Z)-eicosatetraenoate, a derivative of arachidonic acid, was shown to hamper the breast cancer cell proliferation through the activation of PPARγ [521]. Administration of tocopherol (vitamin E) in cancer-bearing mice has been shown to retard tumor growth and induce cancer cell apoptosis through the activation of either PPARγ, or ERβ, and inhibition of ERα [466–468]. In addition, γ-tocopherol and vitamin E administration through diet has been illustrated to upregulate PPARγ and reduce cell proliferation of SW-480 colon cancer cells [455]. Moreover, the addition of all-trans retinoic acid and 9-cis-retinoic acid in the culture medium of T3M-4, AsPc-1, and BxPc-3 pancreatic cancer cells promoted cell death via the activation of RARγ [454]. Two independent studies conducted on lymphoma and leukemia cell lines explored the anti-cancer properties of prostaglandin 15d-PGJ2. It was observed that 10 µM 15d-PGJ2 downregulates STAT, NF-κB, Ap-1, cyclin-dependent kinase inhibitor 1A, adipophilin, microphage activation, and inducible nitric oxide synthase (iNOS) in these cells by activating PPARγ [451, 452]. In addition, treatment of prostate cancer cells with 15S-hydroxyeicosatetraenoic acid arrested cell cycle through the activation of PPARγ [453]. Studies have also shown that

LDL rich in 3-polyunsaturated fatty acids (3-PUFA) isolated from African green monkeys and vervet monkeys upregulates PPARγ and syndecan-1 leading to apoptosis of breast cancer cells [460–462]. Similarly, compound 4k derived from PUFA-alkanolamine reduced inflammatory cytokine production such as IL-6, NF-κB, IL-1β, and TNFα in lung cancer cells in NUR77-dependent manner [471]. Another study showed that treatment of Burkitt B-cell lymphoma cells with docosahexaenoic acid–induced caspases and cell death in a dose-dependent manner activated PPARγ in these cells [465]. Interestingly, a study showed that the addition of aglycones and their metabolites isolated from the urine of human subjects on a tofu diet to growth media reduced breast cancer cell proliferation via activating PPARγ [456]. Another bioactive metabolite sodium gluconate inhibited carcinogen-induced tumor growth in the colon of male Fischer-344 rats by activating RXRγ and RARα [464]. Furthermore, α-linolenic acid, linoleic acid, and their conjugates have been shown to retard tumor cell proliferation and activate apoptotic pathways in various cancer models such as bladder cancer, breast cancer, colon cancer, gastrointestinal cancer, glioblastoma, and hepatocarcinoma [457–459, 463, 469]. Although metabolites have shown beneficial effects in preventing cancer growth, obtaining a wide library of pure and sufficient quantity of metabolites is a key problem.

9 Microbial products targeting nuclear receptors in cancer

Recently, microbially derived compounds have gained tremendous momentum in drug development and research [522]. Growing lines of experimental evidence indictate that microbially derived compounds contain high pharmacological and medicinal properties. Figure 6 shows the various microbial extracts and their derived compounds that target NRs leading to reduced cancer hallmarks.Tabata et al. explored the non-steroidal and selective PR modulator nature of PF1092A, PF1092B, and PF1092C extracts isolated from the rare fungus *P. oblatum* PF1092. PF1092A demonstrated an excellent and moderate affinity for porcine and human PR respectively, in *in vitro* receptor binding assays and it partially activated PR in T47D human breast cancer cells. However, derivative of PF1092C showed better binding affinity in both the PR receptors with lower cross-reactivity nature for other steroidal receptors [472].

In a study, Xie and coworkers explored the efficacy of isolated compounds from the liquid culture of *Penicillium granulatum* MCCC 3A00475, a deep sea–derived fungus. It was observed that out of five penicisteroids D − H isolated, two showed potent RXRα binding affinity. These compounds (50 μM) also exhibited anti-proliferative attributes in A549 lung cancer cells by arresting the cell cycle in the G0/G1

phase and upregulating PARP cleavage leading to apoptosis via RXR-dependent mechanisms [483]. In another study, a combinatorial approach of polysaccharides extracted from *Ganoderma lucidum* (Lingzhi) (750 mg/kg BW), along with the saponins isolated from *Gynostemma pentaphyllum* (300 mg/kg BW), showed a reduction in polyps, the shift of colonic M1 to M2 macrophages, and ameliorated inflammatory gut barrier in ApcMin[/+] colon cancer murine models. The treatment resulted in decreased levels of phospho-STAT3, iNOS, and Src oncogene with modulation of G-protein coupled receptor (GPCR) signaling. In addition, this study demonstrated that GPCR induced the signaling effects in association with PPARγ [484].

In another study, Zhan et al. isolated octaketide cytosporone B (Csn-B) from *Dothiorella* sp. HTF3, an endophytic fungus that served as an agonist for the orphan receptor Nur77. In this study, the authors demonstrated the strong binding affinity of Csn-B towards the Nur77, with its strong apoptotic action through translocalization of Nur77 from the nucleus to the mitochondria. Moreover, Csn-B treatment (5 μg/ml) suppressed 70% growth of BGC-823 human gastric cancer cells and SW620 human colon cancer cells with tumor retardation in the xenograft models [477]. In another study, β-glucan isolated from *Lentinus edodes* (LNT) was explored for its anti-proliferative effects by downregulating Nur77/HIF-1α axis in breast cancer. This study showed that LNT (20 mg/kg BW for 2 weeks) abrogated the development of breast tumors in MMTV-PyMT transgenic mice, and their potential to metastasize to the lungs was associated with a decrease in HIF-1α levels in tumor tissues. Further, LNT was shown to inhibit hypoxia-induced HIF-1α in a Nur77 concentration-dependent manner *in vitro*, which may be mediated through the ubiquitin–proteasome pathway [486].

Sondergaard and his colleagues explored the anti-tumorigenic and agonist activity of fusarin C extracted from *Fusarium graminearum* and *F. avenaceum*. Treatment with fusarin C promoted the proliferation of the MCF-7 breast cancer cell lines in a concentration-dependent manner (up to 50 μM) implicating that it acts as an estrogenic agonist and should be categorized as a mycoestrogen. In this study, fusarin C's toxicity was found to be equivalent to that of other mycoestrogens such as zearalenone. However, its molecular structure was substantially distinct from other known estrogen agonists. In addition, fusarin C toxicity was also investigated in five other human cell lines, Caco-2, U266, PC3, MDA-MB-231, and MCF-10A, where it showed anti-proliferative effects in all the cell lines [488].

Equol is a metabolite derived *in vivo* by gut bacteria from the metabolism of soy phytoestrogen daidzein. As equol is known to be estrogenic, human exposure to it might have significant biological consequences. Equol is known to possess a chiral molecule with two enantiomers: R-equol and S-equol. Muthyala et al., in 2004, studied the binding and

transcriptional activity of the equol enantiomers with ERα and ERβ. It was found that the R isomer exhibited ERα binding selectivity, whereas S isomer had limited ERα selectivity in *in vitro* transfection tests using HEC-1 human endometrial carcinoma cells [473]. Similar results were found in another study, where the effects of equol R- and S-enantiomers were investigated on the motility and invasion of PC3 and DU145 human prostate cancer cells. It was observed that R-equol and S-equol suppressed motility and invasion by downregulating MMP-2 and MMP-9 levels in PC3 and DU145 cells in a dose-dependent manner [474].

Bassiatin, a natural compound isolated from *Fusarium oxysporum* J8-1–2. It was observed that treatment with bassiatin (24 μM) suppressed estrogen-dependent cell proliferation in MCF-7 ERα breast cancer cells. Furthermore, bassiatin (24 μM) in combination with 17β-oestradiol (10 nM) inhibited the mRNA and protein levels of ERα and the estrogen-responsive gene cyclin D1 with enhanced phospho-cyclin D1(Thr286) levels [489]. In a study, indolepropionic acid (IPA), a gut microbiome tryptophan metabolite, was explored for its anti-neoplastic activities in breast cancer. It was observed that IPA is cytostatic and selectively abrogates the growth of SKBR-3 and 4T1 breast cancer cells while having no impact on non-transformed primary fibroblasts. Moreover, IPA treatment mediated the downregulation of NRF2, upregulation of iNOS, and increased mitochondrial reactive species production. It was found that IPA exerted its anti-tumorigenic effects through the activation of the pregnane X receptor (PXR) receptor and aryl hydrocarbon receptor (AHR) [495]. Zhao and his coworkers isolated a novel indole diterpenoid compound, drechmerin H, from the fermentation broth of endophytic fungal *Drechmeria* sp. SYPF 8335 was found in the roots of *Panax notoginseng* and evaluated its activity against the human PXR. It was shown that drechmerin H had a significant agonistic activity for the PXR by *in silico* docking studies, which was validated by *in vitro* in HepG2 cell lines (EC$_{50}$ of 134.91 ± 2.01 nM) [493].

In one of the studies, it was observed that the anti-tumor effects of the bacterial metabolite lithocholic acid (LCA) were dependent on oxidative stress caused by the LCA treatment (0.3 μM), leading to downregulation of the NRF2/kelch-like ECH-associating protein 1 (Keap1) pathway and the activation of iNOS and therefore nitrosative stress in MCF7, SKBR-3, and 4T1 breast cancer cell lines. In addition, LCA-mediated anti-neoplastic effects were through the activation of CAR and Takeda G-protein coupled receptor (TGR5) [494]. Nepelska and his coworkers explored commensal gut bacteria's efficacy in modulating the transcriptional expression of PPARγ. The presence of butyrate and propionate, two of the primary metabolites of gut bacteria, was associated with the activation of PPARγ activity via ERK1/2 signaling. Notably, two strains a *Prevotella* and an *Atopobium* were chosen for further investigation, and

it was found that they upregulated two PPAR-target genes, angiopoietin-like 4 (*ANGPTL4*) and adipose differentiation–related protein (*ADRP)* [491].

Taken together, there is an immense potential for the microbially derived compounds to serve as agonists/antagonists in modulating the transcriptional potential of the NRs, which could pave the way for the development of novel targets for cancer prevention and treatment.

10 Clinical trials

Several studies have reported the anti-cancer properties of natural compounds through the modulation of NRs. However, only a few of these natural compounds are shown to target NRss at clinically significant levels. In this section, we summarize the clinical trials conducted on natural compounds and their reported NRs targeting activities. The clinical trials of various natural compounds that showed to target NRs in humans are listed in Table 3.

In a phase II clinical study, Zhang et al. demonstrated that the administration of lycopene, a carotenoid, of 10 mg/day for 174 days effectively reduced the circulating PSA levels in prostate cancer patients (*n* = 41). The mechanistic studies using prostate cancer cells *in vitro* showed that lycopene remarkably reduced AR expression leading to retarded growth and progression of these cells [527]. In another randomized controlled trial, supplementation of soy protein isolates (40 g/day) for 6 months was shown to significantly suppress the AR expression in the prostate post-intervention biopsy samples compared to pre-intervention biopsy samples [526].

A plethora of studies has shown that irinotecan, a semi-synthetic analog of the natural compound camptothecin, possesses tremendous anti-cancer activities [530–533]. Numerous clinical trials have demonstrated that irinotecan modulates NRs in cancer patients. For instance, in phase I clinical trial, coadministration of FLOFIRI (2400 mg/m^2 of 5-fluorouracil, 200 mg/m^2 of levo-leucovorin, and 180 mg/m^2 of irinotecan) along with efatutazone (0.25 mg and 0.5 mg) was shown to safely and effectively increase the stable disease period in metastatic colorectal cancer patients (*n* = 15) [525]. This treatment regimen was shown to reduce PPARγ and RXR after intervention in tumor specimens of patients with stable disease compared to patients with progressive disease, although the difference was not statistically significant [525]. Another well-recognized chemotherapeutic agent, doxorubicin (a natural anthracycline antibiotic), was shown to reduce ABCA1 via downregulating PPARγ and LXRα in breast cancer patients (*n* = 12) [523]. In another double-blind randomized clinical trial, consumption of *Berberis vulgaris* juice (480 mL/day) for over 8 weeks was shown to downregulate PPARγ, HIF, and VEGF in women

with benign breast diseases [524]. This study also showed that consumption of *B. vulgaris* juice for 8 weeks did not show any adverse side effects in these patients [524]. In a double-blind, placebo-controlled, and randomized clinical trial supplementation of curcumin (100 mg) along with soy isoflavones (40 mg) for 6 months was shown to significantly reduce PSA levels in the patients with either prostate cancer or prostate intraepithelial neoplasia ($n = 85$). The same study showed that curcumin and isoflavone combinatorial treatment reduce AR expression in LNCaP prostate cancer cells suggesting that the AR is a potential molecular target of these drugs [528]. In addition, the safety evaluation showed that curcumin and isoflavone combinatorial treatment did not cause any adverse side effects in prostate cancer patients [528].

Furthermore, monoclonal antibodies have been proven to be potential anti-immunotherapeutic agents and aid in disease relapse in chemoresistant cancer patients [534–537]. Certain monoclonal antibodies are direct modulators of NRs. For example, intravenous administration of figitumumab (monoclonal antibody targeting IGF 1 receptor) at 20 mg/kg every 3 weeks for three cycles decreased the PSA levels and AR expression in localized prostate cancer patients ($n = 16$) [538]. In another clinical study, avelumab (targets PD-L1) administration (10 mg/kg, intravenous) was shown to be effective against refractory prostate cancer treatment by altering the plasma concentration of AR [529]. The study also evidenced the acceptable toxicity for the avelumab treatment of mentioned dosage [529].

Furthermore, the pharmacodynamics and pharmacokinetics of a well-known chemotherapeutic drug, docetaxel, have been shown to be dependent on single nucleotide polymorphisms (SNPs) in *CAR*, *HNF4α*, *PXR*, and *RXR* in Chinese nasopharyngeal cancer patients and Asian breast cancer patients [539, 540]. Another study by Deeken et al. showed that the SNPs in PPARδ were significantly associated with therapeutic response to docetaxel in prostate cancer patients [541].

Collectively, these clinical trials suggest that natural compounds exert their anti-cancer effects through the modulation of NRs and are well-tolerated in cancer patients. However, further studies are required to bring them to the bedside.

11 Conclusion and future perspectives

Several NRs have the potential to be used as cancer therapeutics. As detailed in this review, many established medicines or current clinical studies are based on the activation of single or multiple NRs, either as a standalone treatment or in conjunction with existing chemotherapy or immunotherapy. However, one of the most critical challenges in the sector is the occurrence of adverse side effects, which can arise after extended therapy. This obstacle is also why the development of first-generation LXR ligands was halted before reaching the clinics. The development of resistance to NR ligands is the field's second significant stumbling block. In recent years, traditional medicine has shown a substantial success rate, with increased efficacy and fewer side effects. In addition, many natural products are known to sensitize cancer cells to chemotherapeutic drugs. Therefore, natural products can be used as more effective agents than chemotherapeutic drugs.

Phytochemicals have been developed as potential cancer therapeutics for more than a couple of decades and have shown a wide range of targets both at gross and molecular levels. Phytochemicals of class alkaloids such as berberine, caffeine, capsaicin, and piperine; carotenoids such as astaxanthin, β-carotene, bixin, capsanthin, cryptoxanthin, fucoxanthin, and apo-10′-lycopene; and polyphenols such as acetylshikonin, artemisinin, auraptene, baicalein, N-butylidenephthalide, celastrol, cryptotanshinone, curcumin, ellagic acid, embelin, emodin, genistein, guggulsterone, gypenoside XLIX, hesperidin, honokiol, morusin, resveratrol, and withaferin A have been reported as modulators of human NRs at concentrations ranging from 25 to 200 μM.

Table 3 The clinical trials that show the potential of natural compounds that target NRs and their anti-cancer effects

Cancer	Compound	Phase	NOP	NR	Effects	Reference
Breast cancer	Doxorubicin, paclitaxel, epirubicin, docetaxel	Not reported	12	PPARγ, LXRα	↓ LDLR, ABCA1, HDL-C, ApoA1 ↑ ApoB	[523]
Breast cancer	*Berberis vulgaris*	Not reported	85	PPARγ	↓ VEGF, HIF, IGF-1, IGF-1/IGFBP-1 ratio	[524]
Colorectal cancer	Irinotecan	I	15	PPARγ, RXR	↑ Disease stabilization	[525]
Prostate cancer	Soy protein isolate	Not reported	58	AR	↑ Estradiol, androstenedione, ↓ AR expression	[526]
Prostate cancer	Lycopene	II	41	AR	No significant outcome	[527]
Prostate cancer	Isoflavones and curcumin	Not reported	85	AR	↓ PSA	[528]
Prostate cancer	Avelumab	II	31	AR	↑ Disease control	[529]

ABCA1 ATP-binding cassette subfamily A member 1, *ApoA1* apolipoprotein A1, *ApoB* apolipoprotein B, *AR* androgen receptor, *HDL-C* high density lipoprotein C, *IGF-1* insulin-like growth factor 1, *IGFBP-1* insulin-like growth factor–binding protein 1, *LDLR* low-density lipoprotein receptor, *LXRα* liver X receptor alpha, *PPARγ* peroxisome proliferator–activated receptor gamma, *PSA* prostate-specific antigen, *RXR* retinoid X receptor, *VEGF* vascular endothelial growth factor

Several of these, including piperine, curcumin, genistein, guggulsterone, and resveratrol, have shown profound anti-cancer activities with minor adverse side effects in preclinical and clinical settings. Low bioavailability, solubility, and accuracy restricted these phytochemicals to develop as commercial drugs. Recently, nanoformulations of these compounds also had shown improved bioavailability and accuracy at the molecular level with lesser concentration usage in clinical trials. The drugs docetaxel, and paclitaxel, and their nanoformulations have been the most successful chemotherapeutic agents against several malignancies including bladder, brain, breast, colon, cervical, head and neck, leukemia, pancreatic, and prostate. In the randomized clinical trials, these compounds were shown to be not effective among certain patients who have SNPs in NRs. Therefore, more studies are required to determine how these compounds affect NRs.

A variety of zootherapeutic agents have shown profound anti-oxidant, anti-inflammatory, and anti-cancer activities. The *in vitro* studies have shown that marine animal–derived products and extracts inhibited proliferation and induced apoptosis of cancer cells through modulating NRs including FXR, PXR, LXR, and AR, and the expression of their downstream target genes. Most of these compounds including psammaplin A (10 μM); sintokamide A (5 μg/mL); solomonsterols A (5.2 μM) and B (50 μM); cholestan disulfate (10 μM); theonellasterols B–F (10 μM); theonellasterol H (10 μM); theonellasterol G (50 μM); conicasterol B (10 μM); conicasterol E (10 μM); malaitasterol A (10 μM); gracilioethers E, I, J, and K (10 μM); and cinanthrenol A (10 nM) have been shown to remarkably modulate NRs at very low concentrations and thereby limit cancer cell growth and progression. Although a significant amount of evidence about anti-cancer mechanisms is available for these novel compounds, *in vivo* and clinical studies are lacking. This might be owing to the fact that these species are under continuous threat due to increased pollution, and the second reason is the difficulty and laborious synthesization of these compounds commercially.

Next, the accumulation of numerous secondary metabolites has been shown to be detrimental to cancer cells. This idea was utilized successfully in the preclinical studies and treatment of cancer cells with secondary metabolites including obeticholic acid, eicosatetraenoate, tocopherols, retinoic acid, PUFA, sodium gluconate, α-linolenic acid, and linoleic acid were shown to inhibit cell proliferation, induce apoptosis, and downregulate STAT and NF-κB pathways in cancer cells through modulating NRs. However, the efficacy, safety, and toxicity of these compounds are yet to be tested in appropriate clinical settings with blindfold and placebo-controlled trials.

Moreover, decades of research have proven the beneficial effects of microbiota on human health. One of the most successful chemotherapeutic FDA-approved agents,

doxorubicin, is an antibiotic isolated from *Streptomyces peucetius* var. *caesius*. *In vitro* and *in vivo* have shown that microbial products and extracts significantly modulate NRs in several cancers. Not only that these compounds were shown to target NRs of class hormonal receptors (ER and PR) and metabolic receptors (FXR and PXR) but also certain orphan receptors including CAR and NUR77. In the future, clinical studies must be conducted to prove their efficacy against human cancers.

Furthermore, the current literature rightly points out that there is an enormous amount of evidence present to prove the effectiveness of natural compounds as modulators of NRs in various *in vitro* and *in vivo* cancer models. The majority of these cancer models include breast, liver, and prostate cancers. Nevertheless, studies regarding the role of these chemicals or extracts in modulating NRs during EMT and metastasis are scarcely leaving the question open for appropriate dosage and the choice of the right drug for the specific type and stage of cancer. Another major limitation lies in the limited knowledge about all the NRs. Therefore, in-depth studies are required to unravel the structure, mechanism of action, ligand binding, etc. Endocrine NRs such as ER, PR, and AR have been known for more than a decade, and various synthetic and natural compounds are studied for their potential to modulate these NRs. Recently, NRs involved in metabolisms, such as FXR, LXR, PPARs, RAR, RXR, PXR, and VDR, and orphan receptors such as NURR1 and NUR77 have been the center of attraction for the development of various agonists and antagonists. However, studies on whether the natural compounds affect other NRs such as COUP-TFI, COUP-TFII, DAX-1, ERRα, ERRβ, GCNF, GR, MR, CAR, ERBB, LRH-1, NOR-1, PNR, Rev-Erbα, Rev-Erbβ, RORA, RORB, SHP, TLX, TR2, and TR4 are unexplored.

In conclusion, the use of natural compounds has emerged as a novel alternative in cancer therapeutics with lower side effects, lesser cost, unique structures, and mechanisms. These drugs suppress cancer cell growth, proliferation, and invasion by blocking or activating NRs resulting in the modulation of multiple signaling pathways that induce apoptosis, arrest in the cell cycle, boost autophagy, and reverse EMT changes. The present review also discusses the efficacy of phytochemicals that target NRs as anti-cancer drugs in various *in vitro* and *in vivo* models. Additionally, this review also emphasized animal and microbially derived compounds as agonists/antagonists to NRs in cancer therapy. Together, these data suggest that natural product–derived medications are attractive prospects in anti-cancer therapeutics that need additional investigations to better understand the mechanisms by which they work. As pointed rightly in the present work, an immense variety of natural compounds are evaluated *in vitro* and *in vivo* for their anti-tumor activities as either

agonists or antagonists to NRs. However, only a few clinical trials for these chemicals are performed, leaving the overwhelming majority of natural compounds untested in clinical settings. In addition, care should be taken to determine the effective dose, bioavailability, and toxicity of these compounds if any.

Declarations

Conflict of interest The authors declare no competing interests.

References

1. Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., et al. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians, 71*(3), 209–249, https://doi.org/10.3322/caac.21660.

2. Hanahan, D. (2022). Hallmarks of cancer: New dimensions. *Cancer Discovery, 12*(1), 31–46. https://doi.org/10.1158/2159-8290.CD-21-1059

3. Hanahan, D., & Weinberg, R. A. (2011). Hallmarks of cancer: The next generation. *Cell, 144*(5), 646–674. https://doi.org/10.1016/j.cell.2011.02.013

4. Arora, L., Kumar, A. P., Arfuso, F., Chng, W. J., & Sethi, G. (2018). The role of signal transducer and activator of transcription 3 (STAT3) and its targeted inhibition in hematological malignancies. *Cancers, 10*(9), 327. https://doi.org/10.3390/cancers10090327

5. Bushweller, J. H. (2019). Targeting transcription factors in cancer - From undruggable to reality. *Nature Reviews Cancer, 19*(11), 611–624. https://doi.org/10.1038/s41568-019-0196-7

6. Garg, M., Shanmugam, M. K., Bhardwaj, V., Goel, A., Gupta, R., Sharma, A., et al. (2021). The pleiotropic role of transcription factor STAT3 in oncogenesis and its targeting through natural products for cancer prevention and therapy. *Medicinal Research Reviews, 41*(3), 1291–1336. https://doi.org/10.1002/med.21761

7. Mirzaei, S., Zarrabi, A., Hashemi, F., Zabolian, A., Saleki, H., Ranjbar, A., et al. (2021). Regulation of nuclear factor-kappaB (NF-κB) signaling pathway by non-coding RNAs in cancer: Inhibiting or promoting carcinogenesis? *Cancer Letters, 509*, 63–80. https://doi.org/10.1016/j.canlet.2021.03.025

8. Dhiman, V. K., Bolt, M. J., & White, K. P. (2018). Nuclear receptors in cancer—Uncovering new and evolving roles through genomic analysis. *Nature Reviews Genetics, 19*(3), 160–174. https://doi.org/10.1038/nrg.2017.102

9. Jayaprakash, S., Hegde, M., Girisa, S., Alqahtani, M. S., Abbas, M., Lee, E. H. C., et al. (2022). Demystifying the functional role of nuclear receptors in esophageal cancer. *International Journal of Molecular Sciences, 23*(18), 10952. https://doi.org/10.3390/ijms231810952.

10. Gangwar, S. K., Kumar, A., Jose, S., Alqahtani, M. S., Abbas, M., Sethi, G., et al. (2022). Nuclear receptors in oral cancer-Emerging players in tumorigenesis. *Cancer Letters, 536*, 215666. https://doi.org/10.1016/j.canlet.2022.215666

11. Gangwar, S. K., Kumar, A., Yap, K. C., Jose, S., Parama, D., Sethi, G., et al. (2022). Targeting nuclear receptors in lung cancer-Novel therapeutic prospects. *Pharmaceuticals (Basel), 15*(5), https://doi.org/10.3390/ph15050624.

12. Girisa, S., Rana, V., Parama, D., Dutta, U., & Kunnumakkara, A. B. (2021). Differential roles of farnesoid X receptor (FXR) in modulating apoptosis in cancer cells. *Advances in Protein Chemistry and Structural Biology, 126*, 63–90. https://doi.org/10.1016/bs.apcsb.2021.02.006

13. Girisa, S., Henamayee, S., Parama, D., Rana, V., Dutta, U., & Kunnumakkara, A. B. (2021). Targeting farnesoid X receptor (FXR) for developing novel therapeutics against cancer. *Molecular Biomedecine, 2*(1), 21. https://doi.org/10.1186/s43556-021-00035-2

14. Tang, Q., Chen, Y., Meyer, C., Geistlinger, T., Lupien, M., Wang, Q., et al. (2011). A comprehensive view of nuclear receptor cancer cistromes. *Cancer Research, 71*(22), 6940–6947. https://doi.org/10.1158/0008-5472.CAN-11-2091

15. Santagata, S., Thakkar, A., Ergonul, A., Wang, B., Woo, T., Hu, R., et al. (2014). Taxonomy of breast cancer based on normal cell phenotype predicts outcome. *The Journal of Clinical Investigation, 124*(2), 859–870. https://doi.org/10.1172/JCI70941

16. Font-Diaz, J., Jimenez-Panizo, A., Caelles, C., Vivanco, M. D., Perez, P., Aranda, A., et al. (2021). Nuclear receptors: Lipid and hormone sensors with essential roles in the control of cancer development. *Seminars in Cancer Biology, 73*, 58–75. https://doi.org/10.1016/j.semcancer.2020.12.007

17. Zhao, L., Zhou, S., & Gustafsson, J. -Å. (2019). Nuclear receptors: Recent drug discovery for cancer therapies. *Endocrine Reviews, 40*(5), 1207–1249.

18. Burris, T. P., Solt, L. A., Wang, Y., Crumbley, C., Banerjee, S., Griffett, K., et al. (2013). Nuclear receptors and their selective pharmacologic modulators. *Pharmacological Reviews, 65*(2), 710–778. https://doi.org/10.1124/pr.112.006833

19. Ishigami-Yuasa, M., & Kagechika, H. (2020). Chemical screening of nuclear receptor modulators. *International Journal of Molecular Sciences, 21*(15), 5512. https://doi.org/10.3390/ijms21155512

20. Knapp, P., Gardner, P. H., Raynor, D. K., Woolf, E., & McMillan, B. (2010). Perceived risk of tamoxifen side effects: A study of the use of absolute frequencies or frequency bands, with or without verbal descriptors. *Patient Education and Counseling, 79*(2), 267–271.

21. Pratheeshkumar, P., Sreekala, C., Zhang, Z., Budhraja, A., Ding, S., Son, Y.-O., et al. (2012). Cancer prevention with promising natural products: Mechanisms of action and molecular targets. *Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents), 12*(10), 1159–1184.

22. Harsha, C., Banik, K., Bordoloi, D., & Kunnumakkara, A. B. (2017). Antiulcer properties of fruits and vegetables: A mechanism based perspective. *Food and Chemical Toxicology, 108*, 104–119.

23. Elkordy, A. A., Haj-Ahmad, R. R., Awaad, A. S., & Zaki, R. M. (2021). An overview on natural product drug formulations from conventional medicines to nanomedicines: Past, present and future. *Journal of Drug Delivery Science and Technology, 63*, 102459.

24. Kunnumakkara, A. B., Nair, A. S., Ahn, K. S., Pandey, M. K., Yi, Z., Liu, M., et al. (2007). Gossypin, a pentahydroxy glucosyl flavone, inhibits the transforming growth factor beta-activated

kinase-1-mediated NF-kappaB activation pathway, leading to potentiation of apoptosis, suppression of invasion, and abrogation of osteoclastogenesis. *Blood, 109*(12), 5112–5121. https://doi.org/10.1182/blood-2007-01-067256

25. Muralimanoharan, S. B., Kunnumakkara, A. B., Shylesh, B., Kulkarni, K. H., Haiyan, X., Ming, H., et al. (2009). Butanol fraction containing berberine or related compound from nexrutine inhibits NFkappaB signaling and induces apoptosis in prostate cancer cells. *Prostate, 69*(5), 494–504. https://doi.org/10.1002/pros.20899

26. Kunnumakkara, A. B., Sung, B., Ravindran, J., Diagaradjane, P., Deorukhkar, A., Dey, S., et al. (2012). Zyflamend suppresses growth and sensitizes human pancreatic tumors to gemcitabine in an orthotopic mouse model through modulation of multiple targets. *International Journal of Cancer, 131*(3), E292-303. https://doi.org/10.1002/ijc.26442

27. Huang, M., Lu, J.-J., & Ding, J. (2021). Natural products in cancer therapy: Past, present and future. *Natural Products and Bioprospecting, 11*(1), 5–13.

28. Huang, M.-Y., Zhang, L.-L., Ding, J., & Lu, J-J. (2018). Anticancer drug discovery from Chinese medicinal herbs. *Chinese Medicine, 13*(1), 1–9.

29. Newman, D. J., & Cragg, G. M. (2020). Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019. *Journal of Natural Products, 83*(3), 770–803.

30. Liu, C., Ho, P.C.-L., Wong, F. C., Sethi, G., Wang, L. Z., & Goh, B. C. (2015). Garcinol: Current status of its anti-oxidative, anti-inflammatory and anti-cancer effects. *Cancer Letters, 362*(1), 8–14.

31. Kirtonia, A., Gala, K., Fernandes, S. G., Pandya, G., Pandey, A. K., Sethi, G., et al. Repurposing of drugs: An attractive pharmacological strategy for cancer therapeutics. In *Seminars in Cancer Biology, 2021* (Vol. 68, pp. 258–278): Elsevier

32. Huang, P. X., Chandra, V., & Rastinejad, F. (2010). Structural overview of the nuclear receptor superfamily: Insights into physiology and therapeutics. *Annual Review of Physiology, 72*, 247–272. https://doi.org/10.1146/annurev-physiol-021909-135917

33. Papacleovoulou, G., Abu-Hayyeh, S., & Williamson, C. (2011). Nuclear receptor-driven alterations in bile acid and lipid metabolic pathways during gestation. *Biochimica et Biophysica Acta, 1812*(8), 879–887. https://doi.org/10.1016/j.bbadis.2010.11.001

34. Choi, J. M., & Bothwell, A. L. M. (2012). The nuclear receptor PPARs as important regulators of T-cell functions and autoimmune diseases. *Molecules and Cells, 33*(3), 217–222. https://doi.org/10.1007/s10059-012-2297-y

35. Nagy, Z. S., Czimmerer, Z., & Nagy, L. (2013). Nuclear receptor mediated mechanisms of macrophage cholesterol metabolism. *Molecular and Cellular Endocrinology, 368*(1–2), 85–98. https://doi.org/10.1016/j.mce.2012.04.003

36. Jin, Z., Li, X., & Wan, Y. (2015). Minireview: Nuclear receptor regulation of osteoclast and bone remodeling. *Molecular Endocrinology, 29*(2), 172–186. https://doi.org/10.1210/me.2014-1316

37. Yin, K., & Smith, A. G. (2016). Nuclear receptor function in skin health and disease: Therapeutic opportunities in the orphan and adopted receptor classes. *Cellular and Molecular Life Sciences, 73*(20), 3789–3800. https://doi.org/10.1007/s00018-016-2329-4

38. Makishima, M., Okamoto, A. Y., Repa, J. J., Tu, H., Learned, R. M., Luk, A., et al. (1999). Identification of a nuclear receptor for bile acids. *Science, 284*(5418), 1362–1365. https://doi.org/10.1126/science.284.5418.1362

39. Moore, L. B., Parks, D. J., Jones, S. A., Bledsoe, R. K., Consler, T. G., Stimmel, J. B., et al. (2000). Orphan nuclear receptors constitutive androstane receptor and pregnane X receptor share xenobiotic and steroid ligands. *Journal of Biological Chemistry, 275*(20), 15122–15127. https://doi.org/10.1074/jbc.M001215200

40. Chawla, A., Repa, J. J., Evans, R. M., & Mangelsdorf, D. J. (2001). Nuclear receptors and lipid physiology: Opening the X-files. *Science, 294*(5548), 1866–1870. https://doi.org/10.1126/science.294.5548.1866

41. Orth, D. N., Kovacs, W., & DeBold, C. R. (1998). Williams textbook of endocrinology. In *Williams Textbook of Endocrinology*. WB Saunders Co.

42. Sporn, M. B., Roberts, A. B., & Goodman, D. S. (1994). *The retinoids: Biology, chemistry, and medicine* (pp. 319). Lippincott Williams & Wilkins.

43. Thummel, C. S. (1995). From embryogenesis to metamorphosis: The regulation and function of Drosophila nuclear receptor superfamily members. *Cell, 83*(6), 871–877. https://doi.org/10.1016/0092-8674(95)90203-1

44. Jones, G., Strugnell, S. A., & DeLuca, H. F. (1998). Current understanding of the molecular actions of vitamin D. *Physiological Reviews, 78*(4), 1193–1231. https://doi.org/10.1152/physrev.1998.78.4.1193

45. Forrest, D., & Vennstrom, B. (2000). Functions of thyroid hormone receptors in mice. *Thyroid, 10*(1), 41–52. https://doi.org/10.1089/thy.2000.10.41

46. Germain, P., Staels, B., Dacquet, C., Spedding, M., & Laudet, V. (2006). Overview of nomenclature of nuclear receptors. *Pharmacological Reviews, 58*(4), 685–704.

47. Helsen, C., & Claessens, F. (2014). Looking at nuclear receptors from a new angle. *Molecular and Cellular Endocrinology, 382*(1), 97–106. https://doi.org/10.1016/j.mce.2013.09.009

48. Weikum, E. R., Liu, X., & Ortlund, E. A. (2018). The nuclear receptor superfamily: A structural perspective. *Protein Science, 27*(11), 1876–1892.

49. Schwabe, J. W., Chapman, L., Finch, J. T., & Rhodes, D. (1993). The crystal structure of the estrogen receptor DNA-binding domain bound to DNA: How receptors discriminate between their response elements. *Cell, 75*(3), 567–578. https://doi.org/10.1016/0092-8674(93)90390-c

50. Zhang, J., Chalmers, M. J., Stayrook, K. R., Burris, L. L., Wang, Y., Busby, S. A., et al. (2011). DNA binding alters coactivator interaction surfaces of the intact VDR-RXR complex. *Nature Structural & Molecular Biology, 18*(5), 556–563. https://doi.org/10.1038/nsmb.2046

51. Yu, X., Yi, P., Hamilton, R. A., Shen, H., Chen, M., Foulds, C. E., et al. (2020). Structural insights of transcriptionally active, full-length androgen receptor coactivator complexes. *Molecular Cell, 79*(5), 812–823. e814.

52. Claessens, F., & Gewirth, D. T. (2004). DNA recognition by nuclear receptors. *Essays in Biochemistry, 40*, 59–72. https://doi.org/10.1042/bse0400059

53. Cotnoir-White, D., Laperrière, D., & Mader, S. (2011). Evolution of the repertoire of nuclear receptor binding sites in genomes. *Molecular and Cellular Endocrinology, 334*(1–2), 76–82.

54. Penvose, A., Keenan, J. L., Bray, D., Ramlall, V., & Siggers, T. (2019). Comprehensive study of nuclear receptor DNA binding provides a revised framework for understanding receptor specificity. *Nature Communications, 10*(1), 1–15.

55. Hong, H., Kohli, K., Trivedi, A., Johnson, D. L., & Stallcup, M. R. (1996). GRIP1, a novel mouse protein that serves as a transcriptional coactivator in yeast for the hormone binding domains of steroid receptors. *Proceedings of the National Academy of Sciences, 93*(10), 4948–4952.

56. Onate, S. A., Tsai, S. Y., Tsai, M. J., & O'Malley, B. W. (1995). Sequence and characterization of a coactivator for the steroid hormone receptor superfamily. *Science, 270*(5240), 1354–1357. https://doi.org/10.1126/science.270.5240.1354

57. Kamei, Y., Xu, L., Heinzel, T., Torchia, J., Kurokawa, R., Gloss, B., et al. (1996). A CBP integrator complex mediates

transcriptional activation and AP-1 inhibition by nuclear receptors. *Cell, 85*(3), 403–414.

58. Takeshita, A., Yen, P. M., Misiti, S., Cardona, G. R., Liu, Y., & Chin, W. W. (1996). Molecular cloning and properties of a full-length putative thyroid hormone receptor coactivator. *Endocrinology, 137*(8), 3594–3597.

59. Voegel, J. J., Heine, M., Zechel, C., Chambon, P., & Gronemeyer, H. (1996). TIF2, a 160 kDa transcriptional mediator for the ligand-dependent activation function AF-2 of nuclear receptors. *The EMBO Journal, 15*(14), 3667–3675.

60. Anzick, S. L., Kononen, J., Walker, R. L., Azorsa, D. O., Tanner, M. M., Guan, X.-Y., et al. (1997). AIB1, a steroid receptor coactivator amplified in breast and ovarian cancer. *Science, 277*(5328), 965–968.

61. Torchia, J., Rose, D. W., Inostroza, J., Kamei, Y., Westin, S., Glass, C. K., et al. (1997). The transcriptional co-activator p/CIP binds CBP and mediates nuclear-receptor function. *Nature, 387*(6634), 677–684.

62. McKenna, N. J., & O'Malley, B. W. (2002). Combinatorial control of gene expression by nuclear receptors and coregulators. *Cell, 108*(4), 465–474.

63. Chen, H., Lin, R. J., Schiltz, R. L., Chakravarti, D., Nash, A., Nagy, L., et al. (1997). Nuclear receptor coactivator ACTR is a novel histone acetyltransferase and forms a multimeric activation complex with P/CAF and CBP/p300. *Cell, 90*(3), 569–580.

64. Yoshinaga, S. K., Peterson, C. L., Herskowitz, I., & Yamamoto, K. R. (1992). Roles of SWI1, SWI2, and SWI3 proteins for transcriptional enhancement by steroid receptors. *Science, 258*(5088), 1598–1604.

65. Chakravarti, D. (1996). LaMorte VJ, Nelson MC, Nakajima T, Schulman IG, Juguilon H, Montminy M, Evans RM. *Role of CBP/P300 in nuclear receptor signalling. Nature, 383*, 99–103.

66. Fondell, J. D., Ge, H., & Roeder, R. G. (1996). Ligand induction of a transcriptionally active thyroid hormone receptor coactivator complex. *Proceedings National Academy of Sciences of the United States of America, 93*(16), 8329–8333. https://doi.org/10.1073/pnas.93.16.8329

67. Fryer, C. J., & Archer, T. K. (1998). Chromatin remodelling by the glucocorticoid receptor requires the BRG1 complex. *Nature, 393*(6680), 88–91.

68. Rachez, C., Suldan, Z., Ward, J., Chang, C.-P.B., Burakov, D., Erdjument-Bromage, H., et al. (1998). A novel protein complex that interacts with the vitamin D3 receptor in a ligand-dependent manner and enhances VDR transactivation in a cell-free system. *Genes & Development, 12*(12), 1787–1800.

69. Chen, D. G., Ma, H., Hong, H., Koh, S. S., Huang, S. M., Schurter, B. T., et al. (1999). Regulation of transcription by a protein methyltransferase. *Science, 284*(5423), 2174–2177. https://doi.org/10.1126/science.284.5423.2174

70. Lanz, R. B., McKenna, N. J., Onate, S. A., Albrecht, U., Wong, J. M., Tsai, S. Y., et al. (1999). A steroid receptor coactivator, SRA, functions as an RNA and is present in an SRC-1 complex. *Cell, 97*(1), 17–27. https://doi.org/10.1016/S0092-8674(00)80711-4

71. Nawaz, Z., Lonard, D. M., Smith, C. L., Lev-Lehman, E., Tsai, S. Y., Tsai, M.-J., et al. (1999). The Angelman syndrome-associated protein, E6-AP, is a coactivator for the nuclear hormone receptor superfamily. *Molecular and Cellular Biology, 19*(2), 1182–1189. https://doi.org/10.1128/MCB.19.2.1182

72. Näär, A. M., Lemon, B. D., & Tjian, R. (2001). Transcriptional coactivator complexes. *Annual Review of Biochemistry, 70*(1), 475–501.

73. Wang, H. B., Huang, Z. Q., Xia, L., Feng, Q., Erdjument-Bromage, H., Strahl, B. D., et al. (2001). Methylation of histone H4 at arginine 3 facilitating transcriptional activation by nuclear hormone receptor. *Science, 293*(5531), 853–857. https://doi.org/10.1126/science.1060781

74. Heery, D. M., Kalkhoven, E., Hoare, S., & Parker, M. G. (1997). A signature motif in transcriptional co-activators mediates binding to nuclear receptors. *Nature, 387*(6634), 733–736. https://doi.org/10.1038/42750

75. Bannister, A. J., & Kouzarides, T. (1996). The CBP co-activator is a histone acetyltransferase. *Nature, 384*(6610), 641–643. https://doi.org/10.1038/384641a0

76. Yang, X. J., Ogryzko, V. V., Nishikawa, J., Howard, B. H., & Nakatani, Y. (1996). A p300/CBP-associated factor that competes with the adenoviral oncoprotein E1A. *Nature, 382*(6589), 319–324. https://doi.org/10.1038/382319a0

77. Spencer, T. E., Jenster, G., Burcin, M. M., Allis, C. D., Zhou, J. X., Mizzen, C. A., et al. (1997). Steroid receptor coactivator-1 is a histone acetyltransferase. *Nature, 389*(6647), 194–198. https://doi.org/10.1038/38304

78. Chen, J. D., & Evans, R. M. (1995). A transcriptional corepressor that interacts with nuclear hormone receptors. *Nature, 377*(6548), 454–457. https://doi.org/10.1038/377454a0

79. Horlein, A. J., Naar, A. M., Heinzel, T., Torchia, J., Gloss, B., Kurokawa, R., et al. (1995). Ligand-independent repression by the thyroid-hormone receptor-mediated by a nuclear receptor corepressor. *Nature, 377*(6548), 397–404. https://doi.org/10.1038/377397a0

80. Hu, X., & Lazar, M. A. (1999). The CoRNR motif controls the recruitment of corepressors by nuclear hormone receptors. *Nature, 402*(6757), 93–96. https://doi.org/10.1038/47069

81. Cavailles, V., Dauvois, S., Lhorset, F., Lopez, G., Hoare, S., Kushner, P. J., et al. (1995). Nuclear factor Rip140 modulates transcriptional activation by the estrogen-receptor. *The EMBO Journal, 14*(15), 3741–3751. https://doi.org/10.1002/j.1460-2075.1995.tb00044.x

82. Windahl, S. H., Treuter, E., Ford, J., Zilliacus, J., Gustafsson, J. A., & McEwan, I. J. (1999). The nuclear-receptor interacting protein (RIP) 140 binds to the human glucocorticoid receptor and modulates hormone-dependent transactivation. *Journal of Steroid Biochemistry and Molecular Biology, 71*(3–4), 93–102. https://doi.org/10.1016/S0960-0760(99)00128-4

83. Sever, R., & Glass, C. K. (2013). Signaling by nuclear receptors. *Cold Spring Harbor Perspectives in Biology, 5*(3), a016709. https://doi.org/10.1101/cshperspect.a016709

84. Ong, P. S., Wang, L. Z., Dai, X., Tseng, S. H., Loo, S. J., & Sethi, G. (2016). Judicious toggling of mTOR activity to combat insulin resistance and cancer: Current evidence and perspectives. *Frontiers in Pharmacology, 7*, 395.

85. Dai, Y., Qiao, L., Chan, K. W., Yang, M., Ye, J. Y., Ma, J., et al. (2009). Peroxisome proliferator-activated receptor-gamma contributes to the inhibitory effects of embelin on colon carcinogenesis. *Cancer Research, 69*(11), 4776–4783. https://doi.org/10.1158/0008-5472.Can-08-4754

86. Ramachandran, L., Manu, K. A., Shanmugam, M. K., Li, F., Siveen, K. S., Vali, S., et al. (2012). Isorhamnetin inhibits proliferation and invasion and induces apoptosis through the modulation of peroxisome proliferator-activated receptor γ activation pathway in gastric cancer. *Journal of Biological Chemistry, 287*(45), 38028–38040.

87. Sikka, S., Chen, L., Sethi, G., & Kumar, A. P. (2012). Targeting PPARγ signaling cascade for the prevention and treatment of prostate cancer. *PPAR Research, 2012*, 968040.

88. Zhang, J., Ahn, K. S., Kim, C., Shanmugam, M. K., Siveen, K. S., Arfuso, F., et al. (2016). Nimbolide-induced oxidative stress abrogates STAT3 signaling cascade and inhibits tumor growth in transgenic adenocarcinoma of mouse prostate model. *Antioxidants & Redox Signaling, 24*(11), 575–589.

89. Raghunath, A., Sundarraj, K., Arfuso, F., Sethi, G., & Perumal, E. (2018). Dysregulation of Nrf2 in hepatocellular carcinoma: Role in cancer progression and chemoresistance. *Cancers, 10*(12), 481.

90. Duez, H., & Pourcet, B. (2021). Nuclear receptors in the control of the NLRP3 inflammasome pathway. *Frontiers in Endocrinology, 12*, 630536.

91. Alatshan, A., & Benkő, S. (2021). Nuclear receptors as multiple regulators of nlrp3 inflammasome function. *Frontiers in Immunology, 12*, 630569.

92. Whyte-Allman, S.-K., Hoque, M. T., Jenabian, M.-A., Routy, J.-P., & Bendayan, R. (2017). Xenobiotic nuclear receptors pregnane X receptor and constitutive androstane receptor regulate antiretroviral drug efflux transporters at the blood-testis barrier. *Journal of Pharmacology and Experimental Therapeutics, 363*(3), 324–335.

93. Lemmen, J., Tozakidis, I. E., Bele, P., & Galla, H.-J. (2013). Constitutive androstane receptor upregulates Abcb1 and Abcg2 at the blood–brain barrier after CITCO activation. *Brain Research, 1501*, 68–80.

94. Jigorel, E., Le Vee, M., Boursier-Neyret, C., Parmentier, Y., & Fardel, O. (2006). Differential regulation of sinusoidal and canalicular hepatic drug transporter expression by xenobiotics activating drug-sensing receptors in primary human hepatocytes. *Drug Metabolism and Disposition, 34*(10), 1756–1763.

95. Chisaki, I., Kobayashi, M., Itagaki, S., Hirano, T., & Iseki, K. (2009). Liver X receptor regulates expression of MRP2 but not that of MDR1 and BCRP in the liver. *Biochimica et Biophysica Acta (BBA)-Biomembranes, 1788*(11), 2396–2403.

96. Chen, T. (2010). Overcoming drug resistance by regulating nuclear receptors. *Advanced Drug Delivery Reviews, 62*(13), 1257–1264.

97. Geick, A., Eichelbaum, M., & Burk, O. (2001). Nuclear receptor response elements mediate induction of intestinal MDR1 by rifampin. *Journal of Biological Chemistry, 276*(18), 14581–14587. https://doi.org/10.1074/jbc.M010173200

98. Cerveny, L., Svecova, L., Anzenbacherova, E., Vrzal, R., Staud, F., Dvorak, Z., et al. (2007). Valproic acid induces CYP3A4 and MDR1 gene expression by activation of constitutive androstane receptor and pregnane X receptor pathways. *Drug Metabolism and Disposition, 35*(7), 1032–1041.

99. Ee, P. L. R., Kamalakaran, S., Tonetti, D., He, X., Ross, D. D., & Beck, W. T. (2004). Identification of a novel estrogen response element in the breast cancer resistance protein (ABCG2) gene. *Cancer research, 64*(4), 1247–1251.

100. Szatmari, I., Vámosi, G. r., Brazda, P., Balint, B. L., Benko, S., Széles, L., et al. (2006). Peroxisome proliferator-activated receptor γ-regulated ABCG2 expression confers cytoprotection to human dendritic cells. *Journal of Biological Chemistry, 281*(33), 23812-23823.

101. Burk, O., Arnold, K. A., Geick, A., Tegude, H., & Eichelbaum, M. (2005). A role for constitutive androstane receptor in the regulation of human intestinal MDR1 expression. *Biological Chemistry, 86*(6), 503–513. https://doi.org/10.1515/BC.2005.060

102. Cao, D., Qi, Z., Pang, Y., Li, H., Xie, H., Wu, J., et al. (2019). Retinoic acid-related orphan receptor c regulates proliferation, glycolysis, and chemoresistance via the PD-L1/ITGB6/STAT3 signaling axis in bladder cancer. *Cancer Research, 79*(10), 2604–2618. https://doi.org/10.1158/0008-5472.CAN-18-3842

103. Hu, L., Sun, Y., Luo, J., He, X., Ye, M., Li, G., et al. (2020). Targeting TR4 nuclear receptor with antagonist bexarotene increases docetaxel sensitivity to better suppress the metastatic castration-resistant prostate cancer progression. *Oncogene, 39*(9), 1891–1903.

104. Kai, L., & Levenson, A. S. (2011). Combination of resveratrol and antiandrogen flutamide has synergistic effect on androgen receptor inhibition in prostate cancer cells. *Anticancer Research, 31*(10), 3323–3330.

105. Penson, D. F., Armstrong, A. J., Concepcion, R., Agarwal, N., Olsson, C., Karsh, L., et al. (2016). Enzalutamide versus bicalutamide in castration-resistant prostate cancer: The STRIVE Trial. *Journal of Clinical Oncology, 34*(18), 2098–2106. https://doi.org/10.1200/JCO.2015.64.9285

106. de Bono, J. S., Chowdhury, S., Feyerabend, S., Elliott, T., Grande, E., Melhem-Bertrandt, A., et al. (2018). Antitumour activity and safety of enzalutamide in patients with metastatic castration-resistant prostate cancer previously treated with abiraterone acetate plus prednisone for >= 24 weeks in Europe. *European Urology, 74*(1), 37–45. https://doi.org/10.1016/j.eururo.2017.07.035

107. Lee, H. Y., Chen, H. L., Teoh, J. Y. C., Chen, T. C., Hao, S. Y., Tsai, H. Y., et al. (2021). Abiraterone and enzalutamide had different adverse effects on the cardiovascular system: A systematic review with pairwise and network meta-analyses. *Prostate Cancer and Prostatic Diseases, 24*(1), 244–252. https://doi.org/10.1038/s41391-020-00275-3

108. Johnson, D. B., & Sonthalia, S. (2022). Flutamide. In *StatPearls*. StatPearls Publishing.

109. Argnani, L., Broccoli, A., & Zinzani, P. L. (2017). Cutaneous T-cell lymphomas: Focusing on novel agents in relapsed and refractory disease. *Cancer Treatment Reviews, 61*, 61–69. https://doi.org/10.1016/j.ctrv.2017.10.007

110. Binkhorst, L., Mathijssen, R. H. J., Jager, A., & van Gelder, T. (2015). Individualization of tamoxifen therapy: Much more than just CYP2D6 genotyping. *Cancer Treatment Reviews, 41*(3), 289–299. https://doi.org/10.1016/j.ctrv.2015.01.002

111. Culig, Z. (2014). Targeting the androgen receptor in prostate cancer. *Expert Opinion on Pharmacotherapy, 15*(10), 1427–1437.

112. de The, H., Pandolfi, P. P., & Chen, Z. (2017). Acute promyelocytic leukemia: A paradigm for oncoprotein-targeted cure. *Cancer Cell, 32*(5), 552–560. https://doi.org/10.1016/j.ccell.2017.10.002

113. Facciola, A., Venanzi Rullo, E., Ceccarelli, M., D'Aleo, F., Di Rosa, M., Pinzone, M. R., et al. (2017). Kaposi's sarcoma in HIV-infected patients in the era of new antiretrovirals.*European Review for Medical Pharmacological Sciences*, 21(24), 5868–5869, https://doi.org/10.26355/eurrev_201712_14036.

114. Gniadecki, R., Assaf, C., Bagot, M., Dummer, R., Duvic, M., Knobler, R., et al. (2007). The optimal use of bexarotene in cutaneous T-cell lymphoma. *British Journal of Dermatology, 157*(3), 433–440. https://doi.org/10.1111/j.1365-2133.2007.07975.x

115. Jordan, V. C. (2014). Tamoxifen as the first targeted long-term adjuvant therapy for breast cancer. *Endocrine-Related Cancer, 21*(3), R235–R246. https://doi.org/10.1530/Erc-14-0092

116. McKeage, K., Curran, M. P., & Plosker, G. L. (2004). Fulvestrant. *Drugs, 64*(6), 633–648.

117. Nathan, M. R., & Schmid, P. (2017). A review of fulvestrant in breast cancer. *Oncology and Therapy, 5*(1), 17–29.

118. Pileri, A., Delfino, C., Grandi, V., & Pimpinelli, N. (2013). Role of bexarotene in the treatment of cutaneous T-cell lymphoma: The clinical and immunological sides. *Immunotherapy, 5*(4), 427–433. https://doi.org/10.2217/Imt.13.15

119. Rathkopf, D. E., Beer, T. M., Loriot, Y., Higano, C. S., Armstrong, A. J., Sternberg, C. N., et al. (2018). Radiographic progression-free survival as a clinically meaningful end point in metastatic castration-resistant prostate cancer: The PREVAIL Randomized Clinical Trial. *Jama Oncology, 4*(5), 694–701. https://doi.org/10.1001/jamaoncol.2017.5808

120. Rathkopf, D. E., Smith, M., Ryan, C., Berry, W., Shore, N., Liu, G., et al. (2017). Androgen receptor mutations in patients with castration-resistant prostate cancer treated with apalutamide. *Annals of Oncology, 28*(9), 2264–2271.

121. Scott, S. M., Brown, M., & Come, S. E. (2011). Emerging data on the efficacy and safety of fulvestrant, a unique antiestrogen therapy for advanced breast cancer. *Expert Opinion on Drug Safety, 10*(5), 819–826. https://doi.org/10.1517/14740338.2011.595560

122. Smith, M. R., Antonarakis, E. S., Ryan, C. J., Berry, W. R., Shore, N. D., Liu, G., et al. (2016). Phase 2 study of the safety and antitumor activity of apalutamide (ARN-509), a potent androgen receptor antagonist, in the high-risk nonmetastatic castration-resistant prostate cancer cohort. *European Urology, 70*(6), 963–970.

123. Smith, M. R., Saad, F., Chowdhury, S., Oudard, S., Hadaschik, B. A., Graff, J. N., et al. (2018). Apalutamide treatment and metastasis-free survival in prostate cancer. *New England Journal of Medicine, 378*(15), 1408–1418.

124. Vogel, C. L., Johnston, M. A., Capers, C., & Braccia, D. (2014). Toremifene for breast cancer: A review of 20 years of data. *Clinical Breast Cancer, 14*(1), 1–9. https://doi.org/10.1016/j.clbc.2013.10.014

125. Wiseman, L. R., & Goa, K. L. (1997). Toremifene. *Drugs, 54*(1), 141–160.

126. Warrell, R. P., Jr., Frankel, S. R., Miller, W. H., Jr., Scheinberg, D. A., Itri, L. M., Hittelman, W. N., et al. (1991). Differentiation therapy of acute promyelocytic leukemia with tretinoin (all-trans-retinoic acid). *New England Journal of Medicine, 324*(20), 1385–1393. https://doi.org/10.1056/NEJM199105163242002

127. Wong, Y. N. S., Ferraldeschi, R., Attard, G., & de Bono, J. (2014). Evolution of androgen receptor targeted therapy for advanced prostate cancer. *Nature Reviews Clinical Oncology, 11*(6), 365–376. https://doi.org/10.1038/nrclinonc.2014.72

128. Wu, P. A., & Stern, R. S. (2012). Topical tretinoin, another failure in the pursuit of practical chemoprevention for non-melanoma skin cancer. *Journal of Investigative Dermatology, 132*(6), 1532–1535.

129. Quinn, B. J., Dallos, M., Kitagawa, H., Kunnumakkara, A. B., Memmott, R. M., Hollander, M. C., et al. (2013). Inhibition of lung tumorigenesis by metformin is associated with decreased plasma IGF-I and diminished receptor tyrosine kinase signaling. *Cancer Prevention Research (Philadelphia, Pa.), 6*(8), 801–810. https://doi.org/10.1158/1940-6207.CAPR-13-0058-T

130. Parama, D., Boruah, M., Yachna, K., Rana, V., Banik, K., Harsha, C., et al. (2020). Diosgenin, a steroidal saponin, and its analogs: Effective therapies against different chronic diseases. *Life Sciences, 260*, 118182. https://doi.org/10.1016/j.lfs.2020.118182

131. Kunnumakkara, A. B., Banik, K., Bordoloi, D., Harsha, C., Sailo, B. L., Padmavathi, G., et al. (2018). Googling the guggul (Commiphora and Boswellia) for prevention of chronic diseases. *Frontiers in Pharmacology, 9*, 686. https://doi.org/10.3389/fphar.2018.00686

132. Babu, B. H., Jayram, H. N., Nair, M. G., Ajaikumar, K. B., & Padikkala, J. (2003). Free radical scavenging, antitumor and anti-carcinogenic activity of gossypin. *Journal of Experimental & Clinical Cancer Research, 22*(4), 581–589.

133. Padmavathi, G., Rathnakaram, S. R., Monisha, J., Bordoloi, D., Roy, N. K., & Kunnumakkara, A. B. (2015). Potential of butein, a tetrahydroxychalcone to obliterate cancer. *Phytomedicine, 22*(13), 1163–1171. https://doi.org/10.1016/j.phymed.2015.08.015

134. Henamayee, S., Banik, K., Sailo, B. L., Shabnam, B., Harsha, C., Srilakshmi, S., et al. (2020). Therapeutic emergence of rhein as a potential anticancer drug: A review of its molecular targets and anticancer properties. *Molecules, 25*(10), 2278. https://doi.org/10.3390/molecules25102278

135. Heymach, J. V., Shackleford, T. J., Tran, H. T., Yoo, S. Y., Do, K. A., Wergin, M., et al. (2011). Effect of low-fat diets on plasma levels of NF-kappaB-regulated inflammatory cytokines and angiogenic factors in men with prostate cancer. *Cancer Prevention Research (Philadelphia, Pa.), 4*(10), 1590–1598. https://doi.org/10.1158/1940-6207.CAPR-10-0136

136. Khatoon, E., Banik, K., Harsha, C., Sailo, B. L., Thakur, K. K., Khwairakpam, A. D., et al. (2022). Phytochemicals in cancer cell chemosensitization: Current knowledge and future perspectives. *Seminars in Cancer Biology, 80*, 306–339. https://doi.org/10.1016/j.semcancer.2020.06.014

137. Kunnumakkara, A. B., Koca, C., Dey, S., Gehlot, P., Yodkeeree, S., Danda, D., et al. (2009). Traditional uses of spices: An overview. *Molecular Targets and Therapeutic Uses of Spices: Modern Uses for Ancient Medicine*, 1–24. https://doi.org/10.1142/9789812837912_0001

138. Kunnumakkara, A. B., Bordoloi, D., Sailo, B. L., Roy, N. K., Thakur, K. K., Banik, K., et al. (2019). Cancer drug development: The missing links. *Experimental Biology and Medicine (Maywood, N.J.), 244*(8), 663–689. https://doi.org/10.1177/1535370219839163

139. Delfosse, V., Maire, A. I., Balaguer, P., & Bourguet, W. (2015). A structural perspective on nuclear receptors as targets of environmental compounds. *Acta Pharmacologica Sinica, 36*(1), 88–101.

140. Manu, K. A., Shanmugam, M. K., Li, F., Chen, L., Siveen, K. S., Ahn, K. S., et al. (2014). Simvastatin sensitizes human gastric cancer xenograft in nude mice to capecitabine by suppressing nuclear factor-kappa B-regulated gene products. *Journal of Molecular Medicine, 92*(3), 267–276.

141. Hsieh, Y.-S., Yang, S.-F., Sethi, G., & Hu, D.-N. (2015). Natural bioactives in cancer treatment and prevention. *BioMed Research International, 2015*, 182835. https://doi.org/10.1155/2015/182835

142. Patel, S. M., Venkata, K. C. N., Bhattacharyya, P., Sethi, G., & Bishayee, A. Potential of neem (Azadirachta indica L.) for prevention and treatment of oncologic diseases. In *Seminars in Cancer Biology, 2016* (Vol. 40, pp. 100–115): Elsevier

143. Kim, C., Lee, S.-G., Yang, W. M., Arfuso, F., Um, J.-Y., Kumar, A. P., et al. (2018). Formononetin-induced oxidative stress abrogates the activation of STAT3/5 signaling axis and suppresses the tumor growth in multiple myeloma preclinical model. *Cancer Letters, 431*, 123–141.

144. Benyhe, S. (1994). Morphine: New aspects in the study of an ancient compound. *Life Sciences, 55*(13), 969–979. https://doi.org/10.1016/0024-3205(94)00631-8

145. Mondal, A., Gandhi, A., Fimognari, C., Atanasov, A. G., & Bishayee, A. (2019). Alkaloids for cancer prevention and therapy: Current progress and future perspectives. *European Journal of Pharmacology, 858*, 172472. https://doi.org/10.1016/j.ejphar.2019.172472

146. Huang, M., Gao, H., Chen, Y., Zhu, H., Cai, Y., Zhang, X., et al. (2007). Chimmitecan, a novel 9-substituted camptothecin, with improved anticancer pharmacologic profiles in vitro and in vivo. *Clinical Cancer Research, 13*(4), 1298–1307. https://doi.org/10.1158/1078-0432.CCR-06-1277

147. Li, W., Shao, Y., Hu, L., Zhang, X., Chen, Y., Tong, L., et al. (2007). BM6, a new semi-synthetic vinca alkaloid, exhibits its potent in vivo anti-tumor activities via its high binding affinity for tubulin and improved pharmacokinetic profiles. *Cancer Biology & Therapy, 6*(5), 787–794. https://doi.org/10.4161/cbt.6.5.4006

148. Habtemariam, S. (2016). Berberine and inflammatory bowel disease: A concise review. *Pharmacological Research, 113*(Pt A), 592–599. https://doi.org/10.1016/j.phrs.2016.09.041

149. Ruan, H., Zhan, Y. Y., Hou, J., Xu, B., Chen, B., Tian, Y., et al. (2017). Berberine binds RXRalpha to suppress beta-catenin signaling in colon cancer cells. *Oncogene, 36*(50), 6906–6918. https://doi.org/10.1038/onc.2017.296

150. Cancer, I. A. f. R. o. (1991). Coffee, tea, mate, methylxanthines, and methyglyoxal. *IARC Monograph on the Evaluation of Carcinogenic Risk of Chemicals to Humans, 51*, 1–513.

151. Tolmach, L. J., Jones, R. W., & Busse, P. M. (1977). The action of caffeine on X-irradiated HeLa cells. I. Delayed inhibition of DNA synthesis. *Radiation Research*, *71*(3), 653–665.

152. Busse, P. M., Bose, S. K., Jones, R. W., & Tolmach, L. J. (1978). The action of caffeine on X-irradiated HeLa cells. III. Enhancement of X-ray-induced killing during G2 arrest. *Radiation Research*, *76*(2), 292–307.

153. Lau, C. C., & Pardee, A. B. (1982). Mechanism by which caffeine potentiates lethality of nitrogen-mustard. *Proceedings of the National Academy of Sciences of the United States of America-Biological Sciences, 79*(9), 2942–2946. https://doi.org/10.1073/pnas.79.9.2942

154. Levi-Schaffer, F., & Touitou, E. (1991). Xanthines inhibit 3T3 fibroblast proliferation. *Skin Pharmacology, 4*(4), 286–290. https://doi.org/10.1159/000210963

155. Lou, Y. R., Lu, Y. P., Xie, J. G., Huang, M. T., & Conney, A. H. (1999). Effects of oral administration of tea, decaffeinated tea, and caffeine on the formation and growth of tumors in high-risk SKH-1 mice previously treated with ultraviolet B light. *Nutrition and Cancer, 33*(2), 146–153. https://doi.org/10.1207/S15327914NC330205

156. Nomura, M., Ichimatsu, D., Moritani, S., Koyama, I., Dong, Z., Yokogawa, K., et al. (2005). Inhibition of epidermal growth factor-induced cell transformation and Akt activation by caffeine. *Molecular Carcinogenesis, 44*(1), 67–76. https://doi.org/10.1002/mc.20120

157. Faudone, G., Kilu, W., Ni, X., Chaikuad, A., Sreeramulu, S., Heitel, P., et al. (2021). The transcriptional repressor orphan nuclear receptor TLX is responsive to xanthines. *ACS Pharmacology & Translational Science, 4*(6), 1794–1807.

158. Clark, R., & Lee, S. H. (2016). Anticancer properties of capsaicin against human cancer. *Anticancer Research, 36*(3), 837–843.

159. Kim, C. S., Park, W. H., Park, J. Y., Kang, J. H., Kim, M. O., Kawada, T., et al. (2004). Capsaicin, a spicy component of hot pepper, induces apoptosis by activation of the peroxisome proliferator-activated receptor gamma in HT-29 human colon cancer cells. *Journal of Medicinal Food, 7*(3), 267–273. https://doi.org/10.1089/1096620041938713

160. Bort, A., Sanchez, B. G., Mateos-Gomez, P. A., Diaz-Laviada, I., & Rodriguez-Henche, N. (2019). Capsaicin targets lipogenesis in HepG2 cells through AMPK activation, AKT inhibition and PPARs regulation. *International Journal of Molecular Sciences*, *20*(7), ARTN 1660. https://doi.org/10.3390/ijms20071660

161. Kumar, S., Kamboj, J., & Sharma, S. (2011). Overview for various aspects of the health benefits of Piper longum linn. fruit. *Journal of Acupuncture and Meridian Studies*, *4*(2), 134–140.

162. Zadorozhna, M., Tataranni, T., & Mangieri, D. (2019). Piperine: Role in prevention and progression of cancer. *Molecular Biology Reports, 46*(5), 5617–5629. https://doi.org/10.1007/s11033-019-04927-z

163. Rajarajan, D., Natesh, J., Penta, D., & Meeran, S. M. (2021). Dietary piperine suppresses obesity-associated breast cancer growth and metastasis by regulating the miR-181c-3p/PPARalpha axis. *Journal of Agriculture and Food Chemistry, 69*(51), 15562–15574. https://doi.org/10.1021/acs.jafc.1c05670

164. Vershinin, A. (1999). Biological functions of carotenoids - Diversity and evolution. *BioFactors, 10*(2–3), 99–104.

165. Sandmann, G. (2021). Diversity and evolution of carotenoid biosynthesis from prokaryotes to plants. *Carotenoids: Biosynthetic and Biofunctional Approaches, 1261*, 79–94. https://doi.org/10.1007/978-981-15-7360-6_7

166. Zare, M., Norouzi Roshan, Z., Assadpour, E., & Jafari, S. M. (2021). Improving the cancer prevention/treatment role of carotenoids through various nano-delivery systems. *Critical Reviews in Food Science and Nutrition, 61*(3), 522–534.

167. Zhang, X., Zhao, W.-E., Hu, L., Zhao, L., & Huang, J. (2011). Carotenoids inhibit proliferation and regulate expression of peroxisome proliferators-activated receptor gamma (PPARγ) in K562 cancer cells. *Archives of Biochemistry and Biophysics, 512*(1), 96–106.

168. Liu, C.-L., Lim, Y.-P., & Hu, M.-L. (2012). Fucoxanthin attenuates rifampin-induced cytochrome P450 3A4 (CYP3A4) and multiple drug resistance 1 (MDR1) gene expression through pregnane X receptor (PXR)-mediated pathways in human hepatoma HepG2 and colon adenocarcinoma LS174T cells. *Marine Drugs, 10*(1), 242–257.

169. Hosokawa, M., Kudo, M., Maeda, H., Kohno, H., Tanaka, T., & Miyashita, K. (2004). Fucoxanthin induces apoptosis and enhances the antiproliferative effect of the PPARγ ligand, troglitazone, on colon cancer cells. *Biochimica et Biophysica Acta (BBA)-General Subjects*, *1675*(1–3), 113–119.

170. Lian, F., Hu, K. Q., Russell, R. M., & Wang, X. D. (2006). β-Cryptoxanthin suppresses the growth of immortalized human bronchial epithelial cells and non-small-cell lung cancer cells and up-regulates retinoic acid receptor β expression. *International Journal of Cancer, 119*(9), 2084–2089.

171. Iskandar, A. R., Liu, C., Smith, D. E., Hu, K.-Q., Choi, S.-W., Ausman, L. M., et al. (2013). β-Cryptoxanthin restores nicotine-reduced lung SIRT1 to normal levels and inhibits nicotine-promoted lung tumorigenesis and emphysema in A/J mice. *Cancer Prevention Research, 6*(4), 309–320.

172. Cheng, J., Miao, B., Hu, K.-Q., Fu, X., & Wang, X.-D. (2018). Apo-10'-lycopenoic acid inhibits cancer cell migration and angiogenesis and induces peroxisome proliferator-activated receptor γ. *The Journal of Nutritional Biochemistry, 56*, 26–34.

173. Manach, C., Scalbert, A., Morand, C., Rémésy, C., & Jiménez, L. (2004). Polyphenols: Food sources and bioavailability. *The American journal of Clinical Nutrition, 79*(5), 727–747.

174. Neveu, V., Perez-Jimenez, J., Vos, F., Crespy, V., du Chaffaut, L., Mennen, L., et al. (2010). Phenol-Explorer: An online comprehensive database on polyphenol contents in foods. *Database (Oxford), 2010*, bap024. https://doi.org/10.1093/database/bap024

175. Zhou, Y., Zheng, J., Li, Y., Xu, D.-P., Li, S., Chen, Y.-M., et al. (2016). Natural polyphenols for prevention and treatment of cancer. *Nutrients, 8*(8), 515.

176. Kausar, H., Jeyabalan, J., Aqil, F., Chabba, D., Sidana, J., Singh, I. P., et al. (2012). Berry anthocyanidins synergistically suppress growth and invasive potential of human non-small-cell lung cancer cells. *Cancer Letters, 325*(1), 54–62. https://doi.org/10.1016/j.canlet.2012.05.029

177. Wang, H., Zhang, H., Tang, L., Chen, H., Wu, C., Zhao, M., et al. (2013). Resveratrol inhibits TGF-beta1-induced epithelial-to-mesenchymal transition and suppresses lung cancer invasion and metastasis. *Toxicology, 303*, 139–146. https://doi.org/10.1016/j.tox.2012.09.017

178. Li, A. N., Li, S., Zhang, Y. J., Xu, X. R., Chen, Y. M., & Li, H. B. (2014). Resources and biological activities of natural polyphenols. *Nutrients, 6*(12), 6020–6047. https://doi.org/10.3390/nu6126020

179. Shi, W. F., Leong, M., Cho, E., Farrell, J., Chen, H. C., Tian, J., et al. (2009). Repressive effects of resveratrol on androgen receptor transcriptional activity. *Plos One, 4*(10), ARTN e7398. https://doi.org/10.1371/journal.pone.0007398

180. Rigalli, J. P., Tocchetti, G. N., Arana, M. R., Villanueva, S. S., Catania, V. A., Theile, D., et al. (2016). The phytoestrogen genistein enhances multidrug resistance in breast cancer cell lines by translational regulation of ABC transporters. *Cancer Letters, 376*(1), 165–172. https://doi.org/10.1016/j.canlet.2016.03.040

181. Kretschmer, N., Rinner, B., Deutsch, A. J. A., Lohberger, B., Knausz, H., Kunert, O., et al. (2012). Naphthoquinones from Onosma paniculata induce cell-cycle arrest and apoptosis in melanoma cells. *Journal of Natural Products, 75*(5), 865–869. https://doi.org/10.1021/np2006499

182. Park, S. H., Phuc, N. M., Lee, J., Wu, Z., Kim, J., Kim, H., et al. (2017). Identification of acetylshikonin as the novel CYP2J2 inhibitor with anti-cancer activity in HepG2 cells. *Phytomedicine, 24*, 134–140. https://doi.org/10.1016/j.phymed.2016.12.001

183. Liu, J., Zhou, W., Li, S. S., Sun, Z., Lin, B. Z., Lang, Y. Y., et al. (2008). Modulation of orphan nuclear receptor Nur77-mediated apoptotic pathway by acetylshikonin and analogues. *Cancer Research, 68*(21), 8871–8880. https://doi.org/10.1158/0008-5472.Can-08-1972

184. Moon, J., Koh, S. S., Malilas, W., Cho, I. R., Kaewpiboon, C., Kaowinn, S., et al. (2014). Acetylshikonin induces apoptosis of hepatitis B virus X protein-expressing human hepatocellular carcinoma cells via endoplasmic reticulum stress. *European Journal of Pharmacology, 735*, 132–140. https://doi.org/10.1016/j.ejphar.2014.04.021

185. Lai, H. C., Singh, N. P., & Sasaki, T. (2013). Development of artemisinin compounds for cancer treatment. *Investigational New Drugs, 31*(1), 230–246. https://doi.org/10.1007/s10637-012-9873-z

186. Steely, A. M., Willoughby, J. A., Sr., Sundar, S. N., Aivaliotis, V. I., & Firestone, G. L. (2017). Artemisinin disrupts androgen responsiveness of human prostate cancer cells by stimulating the 26S proteasome-mediated degradation of the androgen receptor protein. *Anti-Cancer Drugs, 28*(9), 1018–1031. https://doi.org/10.1097/CAD.0000000000000547

187. Morrissey, C., Gallis, B., Solazzi, J. W., Kim, B. J., Gulati, R., Vakar-Lopez, F., et al. (2010). Effect of artemisinin derivatives on apoptosis and cell cycle in prostate cancer cells. *Anti-Cancer Drugs, 21*(4), 423–432. https://doi.org/10.1097/CAD.0b013e328336f57b

188. Wang, Z. Z., Wang, C., Wu, Z. Y., Xue, J., Shen, B. X., Zuo, W., et al. (2017). Artesunate suppresses the growth of prostatic cancer cells through inhibiting androgen receptor. *Biological & Pharmaceutical Bulletin, 40*(4), 479–485. https://doi.org/10.1248/bpb.b16-00908

189. Lu, Z.-H., Peng, J.-H., Zhang, R.-X., Wang, F., Sun, H.-P., Fang, Y.-J., et al. (2018). Dihydroartemisinin inhibits colon cancer cell viability by inducing apoptosis through up-regulation of PPARγ expression. *Saudi Journal of Biological Sciences, 25*(2), 372–376.

190. Tayarani-Najaran, Z., Tayarani-Najaran, N., & Eghbali, S. (2021). A review of auraptene as an anticancer agent. *Frontiers in Pharmacology, 12*, 698352. https://doi.org/10.3389/fphar.2021.698352

191. Kawabata, K., Murakami, A., & Ohigashi, H. (2006). Auraptene decreases the activity of matrix metalloproteinases in dextran sulfate sodium-induced ulcerative colitis in ICR mice. *Bioscience Biotechnology and Biochemistry, 70*(12), 3062–3065. https://doi.org/10.1271/bbb.60393

192. Takahashi, N., Kang, M.-S., Kuroyanagi, K., Goto, T., Hirai, S., Ohyama, K., et al. (2008). Auraptene, a citrus fruit compound, regulates gene expression as a PPARα agonist in HepG2 hepatocytes. *BioFactors, 33*(1), 25–32.

193. Jamialahmadi, K., Salari, S., Alamolhodaei, N. S., Avan, A., Gholami, L., & Karimi, G. (2018). Auraptene inhibits migration and invasion of cervical and ovarian cancer cells by repression of matrix metalloproteinasas 2 and 9 activity. *Journal of Pharmacopuncture, 21*(3), 177–184. https://doi.org/10.3831/KPI.2018.21.021

194. Charmforoshan, E., Karimi, E., Oskoueian, E., Es-Haghi, A., & Iranshahi, M. (2019). Inhibition of human breast cancer cells (MCF-7 cell line) growth via cell proliferation, migration, and angiogenesis by auraptene of Ferula szowitsiana root extract. *Journal of Food Measurement and Characterization, 13*(4), 2644–2653. https://doi.org/10.1007/s11694-019-00185-6

195. Guo, Z. X., Hu, X. L., Xing, Z. Q., Xing, R., Lv, R. G., Cheng, X. Y., et al. (2015). Baicalein inhibits prostate cancer cell growth and metastasis via the caveolin-1/AKT/mTOR pathway. *Molecular and Cellular Biochemistry, 406*(1–2), 111–119. https://doi.org/10.1007/s11010-015-2429-8

196. Liu, H., Dong, Y. H., Gao, Y. T., Du, Z. P., Wang, Y. T., Cheng, P., et al. (2016). The fascinating effects of baicalein on cancer: A review. *International Journal of Molecular Sciences, 17*(10), ARTN 1681. https://doi.org/10.3390/ijms17101681

197. Otsuyama, K. I., Ma, Z., Abroun, S., Amin, J., Shamsasenjan, K., Asaoku, H., et al. (2007). PPARbeta-mediated growth suppression of baicalein and dexamethasone in human myeloma cells. *Leukemia, 21*(1), 187–190. https://doi.org/10.1038/sj.leu.2404462

198. Carazo Fernandez, A., Smutny, T., Hyrsova, L., Berka, K., & Pavek, P. (2015). Chrysin, baicalein and galangin are indirect activators of the human constitutive androstane receptor (CAR). *Toxicology Letters, 233*(2), 68–77. https://doi.org/10.1016/j.toxlet.2015.01.013

199. Bonham, M., Posakony, J., Coleman, I., Montgomery, B., Simon, J., & Nelson, P. S. (2005). Characterization of chemical constituents in Scutellaria baicalensis with antiandrogenic and growth-inhibitory activities toward prostate carcinoma. *Clinical Cancer Research, 11*(10), 3905–3914. https://doi.org/10.1158/1078-0432.CCR-04-1974

200. Tsai, N. M., Chen, Y. L., Lee, C. C., Lin, P. C., Cheng, Y. L., Chang, W. L., et al. (2006). The natural compound n-butylidenephthalide derived from Angelica sinensis inhibits malignant brain tumor growth in vitro and in vivo. *Journal of Neurochemistry, 99*(4), 1251–1262. https://doi.org/10.1111/j.1471-4159.2006.04151.x

201. Tsai, N. M., Lin, S. Z., Lee, C. C., Chen, S. P., Su, H. C., Chang, W. L., et al. (2005). The antitumor effects of Angelica sinensis on malignant brain tumors in vitro and in vivo. *Clinical Cancer Research, 11*(9), 3475–3484. https://doi.org/10.1158/1078-0432.CCR-04-1827

202. Wei, C. W., Lin, C. C., Yu, Y. L., Lin, C. Y., Lin, P. C., Wu, M. T., et al. (2009). n-Butylidenephthalide induced apoptosis in the A549 human lung adenocarcinoma cell line by coupled down-regulation of AP-2alpha and telomerase activity. *Acta Pharmacologica Sinica, 30*(9), 1297–1306. https://doi.org/10.1038/aps.2009.124

203. Su, Y. J., Huang, S. Y., Ni, Y. H., Liao, K. F., & Chiu, S. C. (2018). Anti-tumor and radiosensitization effects of N-butylidenephthalide on human breast cancer cells. *Molecules, 23*(2), 240. https://doi.org/10.3390/molecules23020240

204. Chen, Y. L., Jian, M. H., Lin, C. C., Kang, J. C., Chen, S. P., Lin, P. C., et al. (2008). The induction of orphan nuclear receptor nur77 expression by n-butylenephthalide as pharmaceuticals on hepatocellular carcinoma cell therapy. *Molecular Pharmacology, 74*(4), 1046–1058. https://doi.org/10.1124/mol.107.044800

205. Lin, P. C., Chen, Y. L., Chiu, S. C., Yu, Y. L., Chen, S. P., Chien, M. H., et al. (2008). Orphan nuclear receptor, Nurr-77 was a possible target gene of butylidenephthalide chemotherapy on glioblastoma multiform brain tumor. *Journal of Neurochemistry, 106*(3), 1017–1026. https://doi.org/10.1111/j.1471-4159.2008.05432.x

206. Kannaiyan, R., Shanmugam, M. K., & Sethi, G. (2011). Molecular targets of celastrol derived from Thunder of God Vine: Potential role in the treatment of inflammatory disorders and cancer. *Cancer Letters, 303*(1), 9–20. https://doi.org/10.1016/j.canlet.2010.10.025

207. Sanna, V., Chamcheu, J. C., Pala, N., Mukhtar, H., Sechi, M., & Siddiqui, I. A. (2015). Nanoencapsulation of natural triterpenoid celastrol for prostate cancer treatment. *International Journal of Nanomedicine, 10*, 6835–6846. https://doi.org/10.2147/IJN.S93752

208. Lim, H. Y., Ong, P. S., Wang, L., Goel, A., Ding, L., Wong, A.L.-A., et al. (2021). Celastrol in cancer therapy: Recent developments, challenges and prospects. *Cancer Letters, 521*, 252–267.

209. Rajendran, P., Li, F., Shanmugam, M. K., Kannaiyan, R., Goh, J. N., Wong, K. F., et al. (2012). Celastrol suppresses growth and induces apoptosis of human hepatocellular carcinoma through the modulation of STAT3/JAK2 signaling cascade in vitro and in vivo. *Cancer Prevention Research, 5*(4), 631–643. https://doi.org/10.1158/1940-6207.Capr-11-0420

210. Li, X. J., Wang, H. M., Ding, J., Nie, S. Z., Wang, L., Zhang, L. L., et al. (2019). Celastrol strongly inhibits proliferation, migration and cancer stem cell properties through suppression of Pin1 in ovarian cancer cells. *European Journal of Pharmacology, 842*, 146–156. https://doi.org/10.1016/j.ejphar.2018.10.043

211. Yang, H. J., Chen, D., Cui, Q. Z. C., Yuan, X., & Dou, Q. P. (2006). Celastrol, a triterpene extracted from the Chinese "Thunder of God Vine", is a potent proteasome inhibitor and suppresses human prostate cancer growth in nude mice. *Cancer Research, 66*(9), 4758–4765. https://doi.org/10.1158/0008-5472.Can-05-4529

212. Hu, M. J., Luo, Q., Alitongbieke, G., Chong, S. Y., Xu, C. T., Xie, L., et al. (2017). Celastrol-induced Nur77 interaction with TRAF2 alleviates inflammation by promoting mitochondrial ubiquitination and autophagy. *Molecular Cell*, *66*(1), 141-+, https://doi.org/10.1016/j.molcel.2017.03.008.

213. Chan, K., Chui, S., Wong, D., Ha, W., Chan, C., & Wong, R. (2004). Protective effects of Danshensu from the aqueous extract of Salvia miltiorrhiza (Danshen) against homocysteine-induced endothelial dysfunction. *Life Sciences, 75*(26), 3157–3171.

214. Chen, W., Lu, Y., Chen, G., & Huang, S. (2013). Molecular evidence of cryptotanshinone for treatment and prevention of human cancer. *Anti-Cancer Agents in Medicinal Chemistry, 13*(7), 979–987. https://doi.org/10.2174/18715206113139990115

215. Wu, C. Y., Hsieh, C. Y., Huang, K. E., Chang, C., & Kang, H. Y. (2012). Cryptotanshinone down-regulates androgen receptor signaling by modulating lysine-specific demethylase 1 function. *International Journal of Cancer, 131*(6), 1423–1434. https://doi.org/10.1002/ijc.27343

216. Xu, D., Lin, T. H., Li, S., Da, J., Wen, X. Q., Ding, J., et al. (2012). Cryptotanshinone suppresses androgen receptor-mediated growth in androgen dependent and castration resistant prostate cancer cells. *Cancer Letters, 316*(1), 11–22. https://doi.org/10.1016/j.canlet.2011.10.006

217. Moballegh Nasery, M., Abadi, B., Poormoghadam, D., Zarrabi, A., Keyhanvar, P., Khanbabaei, H., et al. (2020). Curcumin delivery mediated by bio-based nanoparticles: A review. *Molecules, 25*(3), 689.

218. Abadi, A. J., Mirzaei, S., Mahabady, M. K., Hashemi, F., Zabolian, A., Hashemi, F., et al. (2022). Curcumin and its derivatives in cancer therapy: Potentiating antitumor activity of cisplatin and reducing side effects. *Phytotherapy Research, 36*(1), 189–213.

219. Gupta, S. C., Sung, B., Kim, J. H., Prasad, S., Li, S., & Aggarwal, B. B. (2013). Multitargeting by turmeric, the golden spice: From kitchen to clinic. *Molecular Nutrition & Food Research, 57*(9), 1510–1528. https://doi.org/10.1002/mnfr.201100741

220. Bordoloi, D., Roy, N. K., Monisha, J., Padmavathi, G., & Kunnumakkara, A. B. (2016). Multi-targeted agents in cancer cell chemosensitization: What we learnt from curcumin thus far. *Recent Patents on Anti-Cancer Drug Discovery, 11*(1), 67–97. https://doi.org/10.2174/1574892810666151020101706

221. Giordano, A., & Tommonaro, G. (2019). Curcumin and cancer. *Nutrients, 11*(10), 2376.

222. Bhatia, M., Bhalerao, M., Cruz-Martins, N., & Kumar, D. (2021). Curcumin and cancer biology: Focusing regulatory effects in different signalling pathways. *Phytotherapy Research, 35*(9), 4913–4929. https://doi.org/10.1002/ptr.7121

223. Prakobwong, S., Gupta, S. C., Kim, J. H., Sung, B., Pinlaor, P., Hiraku, Y., et al. (2011). Curcumin suppresses proliferation and induces apoptosis in human biliary cancer cells through modulation of multiple cell signaling pathways. *Carcinogenesis, 32*(9), 1372–1380. https://doi.org/10.1093/carcin/bgr032

224. Peschel, D., Koerting, R., & Nass, N. (2007). Curcumin induces changes in expression of genes involved in cholesterol homeostasis. *Journal of Nutritional Biochemistry, 18*(2), 113–119. https://doi.org/10.1016/j.jnutbio.2006.03.007

225. Yang, F., Tang, X. W., Ding, L. L., Zhou, Y., Yang, Q. L., Gong, J. T., et al. (2016). Curcumin protects ANIT-induced cholestasis through signaling pathway of FXR-regulated bile acid and inflammation. *Scientific Reports, 6*, 33052. https://doi.org/10.1038/srep33052

226. Jiang, A., Wang, X., Shan, X., Li, Y., Wang, P., Jiang, P., et al. (2015). Curcumin reactivates silenced tumor suppressor gene RARβ by reducing DNA methylation. *Phytotherapy Research, 29*(8), 1237–1245.

227. Lee, Y. K., Lee, W. S., Hwang, J. T., Kwon, D. Y., Surh, Y. J., & Park, O. J. (2009). Curcumin exerts antidifferentiation effect through AMPKα-PPAR-γ in 3T3-L1 adipocytes and antiproliferatory effect through AMPKα-COX-2 in cancer cells. *Journal of Agricultural and Food Chemistry, 57*(1), 305–310.

228. Batie, S., Lee, J. H., Jama, R. A., Browder, D. O., Montano, L. A., Huynh, C. C., et al. (2013). Synthesis and biological evaluation of halogenated curcumin analogs as potential nuclear receptor selective agonists. *Bioorganic & Medicinal Chemistry, 21*(3), 693–702. https://doi.org/10.1016/j.bmc.2012.11.033

229. Bartik, L., Whitfield, G. K., Kaczmarska, M., Lowmiller, C. L., Moffet, E. W., Furmick, J. K., et al. (2010). Curcumin: A novel nutritionally derived ligand of the vitamin D receptor with implications for colon cancer chemoprevention. *Journal of Nutritional Biochemistry, 21*(12), 1153–1161. https://doi.org/10.1016/j.jnutbio.2009.09.012

230. Chen, A. P., & Xu, J. Y. (2005). Activation of PPAR gamma by curcumin inhibits Moser cell growth and mediates suppression of gene expression of cyclin D1 and EGFR. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, *288*(3), G447-G456, https://doi.org/10.1152/ajpgi.00209.2004.

231. Thulasiraman, P., Garriga, G., Danthuluri, V., McAndrews, D. J., & Mohiuddin, I. Q. (2017). Activation of the CRABPII/RAR pathway by curcumin induces retinoic acid mediated apoptosis in retinoic acid resistant breast cancer cells. *Oncology Reports, 37*(4), 2007–2015. https://doi.org/10.3892/or.2017.5495

232. Thulasiraman, P., McAndrews, D. J., & Mohiudddin, I. Q. (2014). Curcumin restores sensitivity to retinoic acid in triple negative breast cancer cells. *Bmc Cancer, 14*, 724. https://doi.org/10.1186/1471-2407-14-724

233. Altenburg, J. D., Bieberich, A. A., Terry, C., Harvey, K. A., VanHorn, J. F., Xu, Z., et al. (2011). A synergistic antiproliferation effect of curcumin and docosahexaenoic acid in SK-BR-3 breast cancer cells: Unique signaling not explained by the effects of either compound alone. *BMC Cancer, 11*(1), 1–16.

234. Mullen, W., Yokota, T., Lean, M. E., & Crozier, A. (2003). Analysis of ellagitannins and conjugates of ellagic acid and quercetin in raspberry fruits by LC-MSn. *Phytochemistry, 64*(2), 617–624. https://doi.org/10.1016/s0031-9422(03)00281-4

235. Berni, A., Grossi, M. R., Pepe, G., Filippi, S., Muthukumar, S., Papeschi, C., et al. (2012). Protective effect of ellagic acid (EA)

on micronucleus formation induced by N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) in mammalian cells, in in vitro assays and in vivo. *Mutation Research, 746*(1), 60–65. https://doi.org/10.1016/j.mrgentox.2012.03.007

236. Kumar, K. N., Raja, S. B., Vidhya, N., & Devaraj, S. N. (2012). Ellagic acid modulates antioxidant status, ornithine decarboxylase expression, and aberrant crypt foci progression in 1,2-dimethylhydrazine-instigated colon preneoplastic lesions in rats. *Journal of Agriculture and Food Chemistry, 60*(14), 3665–3672. https://doi.org/10.1021/jf204128z

237. Khanduja, K. L., Gandhi, R. K., Pathania, V., & Syal, N. (1999). Prevention of N-nitrosodiethylamine-induced lung tumorigenesis by ellagic acid and quercetin in mice. *Food and Chemical Toxicology, 37*(4), 313–318. https://doi.org/10.1016/s0278-6915(99)00021-6

238. Anitha, P., Priyadarsini, R. V., Kavitha, K., Thiyagarajan, P., & Nagini, S. (2013). Ellagic acid coordinately attenuates Wnt/beta-catenin and NF-kappaB signaling pathways to induce intrinsic apoptosis in an animal model of oral oncogenesis. *European Journal of Nutrition, 52*(1), 75–84. https://doi.org/10.1007/s00394-011-0288-y

239. Munagala, R., Aqil, F., Vadhanam, M. V., & Gupta, R. C. (2013). MicroRNA 'signature' during estrogen-mediated mammary carcinogenesis and its reversal by ellagic acid intervention. *Cancer Letters, 339*(2), 175–184. https://doi.org/10.1016/j.canlet.2013.06.012

240. Hong, M. Y., Seeram, N. P., & Heber, D. (2008). Pomegranate polyphenols down-regulate expression of androgen-synthesizing genes in human prostate cancer cells overexpressing the androgen receptor. *Journal of Nutritional Biochemistry, 19*(12), 848–855. https://doi.org/10.1016/j.jnutbio.2007.11.006

241. Kim, S. W., Kim, S. M., Bae, H., Nam, D., Lee, J. H., Lee, S. G., et al. (2013). Embelin inhibits growth and induces apoptosis through the suppression of Akt/mTOR/S6K1 signaling cascades. *The Prostate, 73*(3), 296–305.

242. Ko, J. H., Lee, S. G., Yang, W. M., Um, J. Y., Sethi, G., Mishra, S., et al. (2018). The application of embelin for cancer prevention and therapy. *Molecules, 23*(3), ARTN 621. https://doi.org/10.3390/molecules23030621.

243. Manu, K. A., Shanmugam, M. K., Ong, T. H., Subramaniam, A., Siveen, K. S., Perumal, E., et al. (2013). Emodin suppresses migration and invasion through the modulation of CXCR4 expression in an orthotopic model of human hepatocellular carcinoma. *PLoS One, 8*(3), e57015.

244. Subramaniam, A., Loo, S. Y., Rajendran, P., Manu, K. A., Perumal, E., Li, F., et al. (2013). An anthraquinone derivative, emodin sensitizes hepatocellular carcinoma cells to TRAIL induced apoptosis through the induction of death receptors and downregulation of cell survival proteins. *Apoptosis, 18*(10), 1175–1187.

245. Cha, T. L., Qiu, L., Chen, C. T., Wen, Y., & Hung, M. C. (2005). Emodin down-regulates androgen receptor and inhibits prostate cancer cell growth. *Cancer Research, 65*(6), 2287–2295. https://doi.org/10.1158/0008-5472.CAN-04-3250

246. Hsu, C. M., Hsu, Y. A., Tsai, Y., Shieh, F. K., Huang, S. H., Wan, L., et al. (2010). Emodin inhibits the growth of hepatoma cells: Finding the common anti-cancer pathway using Huh7, Hep3B, and HepG2 cells. *Biochemical and Biophysical Research Communications, 392*(4), 473–478. https://doi.org/10.1016/j.bbrc.2009.10.153

247. Tuli, H. S., Tuorkey, M. J., Thakral, F., Sak, K., Kumar, M., Sharma, A. K., et al. (2019). Molecular mechanisms of action of genistein in cancer: Recent advances. *Frontiers in Pharmacology, 10*, 1336. https://doi.org/10.3389/fphar.2019.01336

248. Bektic, J., Berger, A. P., Pfeil, K., Dobler, G., Bartsch, G., & Klocker, H. (2004). Androgen receptor regulation by physiological concentrations of the isoflavonoid genistein in

androgen-dependent LNCaP cells is mediated by estrogen receptor β. *European Urology, 45*(2), 245–251.

249. Mahmoud, A. M., Al-Alem, U., Ali, M. M., & Bosland, M. C. (2015). Genistein increases estrogen receptor beta expression in prostate cancer via reducing its promoter methylation. *Journal of Steroid Biochemistry and Molecular Biology, 152*, 62–75. https://doi.org/10.1016/j.jsbmb.2015.04.018

250. Basak, S., Pookot, D., Noonan, E. J., & Dahiya, R. (2008). Genistein down-regulates androgen receptor by modulating HDAC6-Hsp90 chaperone function. *Molecular Cancer Therapeutics, 7*(10), 3195–3202. https://doi.org/10.1158/1535-7163.MCT-08-0617

251. Oh, H. Y., Leem, J., Yoon, S. J., Yoon, S., & Hong, S. J. (2010). Lipid raft cholesterol and genistein inhibit the cell viability of prostate cancer cells via the partial contribution of EGFR-Akt/p70S6k pathway and down-regulation of androgen receptor. *Biochemical and Biophysical Research Communications, 393*(2), 319–324. https://doi.org/10.1016/j.bbrc.2010.01.133

252. Gao, S., Liu, G. Z., & Wang, Z. (2004). Modulation of androgen receptor-dependent transcription by resveratrol and genistein in prostate cancer cells. *Prostate, 59*(2), 214–225. https://doi.org/10.1002/pros.10375

253. Zhang, T., Wang, F., Xu, H. X., Yi, L., Qin, Y., Chang, H., et al. (2013). Activation of nuclear factor erythroid 2-related factor 2 and PPARgamma plays a role in the genistein-mediated attenuation of oxidative stress-induced endothelial cell injury. *British Journal of Nutrition, 109*(2), 223–235. https://doi.org/10.1017/S0007114512001110

254. Huang, S. L., Chang, T. C., Chao, C. C. K., & Sun, N. K. (2020). Role of the TLR4-androgen receptor axis and genistein in taxol-resistant ovarian cancer cells. *Biochemical Pharmacology, 177*, 113965. https://doi.org/10.1016/j.bcp.2020.113965

255. Shen, P., Liu, M. H., Ng, T. Y., Chan, Y. H., & Yong, E. L. (2006). Differential effects of isoflavones, from Astragalus membranaceus and Pueraria thomsonii, on the activation of PPARalpha, PPARgamma, and adipocyte differentiation in vitro. *Journal of Nutrition, 136*(4), 899–905. https://doi.org/10.1093/jn/136.4.899

256. Ahn, K. S., Sethi, G., Sung, B., Goel, A., Ralhan, R., & Aggarwal, B. B. (2008). Guggulsterone, a farnesoid X receptor antagonist, inhibits constitutive and inducible STAT3 activation through induction of a protein tyrosine phosphatase SHP-1 (Publication with Expression of Concern. See vol. 78, pg. 5184, 2018). *Cancer Research, 68*(11), 4406–4415, https://doi.org/10.1158/0008-5472.Can-07-6696.

257. Shishodia, S., Harikumar, K. B., Dass, S., Ramawat, K. G., & Aggarwal, B. B. (2008). The guggul for chronic diseases: Ancient medicine, modern targets. *Anticancer Research, 28*(6a), 3647–3664.

258. Girisa, S., Parama, D., Harsha, C., Banik, K., & Kunnumakkara, A. B. (2020). Potential of guggulsterone, a farnesoid X receptor antagonist, in the prevention and treatment of cancer. *Exploration of Targeted Anti-tumor Theraphy, 1*(5), 313–342, https://doi.org/10.37349/etat.2020.00019.

259. Bhat, A. A., Prabhu, K. S., Kuttikrishnan, S., Krishnankutty, R., Babu, J., Mohammad, R. M., et al. (2017). Potential therapeutic targets of guggulsterone in cancer. *Nutrition & Metabolism, 14*, 23. https://doi.org/10.1186/s12986-017-0180-8

260. Guan, B. X., Li, H., Yang, Z. D., Hoque, A., & Xu, X. C. (2013). Inhibition of farnesoid X receptor controls esophageal cancer cell growth in vitro and in nude mouse xenografts. *Cancer, 119*(7), 1321–1329. https://doi.org/10.1002/cncr.27910

261. Chen, Y., Wang, H. H., Chang, H. H., Huang, Y. H., Wang, J. R., Changchien, C. Y., et al. (2021). Guggulsterone induces apoptosis and inhibits lysosomal-dependent migration in human

bladder cancer cells. *Phytomedicine, 87*, 153587. https://doi.org/10.1016/j.phymed.2021.153587

262. Yu, J.-H., Zheng, J.-B., Qi, J., Yang, K., Wu, Y.-H., Wang, K., et al. (2019). Bile acids promote gastric intestinal metaplasia by upregulating CDX2 and MUC2 expression via the FXR/NF-κB signalling pathway. *International Journal of Oncology, 54*(3), 879–892.

263. Urizar, N. L., Liverman, A. B., Dodds, D. T., Silva, F. V., Ordentlich, P., Yan, Y. Z., et al. (2002). A natural product that lowers cholesterol as an antagonist ligand for FXR. *Science, 296*(5573), 1703–1706. https://doi.org/10.1126/science.1072891

264. Lee, J., Lee, K., Lee, J., Lee, K., Jang, K., Heo, J., et al. (2011). Farnesoid X receptor, overexpressed in pancreatic cancer with lymph node metastasis promotes cell migration and invasion. *British Journal of Cancer, 104*(6), 1027–1037.

265. Kong, J. N., He, Q., Wang, G. H., Dasgupta, S., Dinkins, M. B., Zhu, G., et al. (2015). Guggulsterone and bexarotene induce secretion of exosome-associated breast cancer resistance protein and reduce doxorubicin resistance in MDA-MB-231 cells. *International Journal of Cancer, 137*(7), 1610–1620. https://doi.org/10.1002/ijc.29542

266. Tian, H., Gui, Y. N., Wei, Y. H., Shang, B., Sun, J., Ma, S., et al. (2021). Z-guggulsterone induces PD-L1 upregulation partly mediated by FXR, Akt and Erk1/2 signaling pathways in non-small cell lung cancer. *International Immunopharmacology, 93*, 107395. https://doi.org/10.1016/j.intimp.2021.107395

267. Kao, T. H., Huang, S. C., Inbaraj, B. S., & Chen, B. H. (2008). Determination of flavonoids and saponins in Gynostemma pentaphyllum (Thunb.) Makino by liquid chromatography-mass spectrometry. *Analytica Chimica Acta, 626*(2), 200–211, https://doi.org/10.1016/j.aca.2008.07.049.

268. Wang, J., & Zhao, J. (1993). The effect of preventing recurrence of cancer metastasis on jiaogulan soup in clinical study. *Zhejiang Zhong Yi Za Zhii, 28*(20), 529–530.

269. Piao, X. L., Wu, Q., Yang, J., Park, S. Y., Chen, D. J., & Liu, H. M. (2013). Dammarane-type saponins from heat-processed Gynostemma pentaphyllum show fortified activity against A549 cells. *Archives of Pharmacal Research, 36*(7), 874–879. https://doi.org/10.1007/s12272-013-0086-6

270. Piao, X. L., Xing, S. F., Lou, C. X., & Chen, D. J. (2014). Novel dammarane saponins from Gynostemma pentaphyllum and their cytotoxic activities against HepG2 cells. *Bioorganic & Medicinal Chemistry Letters, 24*(20), 4831–4833. https://doi.org/10.1016/j.bmcl.2014.08.059

271. Chen, D. J., Liu, H. M., Xing, S. F., & Piao, X. L. (2014). Cytotoxic activity of gypenosides and gynogenin against non-small cell lung carcinoma A549 cells. *Bioorganic & Medicinal Chemistry Letters, 24*(1), 186–191. https://doi.org/10.1016/j.bmcl.2013.11.043

272. Xing, S. F., Liu, L. H., Zu, M. L., Ding, X. F., Cui, W. Y., Chang, T., et al. (2018). The inhibitory effect of gypenoside stereoisomers, gypenoside L and gypenoside LI, isolated from Gynostemma pentaphyllum on the growth of human lung cancer A549 cells. *Journal of Ethnopharmacology, 219*, 161–172. https://doi.org/10.1016/j.jep.2018.03.012

273. Huang, T. H., Tran, V. H., Roufogalis, B. D., & Li, Y. (2007). Gypenoside XLIX, a naturally occurring gynosaponin, PPAR-alpha dependently inhibits LPS-induced tissue factor expression and activity in human THP-1 monocytic cells. *Toxicology and Applied Pharmacology, 218*(1), 30–36. https://doi.org/10.1016/j.taap.2006.10.013

274. Aggarwal, V., Tuli, H. S., Thakral, F., Singhal, P., Aggarwal, D., Srivastava, S., et al. (2020). Molecular mechanisms of action of hesperidin in cancer: Recent trends and advancements. *Experimental Biology and Medicine (Maywood, N.J.), 245*(5), 486–497. https://doi.org/10.1177/1535370220903671

275. Ahmadi, A., & Shadboorestan, A. (2016). Oxidative stress and cancer; the role of hesperidin, a citrus natural bioflavonoid, as a cancer chemoprotective agent. *Nutrition and Cancer, 68*(1), 29–39.

276. Saiprasad, G., Chitra, P., Manikandan, R., & Sudhandiran, G. (2014). Hesperidin induces apoptosis and triggers autophagic markers through inhibition of Aurora-A mediated phosphoinositide-3-kinase/Akt/mammalian target of rapamycin and glycogen synthase kinase-3 beta signalling cascades in experimental colon carcinogenesis. *European Journal of Cancer, 50*(14), 2489–2507. https://doi.org/10.1016/j.ejca.2014.06.013

277. Wang, Y. X., Yu, H., Zhang, J., Gao, J., Ge, X., & Lou, G. (2015). Hesperidin inhibits HeLa cell proliferation through apoptosis mediated by endoplasmic reticulum stress pathways and cell cycle arrest. *Bmc Cancer, 15*, 682. https://doi.org/10.1186/s12885-015-1706-y

278. Khamis, A. A. A., Ali, E. M. M., Abd El-Moneim, M. A., Abd-Alhaseeb, M. M., Abu El-Magd, M., & Salim, E. I. (2018). Hesperidin, piperine and bee venom synergistically potentiate the anticancer effect of tamoxifen against breast cancer cells. *Biomedicine & Pharmacotherapy, 105*, 1335–1343. https://doi.org/10.1016/j.biopha.2018.06.105

279. Hsu, P. H., Chen, W. H., Chen, J. L., Hsieh, S. C., Lin, S. C., Mai, R. T., et al. (2021). Hesperidin and chlorogenic acid synergistically inhibit the growth of breast cancer cells via estrogen receptor/mitochondrial pathway. *Life-Basel, 11*(9), ARTN 950. https://doi.org/10.3390/life11090950.

280. Banik, K., Ranaware, A. M., Deshpande, V., Nalawade, S. P., Padmavathi, G., Bordoloi, D., et al. (2019). Honokiol for cancer therapeutics: A traditional medicine that can modulate multiple oncogenic targets. *Pharmacological Research, 144*, 192–209.

281. Arora, S., Singh, S., Piazza, G. A., Contreras, C. M., Panyam, J., & Singh, A. P. (2012). Honokiol: A novel natural agent for cancer prevention and therapy. *Current Molecular Medicine, 12*(10), 1244–1252. https://doi.org/10.2174/156652412803833508

282. Ong, C. P., Lee, W. L., Tang, Y. Q., & Yap, W. H. (2020). Honokiol: A review of its anticancer potential and mechanisms. *Cancers, 12*(1), ARTN 48. https://doi.org/10.3390/cancers12010048.

283. Jung, C. G., Horike, H., Cha, B. Y., Uhm, K. O., Yamauchi, R., Yamaguchi, T., et al. (2010). Honokiol increases ABCA1 expression level by activating retinoid X receptor beta. *Biological & Pharmaceutical Bulletin, 33*(7), 1105–1111. https://doi.org/10.1248/bpb.33.1105

284. Lim, S. L., Park, S. Y., Kang, S., Park, D., Kim, S. H., Um, J. Y., et al. (2015). Morusin induces cell death through inactivating STAT3 signaling in prostate cancer cells. *American Journal of Cancer Research, 5*(1), 289-U482.

285. Lin, W. L., Lai, D. Y., Lee, Y. J., Chen, N. F., & Tseng, T. H. (2015). Antitumor progression potential of morusin suppressing STAT3 and NFkappaB in human hepatoma SK-Hep1 cells. *Toxicology Letters, 232*(2), 490–498. https://doi.org/10.1016/j.toxlet.2014.11.031

286. Dat, N. T., Binh, P. T. X., Van Minh, C., Huong, H. T., & Lee, J. J. (2010). Cytotoxic prenylated flavonoids from Morus alba. *Fitoterapia, 81*(8), 1224–1227.

287. Wan, L. Z., Ma, B., & Zhang, Y. Q. (2014). Preparation of morusin from Ramulus mori and its effects on mice with transplanted H22 hepatocarcinoma. *BioFactors, 40*(6), 636–645. https://doi.org/10.1002/biof.1191

288. Lee, J.-C., Won, S.-J., Chao, C.-L., Wu, F.-L., Liu, H.-S., Ling, P., et al. (2008). Morusin induces apoptosis and suppresses NF-κB activity in human colorectal cancer HT-29 cells. *Biochemical and Biophysical Research Communications, 372*(1), 236–242.

289. Li, H., Wang, Q., Dong, L., Liu, C., Sun, Z., Gao, L., et al. (2015). Morusin suppresses breast cancer cell growth in vitro

and in vivo through C/EBPβ and PPARγ mediated lipoapoptosis. *Journal of Experimental & Clinical Cancer Research, 34*(1), 1–12.

290. Baek, S. H., Ko, J.-H., Lee, H., Jung, J., Kong, M., Lee, J.-W., et al. (2016). Resveratrol inhibits STAT3 signaling pathway through the induction of SOCS-1: Role in apoptosis induction and radiosensitization in head and neck tumor cells. *Phytomedicine, 23*(5), 566–577.

291. Ren, B., Kwah, M. X., Liu, C., Ma, Z., Shanmugam, M. K., Ding, L., et al. (2021). Resveratrol for cancer therapy: Challenges and future perspectives. *Cancer Letters, 515*, 63–72. https://doi.org/10.1016/j.canlet.2021.05.001

292. Nonomura, S., Kanagawa, H., & Makimoto, A. (1963). Chemical Constituents of Polygonaceous Plants. I. Studies on the Components of Ko-J O-Kon. (Polygonum Cuspidatum Sieb. Et Zucc.). *Yakugaku Zasshi, 83*, 988–990.

293. Diaz, J., Wuertz, B., Galbraith, A., & Ondrey, F. G. (2016). Effects of chalcones, nicotinamide, and resveratrol on PPAR gamma activation in oral cancer cells. *Cancer Research, 76*, 2611. https://doi.org/10.1158/1538-7445.Am2016-2611

294. Ulrich, S., Loitsch, S. M., Rau, O., von Knethen, A., Brune, B., Schubert-Zsilavecz, M., et al. (2006). Peroxisome proliferator-activated receptor gamma as a molecular target of resveratrol-induced modulation of polyamine metabolism. *Cancer Research, 66*(14), 7348–7354. https://doi.org/10.1158/0008-5472.Can-05-2777

295. Li, Y. T., Tian, X. T., Wu, M. L., Zheng, X., Kong, Q. Y., Cheng, X. X., et al. (2018). Resveratrol suppresses the growth and enhances retinoic acid sensitivity of anaplastic thyroid cancer cells. *International Journal of Molecular Sciences*, 19(4), ARTN 1030. https://doi.org/10.3390/ijms19041030

296. Vanden Berghe, W., Sabbe, L., Kaileh, M., Haegeman, G., & Heyninck, K. (2012). Molecular insight in the multifunctional activities of withaferin A. *Biochemical Pharmacology, 84*(10), 1282–1291. https://doi.org/10.1016/j.bcp.2012.08.027

297. Bargagna-Mohan, P., Hamza, A., Kim, Y. E., Ho, K. A., Y., Mor-Vaknin, N., Wendschlag, N., et al. (2007). The tumor inhibitor and antiangiogenic agent withaferin A targets the intermediate filament protein vimentin. *Chemistry & Biology, 14*(6), 623–634. https://doi.org/10.1016/j.chembiol.2007.04.010

298. Shiragannavar, V. D., Gowda, N. G. S., Kumar, D. P., Mirshahi, F., & Santhekadur, P. K. (2021). Withaferin A acts as a novel regulator of liver X receptor-α in HCC. *Frontiers in Oncology*, 3124.

299. Lim, Y. P., Cheng, C. H., Chen, W. C., Chang, S. Y., Hung, D. Z., Chen, J. J., et al. (2015). Allyl isothiocyanate (AITC) inhibits pregnane X receptor (PXR) and constitutive androstane receptor (CAR) activation and protects against acetaminophen- and amiodarone-induced cytotoxicity. *Archives of Toxicology, 89*(1), 57–72. https://doi.org/10.1007/s00204-014-1230-x

300. Oh, H., Park, S.-H., Kang, M.-K., Kim, Y.-H., Lee, E.-J., Kim, D. Y., et al. (2020). Asaronic acid inhibited glucose-triggered M2-phenotype shift through disrupting the formation of coordinated signaling of IL-4Rα-Tyk2-STAT6 and GLUT1-Akt-mTOR-AMPK. *Nutrients, 12*(7), 2006.

301. Papaioannou, M., Schleich, S., Prade, I., Degen, S., Roell, D., Schubert, U., et al. (2009). The natural compound atraric acid is an antagonist of the human androgen receptor inhibiting cellular invasiveness and prostate cancer cell growth. *Journal of Cellular and Molecular Medicine, 13*(8b), 2210–2223. https://doi.org/10.1111/j.1582-4934.2008.00426.x

302. Schleich, S., Papaioannou, M., Baniahmad, A., & Matusch, R. (2006). Extracts from Pygeum africanum and other ethnobotanical species with antiandrogenic activity. *Planta Medica, 72*(9), 807–813. https://doi.org/10.1055/s-2006-946638

303. Papaioannou, M., Schleich, S., Roell, D., Schubert, U., Tanner, T., Claessens, F., et al. (2010). NBBS isolated from Pygeum africanum bark exhibits androgen antagonistic activity, inhibits AR nuclear translocation and prostate cancer cell growth. *Investigational New Drugs, 28*(6), 729–743. https://doi.org/10.1007/s10637-009-9304-y

304. Fiaschetti, G., Grotzer, M. A., Shalaby, T., Castelletti, D., & Arcaro, A. (2011). Quassinoids: From traditional drugs to new cancer therapeutics. *Current Medicinal Chemistry, 18*(3), 316–328. https://doi.org/10.2174/092986711794839205

305. Moon, S. J., Jeong, B. C., Kim, H. J., Lim, J. E., Kim, H. J., Kwon, G. Y., et al. (2021). Bruceantin targets HSP90 to overcome resistance to hormone therapy in castration-resistant prostate cancer. *Theranostics, 11*(2), 958–973. https://doi.org/10.7150/thno.51478

306. Xu, D., Lin, T. H., Yeh, C. R., Cheng, M. A., Chen, L. M., Chang, C., et al. (2014). The wedelolactone derivative inhibits estrogen receptor-mediated breast, endometrial, and ovarian cancer cells growth. *BioMed Research International, 2014*, 713263. https://doi.org/10.1155/2014/713263

307. Akihisa, T., Higo, N., Tokuda, H., Ukiya, M., Akazawa, H., Tochigi, Y., et al. (2007). Cucurbitane-type triterpenoids from the fruits of Momordica charantia and their cancer chemopreventive effects. *Journal of Natural Products, 70*(8), 1233–1239. https://doi.org/10.1021/np068075p

308. Weng, J.-R., Bai, L.-Y., Chiu, C.-F., Hu, J.-L., Chiu, S.-J., & Wu, C.-Y. (2013). Cucurbitane triterpenoid from *Momordica charantia* induces apoptosis and autophagy in breast cancer cells, in part, through peroxisome proliferator-activated receptor γ activation. *Evidence-Based Complementary and Alternative Medicine, 2013*, 93675. https://doi.org/10.1155/2013/935675

309. Somjen, D., Grafi-Cohen, M., Weisinger, G., Izkhakov, E., Sharon, O., Kraiem, Z., et al. (2012). Growth inhibition of human thyroid carcinoma and goiter cells in vitro by the isoflavone derivative 7-(O)-carboxymethyl daidzein conjugated to Nt-boc-hexylenediamine. *Thyroid, 22*(8), 809–813.

310. Ichikawa, H., Nair, M. S., Takada, Y., Sheeja, D. A., Kumar, M. S., Oommen, O. V., et al. (2006). Isodeoxyelephantopin, a novel sesquiterpene lactone, potentiates apoptosis, inhibits invasion, and abolishes osteoclastogenesis through suppression of nuclear factor-κB (NF-κB) activation and NF-κB-regulated gene expression. *Clinical Cancer Research, 12*(19), 5910–5918.

311. Wolo, M. T., Cowherd, C. M., & Lee, K. H. (1975). Antitumor agents XV: Deoxyelephantopin, an antitumor principle from Elephantopus carolinianus Willd. *Journal of Pharmaceutical Sciences, 64*(9), 1572–1573.

312. Zou, G., Gao, Z., Wang, J., Zhang, Y., Ding, H., Huang, J., et al. (2008). Deoxyelephantopin inhibits cancer cell proliferation and functions as a selective partial agonist against PPARγ. *Biochemical Pharmacology*, 75(6), 1381–1392.

313. Jung, Y. S., Lee, H. S., Cho, H. R., Kim, K. J., Kim, J. H., Safe, S., et al. (2019). Dual targeting of Nur77 and AMPKalpha by isoalantolactone inhibits adipogenesis in vitro and decreases body fat mass in vivo. *International Journal of Obesity, 43*(5), 952–962. https://doi.org/10.1038/s41366-018-0276-x

314. Cao, Y., Chu, Q., & Ye, J. (2004). Chromatographic and electrophoretic methods for pharmaceutically active compounds in Rhododendron dauricum. *Journal of Chromatography. B, Analytical Technologies in the Biomedical and Life Sciences, 812*(1–2), 231–240. https://doi.org/10.1016/j.jchromb.2004.06.048

315. Chae, J., Kim, J. S., Choi, S. T., Lee, S. G., Ojulari, O. V., Kang, Y. J., et al. (2021). Farrerol induces cancer cell death via ERK activation in SKOV3 cells and attenuates TNF-alpha-mediated lipolysis. *International Journal of Molecular Sciences, 22*(17), 9400. https://doi.org/10.3390/ijms22179400

316. Neviani, P., Santhanam, R., Trotta, R., Notari, M., Blaser, B. W., Liu, S. J., et al. (2005). The tumor suppressor PP2A is functionally inactivated in blast crisis CML through the inhibitory activity of the BCR/ABL-regulated SET protein. *Cancer Cell, 8*(5), 355–368. https://doi.org/10.1016/j.ccr.2005.10.015

317. Mayati, A., Moreau, A., Le Vee, M., Bruyere, A., Jouan, E., Denizot, C., et al. (2018). Functional polarization of human hepatoma HepaRG cells in response to forskolin. *Scientific Reports, 8*(1), 16115. https://doi.org/10.1038/s41598-018-34421-8

318. Roullet, J. B., Luft, U. C., Xue, H., Chapman, J., Bychkov, R., Roullet, C. M., et al. (1997). Farnesol inhibits L-type Ca2+ channels in vascular smooth muscle cells. *Journal of Biological Chemistry, 272*(51), 32240–32246. https://doi.org/10.1074/jbc.272.51.32240

319. Mo, H., & Elson, C. E. (1999). Apoptosis and cell-cycle arrest in human and murine tumor cells are initiated by isoprenoids. *Journal of Nutrition, 129*(4), 804–813. https://doi.org/10.1093/jn/129.4.804

320. He, L., Mo, H., Hadisusilo, S., Qureshi, A. A., & Elson, C. E. (1997). Isoprenoids suppress the growth of murine B16 melanomas in vitro and in vivo. *Journal of Nutrition, 127*(5), 668–674. https://doi.org/10.1093/jn/127.5.668

321. Takahashi, N., Kawada, T., Goto, T., Yamamoto, T., Taimatsu, A., Matsui, N., et al. (2002). Dual action of isoprenols from herbal medicines on both PPARγ and PPARα in 3T3-L1 adipocytes and HepG2 hepatocytes. *FEBS Letters, 514*(2–3), 315–322.

322. Kim, Y. S., & Milner, J. A. (2005). Targets for indole-3-carbinol in cancer prevention. *Journal of Nutritional Biochemistry, 16*(2), 65–73. https://doi.org/10.1016/j.jnutbio.2004.10.007

323. Marconett, C. N., Sundar, S. N., Poindexter, K. M., Stueve, T. R., Bjeldanes, L. F., & Firestone, G. L. (2010). Indole-3-carbinol triggers aryl hydrocarbon receptor-dependent estrogen receptor (ER)alpha protein degradation in breast cancer cells disrupting an ERalpha-GATA3 transcriptional cross-regulatory loop. *Molecular Biology of the Cell, 21*(7), 1166–1177. https://doi.org/10.1091/mbc.E09-08-0689

324. Hsu, J. C., Zhang, J., Dev, A., Wing, A., Bjeldanes, L. F., & Firestone, G. L. (2005). Indole-3-carbinol inhibition of androgen receptor expression and downregulation of androgen responsiveness in human prostate cancer cells. *Carcinogenesis, 26*(11), 1896–1904.

325. Patel, A. R., Spencer, S. D., Chougule, M. B., Safe, S., & Singh, M. (2012). Pharmacokinetic evaluation and in vitro-in vivo correlation (IVIVC) of novel methylene-substituted 3,3' diindolylmethane (DIM). *European Journal of Pharmaceutical Sciences, 46*(1–2), 8–16. https://doi.org/10.1016/j.ejps.2012.01.012

326. Boakye, C. H. A., Doddapaneni, R., Shah, P. P., Patel, A. R., Godugu, C., Safe, S., et al. (2013). Chemoprevention of skin cancer with 1,1-bis (3'-indolyl)-1-(aromatic) methane analog through induction of the orphan nuclear receptor, NR4A2 (Nurr1). *Plos One, 8*(8), ARTN e69519. https://doi.org/10.1371/journal.pone.0069519.

327. Yang, L., Zahid, M., Liao, Y., Rogan, E. G., Cavalieri, E. L., Davidson, N. E., et al. (2013). Reduced formation of depurinating estrogen-DNA adducts by sulforaphane or KEAP1 disruption in human mammary epithelial MCF-10A cells. *Carcinogenesis, 34*(11), 2587–2592. https://doi.org/10.1093/carcin/bgt246

328. Palliyaguru, D. L., Yang, L., Chartoumpekis, D. V., Wendell, S. G., Fazzari, M., Skoko, J. J., et al. (2020). Sulforaphane diminishes the formation of mammary tumors in rats exposed to 17beta-estradiol. *Nutrients, 12*(8), 2282. https://doi.org/10.3390/nu12082282

329. Hossain, S., Liu, Z. H., & Wood, R. J. (2020). Histone deacetylase activity and vitamin D-dependent gene expressions in relation to sulforaphane in human breast cancer cells. *Journal of Food Biochemistry, 44*(2), ARTN e13114. https://doi.org/10.1111/jfbc.13114.

330. Hossain, S., Liu, Z. H., & Wood, R. J. (2021). Association between histone deacetylase activity and vitamin D-dependent gene expressions in relation to sulforaphane in human colorectal cancer cells. *Journal of the Science of Food and Agriculture, 101*(5), 1833–1843. https://doi.org/10.1002/jsfa.10797

331. Zhou, C. C., Poulton, E. J., Grun, F., Bammler, T. K., Blumberg, B., Thummel, K. E., et al. (2007). The dietary isothiocyanate sulforaphane is an antagonist of the human steroid and xenobiotic nuclear receptor. *Molecular Pharmacology, 71*(1), 220–229. https://doi.org/10.1124/mol.106.029264

332. Liu, Y. X., Xie, S. R., Wang, Y., Luo, K., Wang, Y., & Cai, Y. Q. (2012). Liquiritigenin inhibits tumor growth and vascularization in a mouse model of hela cells. *Molecules, 17*(6), 7206–7216. https://doi.org/10.3390/molecules17067206

333. Mersereau, J. E., Levy, N., Staub, R. E., Baggett, S., Zogric, T., Chow, S., et al. (2008). Liquiritigenin is a plant-derived highly selective estrogen receptor beta agonist. *Molecular and Cellular Endocrinology, 283*(1–2), 49–57. https://doi.org/10.1016/j.mce.2007.11.020

334. Ranaware, A. M., Banik, K., Deshpande, V., Padmavathi, G., Roy, N. K., Sethi, G., et al. (2018). Magnolol: A neolignan from the magnolia family for the prevention and treatment of cancer. *International Journal of Molecular Sciences, 19*(8), https://doi.org/10.3390/ijms19082362.

335. Peng, C. Y., Yu, C. C., Huang, C. C., Liao, Y. W., Hsieh, P. L., Chu, P. M., et al. (2022). Magnolol inhibits cancer stemness and IL-6/Stat3 signaling in oral carcinomas. *Journal of the Formosan Medical Association, 121*(1 Pt 1), 51–57. https://doi.org/10.1016/j.jfma.2021.01.009

336. Tian, Y., Feng, H., Han, L., Wu, L., Lv, H., Shen, B., et al. (2018). Magnolol alleviates inflammatory responses and lipid accumulation by AMP-activated protein kinase-dependent peroxisome proliferator-activated receptor alpha activation. *Frontiers in Immunology, 9*, 147. https://doi.org/10.3389/fimmu.2018.00147

337. Lu, Y., Sun, Y., Zhu, J., Yu, L., Jiang, X., Zhang, J., et al. (2018). Oridonin exerts anticancer effect on osteosarcoma by activating PPAR-gamma and inhibiting Nrf2 pathway. *Cell Death & Disease, 9*(1), 15. https://doi.org/10.1038/s41419-017-0031-6

338. Rontani, J. F., & Volkman, J. K. (2003). Phytol degradation products as biogeochemical tracers in aquatic environments. *Organic Geochemistry, 34*(1), 1–35, Pii S0146–6380(02)00185–7. https://doi.org/10.1016/S0146-6380(02)00185-7.

339. Goto, T., Takahashi, N., Kato, S., Egawa, K., Ebisu, S., Moriyama, T., et al. (2005). Phytol directly activates peroxisome proliferator-activated receptor alpha (PPARalpha) and regulates gene expression involved in lipid metabolism in PPARalpha-expressing HepG2 hepatocytes. *Biochemical and Biophysical Research Communications, 337*(2), 440–445. https://doi.org/10.1016/j.bbrc.2005.09.077

340. Yang, A. O. S. H., Tongson, J., Kim, K. H., & Park, Y. (2020). Piceatannol attenuates fat accumulation and oxidative stress in steatosis-induced HepG2 cells. *Current Research in Food Science, 3*, 92–99. https://doi.org/10.1016/j.crfs.2020.03.008

341. He, T., Wu, K., Lv, Y., Gong, X., Chen, G. G., & Liang, N. (2009). Effect of 5F from Pteris semipinnata on expression of Nr1d1 in HO-8910PM cell line. *Zhongguo Zhong Yao Za Zhi, 34*(10), 1268–1271.

342. Tan, B. S., Kang, O., Mai, C. W., Tiong, K. H., Khoo, A. S. B., Pichika, M. R., et al. (2013). 6-Shogaol inhibits breast and colon cancer cell proliferation through activation of peroxisomal proliferator activated receptor gamma (PPAR gamma). *Cancer Letters, 336*(1), 127–139. https://doi.org/10.1016/j.canlet.2013.04.014

343. Shanmugam, M. K., Ahn, K. S., Hsu, A., Woo, C. C., Yuan, Y., Tan, K. H. B., et al. (2018). Thymoquinone inhibits bone metastasis of breast cancer cells through abrogation of the CXCR4 signaling axis. *Frontiers in Pharmacology, 9*, 1294. https://doi.org/10.3389/fphar.2018.01294

344. Burits, M., & Bucar, F. (2000). Antioxidant activity of Nigella sativa essential oil. *Phytotherapy Research, 14*(5), 323–328. https://doi.org/10.1002/1099-1573(200008)14:5%3c323::Aid-Ptr621%3e3.0.Co;2-Q

345. Hajhashemi, V., Ghannadi, A., & Jafarabadi, H. (2004). Black cumin seed essential oil, as a potent analgesic and antiinflammatory drug. *Phytotherapy Research, 18*(3), 195–199. https://doi.org/10.1002/ptr.1390

346. Shanmugam, M. K., Arfuso, F., Kumar, A. P., Wang, L., Goh, B. C., Ahn, K. S., et al. (2018). Modulation of diverse oncogenic transcription factors by thymoquinone, an essential oil compound isolated from the seeds of Nigella sativa Linn. *Pharmacological Research, 129*, 357–364.

347. Woo, C. C., Loo, S. Y., Gee, V., Yap, C. W., Sethi, G., Kumar, A. P., et al. (2011). Anticancer activity of thymoquinone in breast cancer cells: Possible involvement of PPAR-γ pathway. *Biochemical Pharmacology, 82*(5), 464–475.

348. Huang, W. W., He, T. T., Chai, C. S., Yang, Y., Zheng, Y. H., Zhou, P., et al. (2012). Triptolide inhibits the proliferation of prostate cancer cells and down-regulates SUMO-specific protease 1 expression. *Plos One, 7*(5), ARTN e37693. https://doi.org/10.1371/journal.pone.0037693.

349. Liu, J., Jiang, Z., Xiao, J., Zhang, Y., Lin, S., Duan, W., et al. (2009). Effects of triptolide from Tripterygium wilfordii on ERalpha and p53 expression in two human breast cancer cell lines. *Phytomedicine, 16*(11), 1006–1013. https://doi.org/10.1016/j.phymed.2009.03.021

350. Li, L. H., Stanton, J. D., Tolson, A. H., Luo, Y., & Wang, H. B. (2009). Bioactive terpenoids and flavonoids from ginkgo biloba extract induce the expression of hepatic drug-metabolizing enzymes through pregnane X receptor, constitutive androstane receptor, and aryl hydrocarbon receptor-mediated pathways. *Pharmaceutical Research, 26*(4), 872–882. https://doi.org/10.1007/s11095-008-9788-8

351. Lakshmi, A., & Subramanian, S. (2014). Chemotherapeutic effect of tangeretin, a polymethoxylated flavone studied in 7, 12-dimethylbenz(a)anthracene induced mammary carcinoma in experimental rats. *Biochimie, 99*, 96–109. https://doi.org/10.1016/j.biochi.2013.11.017

352. Jia, Y., Hoang, M. H., Jun, H. J., Lee, J. H., & Lee, S. J. (2013). Cyanidin, a natural flavonoid, is an agonistic ligand for liver X receptor alpha and beta and reduces cellular lipid accumulation in macrophages and hepatocytes. *Bioorganic & Medicinal Chemistry Letters, 23*(14), 4185–4190. https://doi.org/10.1016/j.bmcl.2013.05.030

353. Tu, W. C., Wang, S. Y., Chien, S. C., Lin, F. M., Chen, L. R., Chiu, C. Y., et al. (2007). Diterpenes from Cryptomeria japonica inhibit androgen receptor transcriptional activity in prostate cancer cells. *Planta Medica, 73*(13), 1407–1409. https://doi.org/10.1055/s-2007-990233

354. Jacobs, M. N., Nolan, G. T., & Hood, S. R. (2005). Lignans, bacteriocides and organochlorine compounds activate the human pregnane X receptor (PXR). *Toxicology and Applied Pharmacology, 209*(2), 123–133. https://doi.org/10.1016/j.taap.2005.03.015

355. Hoang, M. H., Jia, Y., Jun, H. J., Lee, J. H., Lee, B. Y., & Lee, S. J. (2012). Fucosterol is a selective liver X receptor modulator that regulates the expression of key genes in cholesterol homeostasis in macrophages, hepatocytes, and intestinal cells. *Journal of Agricultural and Food Chemistry, 60*(46), 11567–11575. https://doi.org/10.1021/jf3019084

356. Hoang, M. H., Jia, Y., Jun, H. J., Lee, J. H., Lee, D. H., Hwang, B. Y., et al. (2012). Ethyl 2,4,6-trihydroxybenzoate is an agonistic ligand for liver X receptor that induces cholesterol efflux from macrophages without affecting lipid accumulation in HepG2 cells. *Bioorganic & Medicinal Chemistry Letters, 22*(12), 4094–4099. https://doi.org/10.1016/j.bmcl.2012.04.071

357. Jun, H. J., Hoang, M. H., Lee, J. W., Yaoyao, J., Lee, J. H., Lee, D. H., et al. (2012). Iristectorigenin B isolated from Belamcanda chinensis is a liver X receptor modulator that increases ABCA1 and ABCG1 expression in macrophage RAW 264.7 cells. *Biotechnology Letters, 34*(12), 2213–2221, https://doi.org/10.1007/s10529-012-1036-y.

358. Lin, H. R. (2013). Paeoniflorin acts as a liver X receptor agonist. *Journal of Asian Natural Products Research, 15*(1), 35–45. https://doi.org/10.1080/10286020.2012.742510

359. Kma, L. (2014). Plant extracts and plant-derived compounds: Promising players in countermeasure strategy against radiological exposure: A review. *Asian Pacific Journal of Cancer Prevention, 15*(6), 2405–2425.

360. Wentworth, J. M., Agostini, M., Love, J., Schwabe, J. W., & Chatterjee, V. K. (2000). St John's wort, a herbal antidepressant, activates the steroid X receptor. *Journal of Endocrinology, 166*(3), R11-16. https://doi.org/10.1677/joe.0.166r011

361. Yang, Y., Ikezoe, T., Takeuchi, T., Adachi, Y., Ohtsuki, Y., Koeffler, H. P., et al. (2006). Zanthoxyli Fructus induces growth arrest and apoptosis of LNCaP human prostate cancer cells in vitro and in vivo in association with blockade of the AKT and AR signal pathways. *Oncology Reports, 15*(6), 1581–1590.

362. Yang, Y., Ikezoe, T., Zheng, Z., Taguchi, H., Koeffler, H. P., & Zhu, W. G. (2007). Saw Palmetto induces growth arrest and apoptosis of androgen-dependent prostate cancer LNCaP cells via inactivation of STAT 3 and androgen receptor signaling. *International Journal of Oncology, 31*(3), 593–600.

363. Chen, K. C., Peng, C. C., Chiu, W. T., Cheng, Y. T., Huang, G. T., Hsieh, C. L., et al. (2010). Action mechanism and signal pathways of Psidium guajava L. aqueous extract in killing prostate cancer LNCaP cells. *Nutrition and Cancer, 62*(2), 260–270, https://doi.org/10.1080/01635580903407130.

364. Mandal, A., & Bishayee, A. (2015). Mechanism of breast cancer preventive action of pomegranate: Disruption of estrogen receptor and Wnt/beta-catenin signaling pathways. *Molecules, 20*(12), 22315–22328. https://doi.org/10.3390/molecules201219853

365. He, Y. Q., Ma, G. Y., Peng, J. N., Ma, Z. Y., & Hamann, M. T. (2012). Liver X receptor and peroxisome proliferator-activated receptor agonist from Cornus alternifolia. *Biochimica et Biophysica Acta, 1820*(7), 1021–1026. https://doi.org/10.1016/j.bbagen.2012.02.004

366. Chen, J., Power, K. A., Mann, J., Cheng, A., & Thompson, L. U. (2007). Dietary flaxseed interaction with tamoxifen induced tumor regression in athymic mice with MCF-7 xenografts by downregulating the expression of estrogen related gene products and signal transduction pathways. *Nutrition and Cancer, 58*(2), 162–170. https://doi.org/10.1080/01635580701328271

367. Jeyabalan, J., Aqil, F., Munagala, R., Annamalai, L., Vadhanam, M. V., & Gupta, R. C. (2014). Chemopreventive and therapeutic activity of dietary blueberry against estrogen-mediated breast cancer. *Journal of Agriculture and Food Chemistry, 62*(18), 3963–3971. https://doi.org/10.1021/jf403734j

368. Nejati-Koshki, K., Akbarzadeh, A., & Pourhassan-Moghaddam, M. (2014). Curcumin inhibits leptin gene expression and secretion in breast cancer cells by estrogen receptors. *Cancer Cell International, 14*, 66. https://doi.org/10.1186/1475-2867-14-66

369. Hallman, K., Aleck, K., Dwyer, B., Lloyd, V., Quigley, M., Sitto, N., et al. (2017). The effects of turmeric (curcumin) on tumor suppressor protein (p53) and estrogen receptor (ERalpha) in

breast cancer cells. *Breast Cancer (Dove Med Press), 9*, 153–161. https://doi.org/10.2147/BCTT.S125783

370. Sanaei, M., Kavoosi, F., & Arabloo, M. (2020). Effect of curcumin in comparison with trichostatin A on the reactivation of estrogen receptor alpha gene expression, cell growth inhibition and apoptosis induction in hepatocellular carcinoma Hepa 1–6 cell lline. *Asian Pacific Journal of Cancer Prevention: APJCP, 21*(4), 1045.

371. Sun, M., Estrov, Z., Ji, Y., Coombes, K. R., Harris, D. H., & Kurzrock, R. (2008). Curcumin (diferuloylmethane) alters the expression profiles of microRNAs in human pancreatic cancer cells. *Molecular Cancer Therapeutics, 7*(3), 464–473. https://doi.org/10.1158/1535-7163.MCT-07-2272

372. Nakamura, K., Yasunaga, Y., Segawa, T., Ko, D., Moul, J. W., Srivastava, S., et al. (2002). Curcumin down-regulates AR gene expression and activation in prostate cancer cell lines. *International Journal of Oncology, 21*(4), 825–830.

373. Choi, H., Lim, J., & Hong, J. (2010). Curcumin interrupts the interaction between the androgen receptor and Wnt/β-catenin signaling pathway in LNCaP prostate cancer cells. *Prostate Cancer and Prostatic Diseases, 13*(4), 343–349.

374. Zhang, H. N., Yu, C. X., Zhang, P. J., Chen, W. W., Jiang, A. L., Kong, F., et al. (2007). Curcumin downregulates homeobox gene NKX3.1 in prostate cancer cell LNCaP.*Acta Pharmacologica Sinica, 28*(3), 423–430, https://doi.org/10.1111/j.1745-7254.2007.00501.x.

375. Guo, H., Xu, Y. M., Ye, Z. Q., Yu, J. H., & Hu, X. Y. (2013). Curcumin induces cell cycle arrest and apoptosis of prostate cancer cells by regulating the expression of IkappaBalpha, c-Jun and androgen receptor. *Die Pharmazie, 68*(6), 431–434.

376. Dorai, T., Gehani, N., & Katz, A. (2000). Therapeutic potential of curcumin in human prostate cancer - I. curcumin induces apoptosis in both androgen-dependent and androgen-independent prostate cancer cells. *Prostate Cancer and Prostatic Diseases, 3*(2), 84–93, https://doi.org/10.1038/sj.pcan.4500399.

377. Thangapazham, R. L., Shaheduzzaman, S., Kim, K. H., Passi, N., Tadese, A., Vahey, M., et al. (2008). Androgen responsive and refractory prostate cancer cells exhibit distinct curcumin regulated transcriptome. *Cancer Biology & Therapy, 7*(9), 1427–1435. https://doi.org/10.4161/cbt.7.9.6469

378. Yallapu, M. M., Khan, S., Maher, D. M., Ebeling, M. C., Sundram, V., Chauhan, N., et al. (2014). Anti-cancer activity of curcumin loaded nanoparticles in prostate cancer. *Biomaterials, 35*(30), 8635–8648. https://doi.org/10.1016/j.biomaterials.2014.06.040

379. Sharma, V., Kumar, L., Mohanty, S. K., Maikhuri, J. P., Rajender, S., & Gupta, G. (2016). Sensitization of androgen refractory prostate cancer cells to anti androgens through re-expression of epigenetically repressed androgen receptor - Synergistic action of quercetin and curcumin. *Molecular and Cellular Endocrinology, 431*(C), 12–23, https://doi.org/10.1016/j.mce.2016.04.024.

380. Narayanan, N. K., Nargi, D., Randolph, C., & Narayanan, B. A. (2009). Liposome encapsulation of curcumin and resveratrol in combination reduces prostate cancer incidence in PTEN knockout mice. *International Journal of Cancer, 125*(1), 1–8. https://doi.org/10.1002/ijc.24336

381. Pham, N. K., Bui, H. T., Tran, T. H., Hoang, T. N. A., Vu, T. H., Do, D. T., et al. (2021). Dammarane triterpenes and phytosterols from Dysoxylum tpongense Pierre and their anti-inflammatory activity against liver X receptors and NF-κB activation. *Steroids, 175*, 108902.

382. Schleich, S., Papaioannou, M., Baniahmad, A., & Matusch, R. (2006). Activity-guided isolation of an antiandrogenic compound of Pygeum africanum. *Planta medica, 72*(06), 547–551.

383. Levenson, A. S., Gehm, B. D., Pearce, S. T., Horiguchi, J., Simons, L. A., Ward, J. E., et al. (2003). Resveratrol acts as an estrogen receptor (ER) agonist in breast cancer cells stably transfected with ER alpha. *International Journal of Cancer, 104*(5), 587–596. https://doi.org/10.1002/ijc.10992

384. Mitchell, S. H., Zhu, W., & Young, C. Y. F. (1999). Resveratrol inhibits the expression and function of the androgen receptor in LNCaP prostate cancer cells. *Cancer Research, 59*(23), 5892–5895.

385. Wang, Y., Romigh, T., He, X., Orloff, M. S., Silverman, R. H., Heston, W. D., et al. (2010). Resveratrol regulates the PTEN/AKT pathway through androgen receptor-dependent and -independent mechanisms in prostate cancer cell lines. *Human Molecular Genetics, 19*(22), 4319–4329. https://doi.org/10.1093/hmg/ddq354

386. Harada, N., Murata, Y., Yamaji, R., Miura, T., Inui, H., & Nakano, Y. (2007). Resveratrol down-regulates the androgen receptor at the post-translational level in prostate cancer cells. *Journal of Nutritional Science and Vitaminology, 53*(6), 556–560. https://doi.org/10.3177/jnsv.53.556

387. Mitani, T., Harada, N., Tanimori, S., Nakano, Y., Inui, H., & Yamaji, R. (2014). Resveratrol inhibits hypoxia-inducible factor-1alpha-mediated androgen receptor signaling and represses tumor progression in castration-resistant prostate cancer. *Journal of Nutritional Science and Vitaminology (Tokyo), 60*(4), 276–282.

388. Ye, M., Tian, H., Lin, S., Mo, J., Li, Z., Chen, X., et al. (2020). Resveratrol inhibits proliferation and promotes apoptosis via the androgen receptor splicing variant 7 and PI3K/AKT signaling pathway in LNCaP prostate cancer cells. *Oncology Letters, 20*(5), 169. https://doi.org/10.3892/ol.2020.12032

389. Qi, H. Y., Jiang, Z. Y., Wang, C. Q., Yang, Y., Li, L., He, H., et al. (2017). Sensitization of tamoxifen-resistant breast cancer cells by Z-ligustilide through inhibiting autophagy and accumulating DNA damages. *Oncotarget, 8*(17), 29300–29317, https://doi.org/10.18632/oncotarget.16832.

390. Shrestha, R., Mohankumar, K., & Safe, S. (2020). Bis-indole derived nuclear receptor 4A1 (NR4A1) antagonists inhibit TGFβ-induced invasion of embryonal rhabdomyosarcoma cells. *American Journal of Cancer Research, 10*(8), 2495.

391. Yeh, S.-L., Yeh, C.-L., Chan, S.-T., & Chuang, C.-H. (2011). Plasma rich in quercetin metabolites induces G2/M arrest by upregulating PPAR-γ expression in human A549 lung cancer cells. *Planta Medica, 77*(10), 992–998.

392. Krausova, L., Stejskalova, L., Wang, H., Vrzal, R., Dvorak, Z., Mani, S., et al. (2011). Metformin suppresses pregnane X receptor (PXR)-regulated transactivation of CYP3A4 gene. *Biochemical Pharmacology, 82*(11), 1771–1780. https://doi.org/10.1016/j.bcp.2011.08.023

393. Helleboid, S., Haug, C., Lamottke, K., Zhou, Y., Wei, J., Daix, S., et al. (2014). The identification of naturally occurring neoruscogenin as a bioavailable, potent, and high-affinity agonist of the nuclear receptor RORα (NR1F1). *Journal of Biomolecular Screening, 19*(3), 399–406.

394. Ao, M., Zhang, J., Qian, Y., Li, B., Wang, X., Chen, J., et al. (2022). Design and synthesis of adamantyl-substituted flavonoid derivatives as anti-inflammatory Nur77 modulators: Compound B7 targets Nur77 and improves LPS-induced inflammation in vitro and in vivo. *Bioorganic Chemistry, 120*, 105645.

395. Zhao, J., Khan, S. I., Wang, M., Vasquez, Y., Yang, M. H., Avula, B., et al. (2014). Octulosonic acid derivatives from Roman chamomile (Chamaemelum nobile) with activities against inflammation and metabolic disorder. *Journal of Natural Products, 77*(3), 509–515.

396. Tamehiro, N., Sato, Y., Suzuki, T., Hashimoto, T., Asakawa, Y., Yokoyama, S., et al. (2005). Riccardin C: A natural product that functions as a liver X receptor (LXR) α agonist and an LXRβ antagonist. *FEBS Letters, 579*(24), 5299–5304.

397. Uemura, T., Goto, T., Kang, M. S., Mizoguchi, N., Hirai, S., Lee, J. Y., et al. (2011). Diosgenin, the main aglycon of fenugreek, inhibits LXRα activity in HepG2 cells and decreases plasma and hepatic triglycerides in obese diabetic mice. *The Journal of Nutrition, 141*(1), 17–23.

398. Goldwasser, J., Cohen, P. Y., Yang, E., Balaguer, P., Yarmush, M. L., & Nahmias, Y. (2010). Transcriptional regulation of human and rat hepatic lipid metabolism by the grapefruit flavonoid naringenin: Role of PPARα PPARγ and LXRα. *PloS One, 5*(8), e12399.

399. Sheng, X., Wang, M., Lu, M., Xi, B., Sheng, H., & Zang, Y. Q. (2011). Rhein ameliorates fatty liver disease through negative energy balance, hepatic lipogenic regulation, and immunomodulation in diet-induced obese mice. *American Journal of Physiology-Endocrinology and Metabolism, 300*(5), E886–E893.

400. Montserrat-de la Paz, S., Fernández-Arche, M., Bermúdez, B., & García-Giménez, M. D. (2015). The sterols isolated from evening primrose oil inhibit human colon adenocarcinoma cell proliferation and induce cell cycle arrest through upregulation of LXR. *Journal of Functional Foods*, *12*, 64–69.

401. Kao, T.-C., Shyu, M.-H., & Yen, G.-C. (2010). Glycyrrhizic acid and 18β-glycyrrhetinic acid inhibit inflammation via PI3K/Akt/GSK3β signaling and glucocorticoid receptor activation. *Journal of Agricultural and Food Chemistry, 58*(15), 8623–8629.

402. Kao, T.-C., Wu, C.-H., & Yen, G.-C. (2013). Glycyrrhizic acid and 18β-glycyrrhetinic acid recover glucocorticoid resistance via PI3K-induced AP1 CRE and NFAT activation. *Phytomedicine, 20*(3–4), 295–302.

403. Chintharlapalli, S., Papineni, S., Jutooru, I., McAlees, A., & Safe, S. (2007). Structure-dependent activity of glycyrrhetinic acid derivatives as peroxisome proliferator–activated receptor γ agonists in colon cancer cells. *Molecular Cancer Therapeutics, 6*(5), 1588–1598.

404. Lee, Y., Chung, E., Lee, K. Y., Lee, Y. H., Huh, B., & Lee, S. K. (1997). Ginsenoside-Rg1, one of the major active molecules from Panax ginseng, is a functional ligand of glucocorticoid receptor. *Molecular and Cellular Endocrinology, 133*(2), 135–140.

405. Ferron, P.-J., Hogeveen, K., De Sousa, G., Rahmani, R., Dubreil, E., Fessard, V. r., et al. (2016). Modulation of CYP3A4 activity alters the cytotoxicity of lipophilic phycotoxins in human hepatic HepaRG cells. *Toxicology in Vitro*, *33*, 136-146.

406. Cui, K., Wu, H., Li, Z., Li, H., Yang, R., Guo, H., et al. (2021). Ferulic acid and P-coumaric acid inhibit colon cancer growth through GR/lncRNA 495810/PKM2 mediated aerobic glycolysis. Available at SSRN 3844821. https://doi.org/10.2139/ssrn.3844821

407. Gasmi, J., & Sanderson, J. T. (2010). Growth inhibitory, antiandrogenic, and pro-apoptotic effects of punicic acid in LNCaP human prostate cancer cells. *Journal of Agricultural and Food Chemistry, 58*(23), 12149–12156.

408. Cvoro, A., Paruthiyil, S., Jones, J. O., Tzagarakis-Foster, C., Clegg, N. J., Tatomer, D., et al. (2007). Selective activation of estrogen receptor-β transcriptional pathways by an herbal extract. *Endocrinology, 148*(2), 538–547.

409. Liu, L., Ma, H., Tang, Y., Chen, W., Lu, Y., Guo, J., et al. (2012). Discovery of estrogen receptor α modulators from natural compounds in Si-Wu-Tang series decoctions using estrogen-responsive MCF-7 breast cancer cells. *Bioorganic & Medicinal Chemistry Letters, 22*(1), 154–163.

410. Huang, T.H.-W., Razmovski-Naumovski, V., Salam, N. K., Duke, R. K., Duke, C. C., & Roufogalis, B. D. (2005). A novel LXR-α activator identified from the natural product Gynostemma pentaphyllum. *Biochemical Pharmacology, 70*(9), 1298–1308.

411. Yuan, H.-Q., Kong, F., Wang, X.-L., Young, C. Y., Hu, X.-Y., & Lou, H.-X. (2008). Inhibitory effect of acetyl-11-keto-β-boswellic acid on androgen receptor by interference of Sp1 binding activity in prostate cancer cells. *Biochemical Pharmacology, 75*(11), 2112–2121.

412. Chung, B. H., Lee, H.-Y., Lee, J. S., & Young, C. Y. (2006). Perillyl alcohol inhibits the expression and function of the androgen receptor in human prostate cancer cells. *Cancer Letters, 236*(2), 222–228.

413. Pathirana, C., Stein, R. B., Berger, T. S., Fenical, W., Ianiro, T., Mais, D. E., et al. (1995). Nonsteroidal human progesterone receptor modulators from the marine alga Cymopolia barbata. *Molecular Pharmacology, 47*(3), 630–635.

414. Zhao, Z., Wang, L., James, T., Jung, Y., Kim, I., Tan, R., et al. (2015). Reciprocal regulation of ERα and ERβ stability and activity by diptoindonesin G. *Chemistry & Biology, 22*(12), 1608–1621.

415. Lin, W., Huang, J., Liao, X., Yuan, Z., Feng, S., Xie, Y., et al. (2016). Neo-tanshinlactone selectively inhibits the proliferation of estrogen receptor positive breast cancer cells through transcriptional down-regulation of estrogen receptor alpha. *Pharmacological Research, 111*, 849–858.

416. Onogi, K., Niwa, K., Tang, L., Yun, W., Mori, H., & Tamaya, T. (2006). Inhibitory effects of Hochu-ekki-to on endometrial carcinogenesis induced by N-methyl-N-nitrosourea and 17β-estradiol in mice. *Oncology Reports, 16*(6), 1343–1348.

417. Marconett, C. N., Morgenstern, T. J., San Roman, A. K., Sundar, S. N., Singhal, A. K., & Firestone, G. L. (2010). BZL101, a phytochemical extract from the Scutellaria barbata plant, disrupts proliferation of human breast and prostate cancer cells through distinct mechanisms dependent on the cancer cell phenotype. *Cancer Biology & Therapy, 10*(4), 397–405.

418. Mora, F. D., Jones, D. K., Desai, P. V., Patny, A., Avery, M. A., Feller, D. R., et al. (2006). Bioassay for the identification of natural product-based activators of peroxisome proliferator-activated receptor-gamma (PPARgamma): The marine sponge metabolite psammaplin A activates PPARgamma and induces apoptosis in human breast tumor cells. *Journal of Natural Products, 69*(4), 547–552. https://doi.org/10.1021/np050397q

419. Sadar, M. D., Williams, D. E., Mawji, N. R., Patrick, B. O., Wikanta, T., Chasanah, E., et al. (2008). Sintokamides A to E, chlorinated peptides from the sponge Dysidea sp that inhibit transactivation of the N-terminus of the androgen receptor in prostate cancer cells. *Organic Letters, 10*(21), 4947–4950. https://doi.org/10.1021/ol802021w

420. Festa, C., De Marino, S., D'Auria, M. V., Bifulco, G., Renga, B., Fiorucci, S., et al. (2011). Solomonsterols A and B from Theonella swinhoei. The first example of C-24 and C-23 sulfated sterols from a marine source endowed with a PXR agonistic activity. *Journal of Medicinal Chemistry*, *54*(1), 401–405, https://doi.org/10.1021/jm100968b.

421. Sepe, V., Ummarino, R., D'Auria, M. V., Mencarelli, A., D'Amore, C., Renga, B., et al. (2011). Total synthesis and pharmacological characterization of solomonsterol A, a potent marine pregnane-X-receptor agonist endowed with anti-inflammatory activity. *Journal of Medicinal Chemistry, 54*(13), 4590–4599. https://doi.org/10.1021/jm200241s

422. Sepe, V., Ummarino, R., D'Auria, M. V., Lauro, G., Bifulco, G., D'Amore, C., et al. (2012). Modification in the side chain of solomonsterol A: discovery of cholestan disulfate as a potent pregnane-X-receptor agonist. Organic & Biomolecular Chemistry, 10(31), 6350-6362, doi:10.1039/c2ob25800e.

423. De Marino, S., Ummarino, R., D'Auria, M. V., Chini, M. G., Bifulco, G., Renga, B., et al. (2011). Theonellasterols and conicasterols from Theonella swinhoei. Novel marine natural ligands for human nuclear receptors. *Journal of Medicinal Chemistry*, *54*(8), 3065–3075, https://doi.org/10.1021/jm200169t.

424. Renga, B., Mencarelli, A., D'Amore, C., Cipriani, S., D'Auria, M. V., Sepe, V., et al. (2012). Discovery that theonellasterol a marine sponge sterol is a highly selective FXR antagonist that protects against liver injury in cholestasis. *PloS One, 7*(1), ARTN e30443. https://doi.org/10.1371/journal.pone.0030443.

425. Sepe, V., Ummarino, R., D'Auria, M. V., Taglialatela-Scafati, O., De Marino, S., D'Amore, C., et al. (2012). Preliminary structure-activity relationship on theonellasterol, a new chemotype of FXR antagonist, from the marine sponge *Theonella swinhoei. Marine Drugs, 10*(11), 2448–2466. https://doi.org/10.3390/md10112448

426. Sepe, V., Ummarino, R., D'Auria, M. V., Chini, M. G., Bifulco, G., Renga, B., et al. (2012). Conicasterol E, a small heterodimer partner sparing farnesoid X receptor modulator endowed with a pregnane X receptor agonistic activity, from the marine sponge Theonella swinhoei. *Journal of Medicinal Chemistry, 55*(1), 84–93. https://doi.org/10.1021/jm201004p

427. Chini, M. G., Jones, C. R., Zampella, A., D'Auria, M. V., Renga, B., Fiorucci, S., et al. (2012). Quantitative NMR-derived interproton distances combined with quantum mechanical calculations of 13C chemical shifts in the stereochemical determination of conicasterol F, a nuclear receptor ligand from Theonella swinhoei. *Journal of Organic Chemistry, 77*(3), 1489–1496. https://doi.org/10.1021/jo2023763

428. De Marino, S., Sepe, V., D'Auria, M. V., Bifulco, G., Renga, B., Petek, S., et al. (2011). Towards new ligands of nuclear receptors. Discovery of malaitasterol A, an unique bis-secosterol from marine sponge Theonella swinhoei. *Organic & Biomolecular Chemistry, 9*(13), 4856–4862, https://doi.org/10.1039/c1ob05378g.

429. De Marino, S., Ummarino, R., D'Auria, M. V., Chini, M. G., Bifulco, G., D'Amore, C., et al. (2012). 4-Methylenesterols from Theonella swinhoei sponge are natural pregnane-X-receptor agonists and farnesoid-X-receptor antagonists that modulate innate immunity. *Steroids, 77*(5), 484–495. https://doi.org/10.1016/j.steroids.2012.01.006

430. Sepe, V., D'Amore, C., Ummarino, R., Renga, B., D'Auria, M. V., Novellino, E., et al. (2014). Insights on pregnane-X-receptor modulation. Natural and semisynthetic steroids from Theonella marine sponges. *European Journal of Medicinal Chemistry, 73*, 126–134. https://doi.org/10.1016/j.ejmech.2013.12.005

431. Festa, C., Lauro, G., De Marino, S., D'Auria, M. V., Monti, M. C., Casapullo, A., et al. (2012). Plakilactones from the marine sponge Plakinastrella mamillaris. Discovery of a new class of marine ligands of peroxisome proliferator-activated receptor γ. *Journal of Medicinal Chemistry, 55*(19), 8303–8317.

432. Festa, C., D'Amore, C., Renga, B., Lauro, G., De Marino, S., D'Auria, M. V., et al. (2013). Oxygenated polyketides from Plakinastrella mamillaris as a new chemotype of PXR agonists. *Marine Drugs, 11*(7), 2314–2327. https://doi.org/10.3390/md11072314

433. Chianese, G., Sepe, V., Limongelli, V., Renga, B., D'Amore, C., Zampella, A., et al. (2014). Incisterols, highly degraded marine sterols, are a new chemotype of PXR agonists. *Steroids, 83*, 80–85. https://doi.org/10.1016/j.steroids.2014.02.003

434. Meimetis, L. G., Williams, D. E., Mawji, N. R., Banuelos, C. A., Lal, A. A., Park, J. J., et al. (2012). Niphatenones, glycerol ethers from the sponge Niphates digitalis block androgen receptor transcriptional activity in prostate cancer cells: Structure elucidation, synthesis, and biological activity. *Journal of Medicinal Chemistry, 55*(1), 503–514. https://doi.org/10.1021/jm2014056

435. Wang, S. S., Wang, Z., Lin, S. C., Zheng, W. L., Wang, R., Jin, S. K., et al. (2012). Revealing a natural marine product as a novel agonist for retinoic acid receptors with a unique binding mode and inhibitory effects on cancer cells. *Biochemical Journal, 446*, 79–87. https://doi.org/10.1042/Bj20120726

436. Di Leva, F. S., Festa, C., D'Amore, C., De Marino, S., Renga, B., D'Auria, M. V., et al. (2013). Binding mechanism of the farnesoid X receptor marine antagonist suvanine reveals a strategy to forestall drug modulation on nuclear receptors. Design, synthesis, and biological evaluation of novel ligands. *Journal of Medicinal Chemistry, 56*(11), 4701–4717, https://doi.org/10.1021/jm400419e.

437. Zhou, M., Peng, B. R., Tian, W., Su, J. H., Wang, G., Lin, T., et al. (2020). 12-Deacetyl-12-epi-scalaradial, a scalarane sesterterpenoid from a marine sponge Hippospongia sp., induces HeLa cells apoptosis via MAPK/ERK pathway and modulates nuclear receptor Nur77. *Marine Drugs, 18*(7), 375. https://doi.org/10.3390/md18070375

438. Wu, Y., Liao, H., Liu, L.-Y., Sun, F., Chen, H.-F., Jiao, W.-H., et al. (2020). Phakefustatins A-C: Kynurenine-bearing cycloheptapeptides as RXRα modulators from the marine sponge Phakellia fusca. *Organic Letters, 22*(17), 6703–6708.

439. Machida, K., Abe, T., Arai, D., Okamoto, M., Shimizu, I., de Voogd, N. J., et al. (2014). Cinanthrenol A, an estrogenic steroid containing phenanthrene nucleus, from a marine sponge Cinachyrella sp. *Organic Letters, 16*(6), 1539–1541.

440. Parrish, S. M., Neupane, R. P., Harper, M. K., Head, J., & Williams, P. G. (2019). Myrmenaphthol A, isolated from a Hawaiian sponge of the genus Myrmekioderma. *Journal of Natural Products, 82*(9), 2668–2671. https://doi.org/10.1021/acs.jnatprod.9b00665

441. Imperatore, C., D'Aniello, F., Aiello, A., Fiorucci, S., D'Amore, C., Sepe, V., et al. (2014). Phallusiasterols A and B: Two new sulfated sterols from the Mediterranean tunicate Phallusia fumigata and their effects as modulators of the PXR receptor. *Marine Drugs, 12*(4), 2066–2078. https://doi.org/10.3390/md12042066

442. Imperatore, C., Senese, M., Aiello, A., Luciano, P., Fiorucci, S., D'Amore, C., et al. (2016). Phallusiasterol C, A new disulfated steroid from the Mediterranean Tunicate Phallusia fumigata. *Marine Drugs, 14*(6), 117. https://doi.org/10.3390/md14060117

443. Fidler, A. E., Holland, P. T., Reschly, E. J., Ekins, S., & Krasowski, M. D. (2012). Activation of a tunicate (Ciona intestinalis) xenobiotic receptor orthologue by both natural toxins and synthetic toxicants. *Toxicon, 59*(2), 365–372. https://doi.org/10.1016/j.toxicon.2011.12.008

444. Mensah-Osman, E., Lin, H.-L., Reinke, D., Hollenberg, P., & Baker, L. (2005). Ecteinascidin-743 is a potent inhibitor of P450 3A4 enzyme and accumulates cytoplasmic PXR to inhibit transcription of P450 3A4 and MDR1: Implications for the enhancement of cytotoxicity to chemotherapeutic agents in osteosarcoma. *Journal of Clinical Oncology, 23*(16_suppl), 9026–9026.

445. Sepe, V., Di Leva, F. S., D'Amore, C., Festa, C., De Marino, S., Renga, B., et al. (2014). Marine and semi-synthetic hydroxysteroids as new scaffolds for pregnane X receptor modulation. *Marine Drugs, 12*(6), 3091–3115. https://doi.org/10.3390/md12063091

446. Sepe, V., Bifulco, G., Renga, B., D'Amore, C., Fiorucci, S., & Zampella, A. (2011). Discovery of sulfated sterols from marine invertebrates as a new class of marine natural antagonists of farnesoid-X-receptor. *Journal of Medicinal Chemistry, 54*(5), 1314–1320. https://doi.org/10.1021/jm101336m

447. Popolo, A., Piccinelli, A. L., Morello, S., Sorrentino, R., Osmany, C. R., Rastrelli, L., et al. (2011). Cytotoxic activity of nemorosone in human MCF-7 breast cancer cells. *Canadian Journal of Physiology and Pharmacology, 89*(1), 50–57. https://doi.org/10.1139/y10-100

448. Moutsatsou, P., Papoutsi, Z., Kassi, E., Heldring, N., Zhao, C. Y., Tsiapara, A., et al. (2010). Fatty acids derived from royal jelly are modulators of estrogen receptor functions. *PloS One, 5*(12), ARTN e15594. https://doi.org/10.1371/journal.pone.0015594.

449. Zhao, Z., Hong, W., Zeng, Z., Wu, Y., Hu, K., Tian, X., et al. (2012). Mucroporin-M1 inhibits hepatitis B virus replication by activating the mitogen-activated protein kinase (MAPK) pathway and down-regulating HNF4alpha in vitro and in vivo. *Journal of Biological Chemistry, 287*(36), 30181–30190. https://doi.org/10.1074/jbc.M112.370312

450. Deng, Z., Zheng, L. F., Xie, X. W., Wei, H. K., & Peng, J. (2020). GPA peptide enhances Nur77 expression in intestinal epithelial cells to exert a protective effect against DSS-induced colitis. *The Faseb Journal, 34*(11), 15364–15378. https://doi.org/10.1096/fj.202000391RR

451. Ricote, M., Li, A. C., Willson, T. M., Kelly, C. J., & Glass, C. K. (1998). The peroxisome proliferator-activated receptor-gamma is a negative regulator of macrophage activation. *Nature, 391*(6662), 79–82. https://doi.org/10.1038/34178

452. Shiraki, T., Kamiya, N., Shiki, S., Kodama, T. S., Kakizuka, A., & Jingami, H. (2005). α, β-unsaturated ketone is a core moiety of natural ligands for covalent binding to peroxisome proliferator-activated receptor γ. *Journal of Biological Chemistry, 280*(14), 14145–14153.

453. Shappell, S. B., Gupta, R. A., Manning, S., Whitehead, R., Boeglin, W. E., Schneider, C., et al. (2001). 15S-Hydroxyeicosatetraenoic acid activates peroxisome proliferator-activated receptor gamma and inhibits proliferation in PC3 prostate carcinoma cells. *Cancer Research, 61*(2), 497–503.

454. Pettersson, F., Dalgleish, A. G., Bissonnette, R. P., & Colston, K. W. (2002). Retinoids cause apoptosis in pancreatic cancer cells via activation of RAR-gamma and altered expression of Bcl-2/Bax. *British Journal of Cancer, 87*(5), 555–561. https://doi.org/10.1038/sj.bjc.6600496

455. Campbell, S. E., Stone, W. L., Whaley, S. G., Qui, M., & Krishnan, K. (2003). Gamma (gamma) tocopherol upregulates peroxisome proliferator activated receptor (PPAR) gamma (gamma) expression in SW 480 human colon cancer cell lines. *BMC Cancer, 3*, 25. https://doi.org/10.1186/1471-2407-3-25

456. Kinjo, J., Tsuchihashi, R., Morito, K., Hirose, T., Aomori, T., Nagao, T., et al. (2004). Interactions of phytoestrogens with estrogen receptors alpha and beta (III). Estrogenic activities of soy isoflavone aglycones and their metabolites isolated from human urine. *Biological & Pharmaceutical Bulletin, 27*(2), 185–188, https://doi.org/10.1248/bpb.27.185.

457. Maggiora, M., Bologna, M., Ceru, M. P., Possati, L., Angelucci, A., Cimini, A., et al. (2004). An overview of the effect of linoleic and conjugated-linoleic acids on the growth of several human tumor cell lines. *International Journal of Cancer, 112*(6), 909–919. https://doi.org/10.1002/ijc.20519

458. Kuniyasu, H., Yoshida, K., Sasaki, T., Sasahira, T., Fujii, K., & Ohmori, H. (2006). Conjugated linoleic acid inhibits peritoneal metastasis in human gastrointestinal cancer cells. *International Journal of Cancer, 118*(3), 571–576. https://doi.org/10.1002/ijc.21368

459. Evans, N. P., Misyak, S. A., Schmelz, E. M., Guri, A. J., Hontecillas, R., & Bassaganya-Riera, J. (2010). Conjugated linoleic acid ameliorates inflammation-induced colorectal cancer in mice through activation of PPARγ. *The Journal of Nutrition, 140*(3), 515–521.

460. Sun, H., Berquin, I. M., & Edwards, I. J. (2005). Omega-3 polyunsaturated fatty acids regulate syndecan-1 expression in human breast cancer cells. *Cancer Research, 65*(10), 4442–4447. https://doi.org/10.1158/0008-5472.CAN-04-4200

461. Sun, H., Berquin, I. M., Owens, R. T., O'Flaherty, J. T., & Edwards, I. J. (2008). Peroxisome proliferator-activated receptor gamma-mediated up-regulation of syndecan-1 by n-3 fatty acids promotes apoptosis of human breast cancer cells. *Cancer Research, 68*(8), 2912–2919. https://doi.org/10.1158/0008-5472.CAN-07-2305

462. Edwards, I. J., Sun, H., Hu, Y., Berquin, I. M., O'Flaherty, J. T., Cline, J. M., et al. (2008). In vivo and in vitro regulation of syndecan 1 in prostate cells by n-3 polyunsaturated fatty acids. *Journal of Biological Chemistry, 283*(26), 18441–18449. https://doi.org/10.1074/jbc.M802107200

463. Lampen, A., Leifheit, M., Voss, J., & Nau, H. (2005). Molecular and cellular effects of cis-9, trans-11-conjugated linoleic acid in enterocytes: Effects on proliferation, differentiation, and gene expression. *Biochimica et Biophysica Acta, 1735*(1), 30–40. https://doi.org/10.1016/j.bbalip.2005.01.007

464. Kameue, C., Tsukahara, T., & Ushida, K. (2006). Alteration of gene expression in the colon of colorectal cancer model rat by dietary sodium gluconate. *Bioscience Biotechnology and Biochemistry, 70*(3), 606–614. https://doi.org/10.1271/bbb.70.606

465. Zand, H., Rhimipour, A., Bakhshayesh, M., Shafiee, M., Nour Mohammadi, I., & Salimi, S. (2007). Involvement of PPAR-gamma and p53 in DHA-induced apoptosis in Reh cells. *Molecular and Cellular Biochemistry, 304*(1–2), 71–77. https://doi.org/10.1007/s11010-007-9487-5

466. Lee, H. J., Ju, J., Paul, S., So, J. Y., DeCastro, A., Smolarek, A., et al. (2009). Mixed tocopherols prevent mammary tumorigenesis by inhibiting estrogen action and activating PPAR-gamma. *Clinical Cancer Research, 15*(12), 4242–4249. https://doi.org/10.1158/1078-0432.CCR-08-3028

467. Smolarek, A. K., So, J. Y., Burgess, B., Kong, A.-N.T., Reuhl, K., Lin, Y., et al. (2012). Dietary administration of δ-and γ-tocopherol inhibits tumorigenesis in the animal model of estrogen receptor–positive, but not HER-2 breast cancer. *Cancer Prevention Research, 5*(11), 1310–1320.

468. Smolarek, A. K., So, J. Y., Thomas, P. E., Lee, H. J., Paul, S., Dombrowski, A., et al. (2013). Dietary tocopherols inhibit cell proliferation, regulate expression of ERalpha, PPARgamma, and Nrf2, and decrease serum inflammatory markers during the development of mammary hyperplasia. *Molecular Carcinogenesis, 52*(7), 514–525. https://doi.org/10.1002/mc.21886

469. Yang, L., Yuan, J., Liu, L., Shi, C., Wang, L., Tian, F., et al. (2013). α-linolenic acid inhibits human renal cell carcinoma cell proliferation through PPAR-γ activation and COX-2 inhibition. *Oncology Letters, 6*(1), 197–202.

470. Attia, Y. M., Tawfiq, R. A., Ali, A. A., & Elmazar, M. M. (2017). The FXR agonist, obeticholic acid, suppresses HCC proliferation & metastasis: Role of IL-6/STAT3 signalling pathway. *Science and Reports, 7*(1), 12502. https://doi.org/10.1038/s41598-017-12629-4

471. Fang, H., Zhang, J., Ao, M., He, F., Chen, W., Qian, Y., et al. (2020). Synthesis and discovery of ω-3 polyunsaturated fatty acid-alkanolamine (PUFA-AA) derivatives as anti-inflammatory agents targeting Nur77. *Bioorganic Chemistry, 105*, 104456.

472. Tabata, Y., Iizuka, Y., Kashiwa, J., Masuda, N. T., Shinei, R., Kurihara, K.-I., et al. (2001). Fungal metabolites, PF1092 compounds and their derivatives, are nonsteroidal and selective progesterone receptor modulators. *European Journal of Pharmacology, 430*(2–3), 159–165.

473. Muthyala, R. S., Ju, Y. H., Sheng, S. B., Williams, L. D., Doerge, D. R., Katzenellenbogen, B. S., et al. (2004). Equol, a natural estrogenic metabolite from soy isoflavones: Convenient preparation and resolution of R- and S-equols and their differing binding and biological activity through estrogen receptors alpha and beta. *Bioorganic & Medicinal Chemistry, 12*(6), 1559–1567. https://doi.org/10.1016/j.bmc.2003.11.035

474. Zheng, W., Zhang, Y., Ma, D., Li, G., & Wang, P. (2011). Anti-invasion effects of R- and S-enantiomers of equol on prostate cancer PC3, DU145 cells. *Wei Sheng Yan Jiu, 40*(4), 423–425, 430.

475. Kelly, D., Campbell, J. I., King, T. P., Grant, G., Jansson, E. A., Coutts, A. G., et al. (2004). Commensal anaerobic gut bacteria

attenuate inflammation by regulating nuclear-cytoplasmic shuttling of PPAR-gamma and RelA. *Nature Immunology, 5*(1), 104–112. https://doi.org/10.1038/ni1018

476. Lee, S. K., Kim, H. J., Chi, S. G., Jang, J. Y., Nam, K. D., Kim, N. H., et al. (2005). Saccharomyces boulardii activates expression of peroxisome proliferator-activated receptor-gamma in HT-29 cells. *The Korean Journal of Gastroenterology, 45*(5), 328–334.

477. Zhan, Y. P., Du, X. P., Chen, H. Z., Liu, J. J., Zhao, B. X., Huang, D. H., et al. (2008). Cytosporone B is an agonist for nuclear orphan receptor Nur77. *Nature Chemical Biology, 4*(9), 548–556. https://doi.org/10.1038/nchembio.106

478. Zaidman, B. Z., Wasser, S. P., Nevo, E., & Mahajna, J. (2008). Coprinus comatus and Ganoderma lucidum interfere with androgen receptor function in LNCaP prostate cancer cells. *Molecular Biology Reports, 35*(2), 107–117. https://doi.org/10.1007/s11033-007-9059-5

479. Moon, H. S., Lim, H., Moon, S., Oh, H. L., Kim, Y. T., Kim, M. K., et al. (2009). Benzyldihydroxyoctenone, a novel anticancer agent, induces apoptosis via mitochondrial-mediated pathway in androgen-sensitive LNCaP prostate cancer cells. *Bioorganic & Medicinal Chemistry Letters, 19*(3), 742–744. https://doi.org/10.1016/j.bmcl.2008.12.029

480. Venkatesh, M., Mukherjee, S., Wang, H., Li, H., Sun, K., Benechet, A. P., et al. (2014). Symbiotic bacterial metabolites regulate gastrointestinal barrier function via the xenobiotic sensor PXR and Toll-like receptor 4. *Immunity, 41*(2), 296–310. https://doi.org/10.1016/j.immuni.2014.06.014

481. Meng, J., Fan, Y., Su, M., Chen, C., Ren, T., Wang, J., et al. (2014). WLIP derived from Lasiosphaera fenzlii Reich exhibits anti-tumor activity and induces cell cycle arrest through PPAR-γ associated pathways. *International Immunopharmacology, 19*(1), 37–44.

482. Byndloss, M. X., Olsan, E. E., Rivera-Chavez, F., Tiffany, C. R., Cevallos, S. A., Lokken, K. L., et al. (2017). Microbiota-activated PPAR-gamma signaling inhibits dysbiotic Enterobacteriaceae expansion. *Science, 357*(6351), 570–575. https://doi.org/10.1126/science.aam9949

483. Xie, C. L., Zhang, D., Xia, J. M., Hu, C. C., Lin, T., Lin, Y. K., et al. (2019). Steroids from the deep-sea-derived fungus *Penicillium granulatum* MCCC 3A00475 induced apoptosis via retinoid X receptor (RXR)-alpha pathway. *Marine Drugs, 17*(3), 178. https://doi.org/10.3390/md17030178

484. Khan, I., Huang, G., Li, X.-A., Liao, W., Leong, W. K., Xia, W., et al. (2019). Mushroom polysaccharides and jiaogulan saponins exert cancer preventive effects by shaping the gut microbiota and microenvironment in ApcMin/+ mice. *Pharmacological Research, 148*, 104448.

485. Dvorak, Z., Kopp, F., Costello, C. M., Kemp, J. S., Li, H., Vrzalova, A., et al. (2020). Targeting the pregnane X receptor using microbial metabolite mimicry. *Embo Molecular Medicine, 12*(4), ARTN e11621. https://doi.org/10.15252/emmm.201911621.

486. Zhang, X., Li, T., Liu, S., Xu, Y., Meng, M., Li, X., et al. (2020). beta-glucan from Lentinus edodes inhibits breast cancer progression via the Nur77/HIF-1alpha axis. *Bioscience Reports*, *40*(12). 10.1042/BSR20201006.

487. Wang, D., Zhu, X., Tang, X., Li, H., Yizhen, X., & Chen, D. (2020). Auxiliary antitumor effects of fungal proteins from Hericium erinaceus by target on the gut microbiota. *Journal of Food Science, 85*(6), 1872–1890. https://doi.org/10.1111/1750-3841.15134

488. Sondergaard, T. E., Hansen, F. T., Purup, S., Nielsen, A. K., Bonefeld-Jorgensen, E. C., Giese, H., et al. (2011). Fusarin C acts like an estrogenic agonist and stimulates breast cancer cells in vitro. *Toxicology Letters, 205*(2), 116–121. https://doi.org/10.1016/j.toxlet.2011.05.1029

489. Meng, L., Feng, B., Tao, H., Yang, T., Meng, Y., Zhu, W., et al. (2011). A novel antioestrogen agent (3R,6R)-bassiatin inhibits cell proliferation and cell cycle progression by repressing cyclin D1 expression in 17beta-oestradiol-treated MCF-7 cells. *Cell Biology International, 35*(6), 599–605. https://doi.org/10.1042/CBI20100765

490. Simmons, L., Kaufmann, K., Garcia, R., Schwar, G., Huch, V., & Muller, R. (2011). Bendigoles D-F, bioactive sterols from the marine sponge-derived Actinomadura sp. SBMs009. *Bioorganic & Medicinal Chemistry*, *19*(22), 6570–6575. https://doi.org/10.1016/j.bmc.2011.05.044.

491. Nepelska, M., de Wouters, T., Jacouton, E., Beguet-Crespel, F., Lapaque, N., Dore, J., et al. (2017). Commensal gut bacteria modulate phosphorylation-dependent PPARgamma transcriptional activity in human intestinal epithelial cells. *Science and Reports, 7*, 43199. https://doi.org/10.1038/srep43199

492. Aichinger, G., Beisl, J., & Marko, D. (2018). The hop polyphenols xanthohumol and 8-prenyl-naringenin antagonize the estrogenic effects of fusarium mycotoxins in human endometrial cancer cells. *Frontiers in Nutrition, 5*, 85. https://doi.org/10.3389/fnut.2018.00085

493. Zhao, J. C., Luan, Z. L., Liang, J. H., Cheng, Z. B., Sun, C. P., Wang, Y. L., et al. (2018). Drechmerin H, a novel 1(2), 2(18)-diseco indole diterpenoid from the fungus Drechmeria sp as a natural agonist of human pregnane X receptor. *Bioorganic Chemistry, 79*, 250–256. https://doi.org/10.1016/j.bioorg.2018.05.001

494. Kovacs, P., Csonka, T., Kovacs, T., Sari, Z., Ujlaki, G., Sipos, A., et al. (2019). Lithocholic acid, a metabolite of the microbiome, increases oxidative stress in breast cancer. *Cancers*, *11*(9), ARTN 1255. https://doi.org/10.3390/cancers11091255.

495. Sari, Z., Miko, E., Kovacs, T., Janko, L., Csonka, T., Lente, G., et al. (2020). Indolepropionic acid, a metabolite of the microbiome, has cytostatic properties in breast cancer by activating AHR and PXR receptors and inducing oxidative stress. *Cancers*, *12*(9), ARTN 2411. https://doi.org/10.3390/cancers12092411.

496. Zhao, Y., Zhao, C. X., Lu, J., Wu, J., Li, C. H., Hu, Z. Y., et al. (2019). Sesterterpene MHO7 suppresses breast cancer cells as a novel estrogen receptor degrader. *Pharmacological Research, 146*, 104294. https://doi.org/10.1016/j.phrs.2019.104294

497. Li, T., Hu, S. M., Pang, X. Y., Wang, J. F., Yin, J. Y., Li, F. H., et al. (2020). The marine-derived furanone reduces intracellular lipid accumulation in vitro by targeting LXRalpha and PPARalpha. *Journal of Cellular and Molecular Medicine, 24*(6), 3384–3398. https://doi.org/10.1111/jcmm.15012

498. Liang, Z., Gu, T., Wang, J., She, J., Ye, Y., Cao, W., et al. (2021). Chromene and chromone derivatives as liver X receptors modulators from a marine-derived Pestalotiopsis neglecta fungus. *Bioorganic Chemistry, 112*, 104927.

499. Lev, E. (2003). Traditional healing with animals (zootherapy): Medieval to present-day Levantine practice. *Journal of Ethnopharmacology, 85*(1), 107–118. https://doi.org/10.1016/s0378-8741(02)00377-x

500. Alves, R. R. N., Rosa, I. L., & Santana, G. G. (2007). The role of animal-derived remedies as complementary medicine in Brazil. *BioScience, 57*(11), 949–955. https://doi.org/10.1641/B571107

501. Quave, C. L., Lohani, U., Verde, A., Fajardo, J., Rivera, D., Obon, C., et al. (2010). A comparative assessment of zootherapeutic remedies from selected areas in Albania, Italy, Spain and Nepal. *Journal of Ethnobiology, 30*(1), 92–125. https://doi.org/10.2993/0278-0771-30.1.92

502. Dominguez-Martin, E. M., Tavares, J., Rijo, P., & Diaz-Lanza, A. M. (2020). Zoopharmacology: A way to discover new cancer treatments. *Biomolecules*, *10*(6), https://doi.org/10.3390/biom10060817.

503. Jang, A., Jo, C., Kang, K. S., & Lee, M. (2008). Antimicrobial and human cancer cell cytotoxic effect of synthetic

angiotensin-converting enzyme (ACE) inhibitory peptides. *Food Chemistry, 107*(1), 327–336. https://doi.org/10.1016/j.foodchem.2007.08.036

504. Yu, L., Yang, L., An, W., & Su, X. L. (2014). Anticancer bioactive peptide-3 inhibits human gastric cancer growth by suppressing gastric cancer stem cells. *Journal of Cellular Biochemistry, 115*(4), 697–711. https://doi.org/10.1002/jcb.24711

505. Su, L. Y., Xu, G. H., Shen, J., Tuo, Y., Zhang, X. G., Jia, S. Q., et al. (2010). Anticancer bioactive peptide suppresses human gastric cancer growth through modulation of apoptosis and the cell cycle. *Oncology Reports, 23*(1), 3–9. https://doi.org/10.3892/or_00000599

506. Ganjam, L. S., Thornton, W. H., Marshall, R. T., & Macdonald, R. S. (1997). Antiproliferative effects of yogurt fractions obtained by membrane dialysis on cultured mammalian intestinal cells. *Journal of Dairy Science, 80*(10), 2325–2329. https://doi.org/10.3168/jds.S0022-0302(97)76183-6

507. Wu, X., Chen, D., & Xie, G. R. (2006). Effects of Gekko sulfated polysaccharide on the proliferation and differentiation of hepatic cancer cell line. *Cell Biology International, 30*(8), 659–664. https://doi.org/10.1016/j.cellbi.2006.04.005

508. Ding, X.-L., Man, Y.-N., Hao, J., Zhu, C.-H., Liu, C., Yang, X., et al. (2016). The antitumor effect of Gekko sulfated glycopeptide by inhibiting bFGF-induced lymphangiogenesis. *BioMed Research International, 2016*, 7396392. https://doi.org/10.1155/2016/7396392

509. Calcabrini, C., Catanzaro, E., Bishayee, A., Turrini, E., & Fimognari, C. (2017). Marine sponge natural products with anticancer potential: An updated review. *Marine Drugs, 15*(10), 310.

510. He, S., Mao, X., Zhang, T., Guo, X., Ge, Y., Ma, C., et al. (2016). Separation and nanoencapsulation of antitumor peptides from Chinese three-striped box turtle (Cuora trifasciata). *Journal of Microencapsulation, 33*(4), 344–354. https://doi.org/10.1080/02652048.2016.1194904

511. El Ouar, I., Braicu, C., Naimi, D., Irimie, A., & Berindan-Neagoe, I. (2017). Effect of Helix aspersa extract on TNFα, NF-κB and some tumor suppressor genes in breast cancer cell line Hs578T. *Pharmacognosy Magazine, 13*(50), 281.

512. Jeyamogan, S., Khan, N. A., & Siddiqui, R. (2017). Animals living in polluted environments are a potential source of anti-tumor molecule(s). *Cancer Chemotherapy and Pharmacology, 80*(5), 919–924.

513. Wang, L. H., Dong, C., Li, X., Han, W. Y., & Su, X. L. (2017). Anticancer potential of bioactive peptides from animal sources (review). *Oncology Reports, 38*(2), 637–651. https://doi.org/10.3892/or.2017.5778

514. Yang, C., Li, Q., & Li, Y. (2014). Targeting nuclear receptors with marine natural products. *Marine Drugs, 12*(2), 601–635.

515. Ramesh, C., Tulasi, B. R., Raju, M., Thakur, N., & Dufossé, L. (2021). Marine natural products from tunicates and their associated microbes. *Marine Drugs, 19*(6), 308.

516. Waheed, M., Hussain, M. B., Javed, A., Mushtaq, Z., Hassan, S., Shariati, M. A., et al. (2019). Honey and cancer: A mechanistic review. *Clinical Nutrition, 38*(6), 2499–2503.

517. Arung, E. T., Ramadhan, R., Khairunnisa, B., Amen, Y., Matsumoto, M., Nagata, M., et al. (2021). Cytotoxicity effect of honey, bee pollen, and propolis from seven stingless bees in some cancer cell lines. *Saudi Journal of Biological Sciences, 28*(12), 7182–7189.

518. Ding, J., Chua, P.-J., Bay, B.-H., & Gopalakrishnakone, P. (2014). Scorpion venoms as a potential source of novel cancer therapeutic compounds. *Experimental Biology and Medicine, 239*(4), 387–393.

519. Sarfo-Poku, C., Eshun, O., & Lee, K. H. (2016). Medical application of scorpion venom to breast cancer: A mini-review. *Toxicon, 122*, 109–112.

520. Lee, N., Spears, M. E., Carlisle, A. E., & Kim, D. (2020). Endogenous toxic metabolites and implications in cancer therapy. *Oncogene, 39*(35), 5709–5720.

521. O'Flaherty, J. T., Rogers, L. C., Paumi, C. M., Hantgan, R. R., Thomas, L. R., Clay, C. E., et al. (2005). 5-Oxo-ETE analogs and the proliferation of cancer cells. *Biochimica et Biophysica Acta, 1736*(3), 228–236. https://doi.org/10.1016/j.bbalip.2005.08.009

522. Pham, J. V., Yilma, M. A., Feliz, A., Majid, M. T., Maffetone, N., Walker, J. R., et al. (2019). A review of the microbial production of bioactive natural products and biologics. *Frontiers in Microbiology, 10*, 1404.

523. Sharma, M., Tuaine, J., McLaren, B., Waters, D. L., Black, K., Jones, L. M., et al. (2016). Chemotherapy agents alter plasma lipids in breast cancer patients and show differential effects on lipid metabolism genes in liver cells. *Plos One, 11*(1), ARTN e0148049. https://doi.org/10.1371/journal.pone.0148049.

524. Pirouzpanah, S., Asemani, S., Shayanfar, A., Baradaran, B., & Montazeri, V. (2019). The effects of Berberis vulgaris consumption on plasma levels of IGF-1, IGFBPs, PPAR-gamma and the expression of angiogenic genes in women with benign breast disease: A randomized controlled clinical trial. *BMC Complementary and Alternative Medicine, 19*(1), 324. https://doi.org/10.1186/s12906-019-2715-1

525. Komatsu, Y., Yoshino, T., Yamazaki, K., Yuki, S., Machida, N., Sasaki, T., et al. (2014). Phase 1 study of efatutazone, a novel oral peroxisome proliferator-activated receptor gamma agonist, in combination with FOLFIRI as second-line therapy in patients with metastatic colorectal cancer. *Investigational New Drugs, 32*(3), 473–480. https://doi.org/10.1007/s10637-013-0056-3

526. Hamilton-Reeves, J. M., Rebello, S. A., Thomas, W., Slaton, J. W., & Kurzer, M. S. (2007). Isoflavone-rich soy protein isolate suppresses androgen receptor expression without altering estrogen receptor-beta expression or serum hormonal profiles in men at high risk of prostate cancer. *Journal of Nutrition, 137*(7), 1769–1775. https://doi.org/10.1093/jn/137.7.1769

527. Zhang, X., Wang, Q., Neil, B., & Chen, X. A. (2010). Effect of lycopene on androgen receptor and prostate-specific antigen velocity. *Chinese Medical Journal, 123*(16), 2231–2236. https://doi.org/10.3760/cma.j.issn.0366-6999.2010.16.014

528. Ide, H., Tokiwa, S., Sakamaki, K., Nishio, K., Isotani, S., Muto, S., et al. (2010). Combined inhibitory effects of soy isoflavones and curcumin on the production of prostate-specific antigen. *Prostate, 70*(10), 1127–1133. https://doi.org/10.1002/pros.21147

529. Kwan, E. M., Spain, L., Anton, A., Gan, C. L., Garrett, L., Chang, D., et al. (2022). Avelumab combined with stereotactic ablative body radiotherapy in metastatic castration-resistant prostate cancer: The phase 2 ICE-PAC clinical trial. *European Urology, 81*(3), 253–262.

530. Bailly, C. (2019). Irinotecan: 25 years of cancer treatment. *Pharmacological Research, 148*, 104398.

531. Kciuk, M., Marciniak, B., & Kontek, R. (2020). Irinotecan—Still an important player in cancer chemotherapy: A comprehensive overview. *International Journal of Molecular Sciences, 21*(14), 4919.

532. Noda, K., Nishiwaki, Y., Kawahara, M., Negoro, S., Sugiura, T., Yokoyama, A., et al. (2002). Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. *New England Journal of Medicine, 346*(2), 85–91.

533. Fuchs, C., Mitchell, E. P., & Hoff, P. M. (2006). Irinotecan in the treatment of colorectal cancer. *Cancer Treatment Reviews, 32*(7), 491–503.

534. Feldman, E., Kalaycio, M., Weiner, G., Frankel, S., Schulman, P., Schwartzberg, L., et al. (2003). Treatment of relapsed or refractory acute myeloid leukemia with humanized anti-CD33 monoclonal antibody HuM195. *Leukemia, 17*(2), 314–318.

535. Grillo-López, A. J., White, C. A., Varns, C., Shen, D., Wei, A., McClure, A., et al. Overview of the clinical development of rituximab: First monoclonal antibody approved for the treatment of lymphoma. In *Seminars in Oncology*, *1999* (Vol. 26, pp. 66–73, Vol. 5 Suppl 14)

536. Seiden, M., Burris, H., Matulonis, U., Hall, J., Armstrong, D., Speyer, J., et al. (2007). A phase II trial of EMD72000 (matuzumab), a humanized anti-EGFR monoclonal antibody, in patients with platinum-resistant ovarian and primary peritoneal malignancies. *Gynecologic Oncology, 104*(3), 727–731.

537. Smaletz, O., Ismael, G., Estevez-Diz, M. D. P., Nascimento, I. L., de Morais, A. L. G., Cunha-Junior, G. F., et al. (2021). Phase II consolidation trial with anti-Lewis-Y monoclonal antibody (hu3S193) in platinum-sensitive ovarian cancer after a second remission. *International Journal of Gynecologic Cancer, 31*(4), 62–568. https://doi.org/10.1136/ijgc-2020-002239

538. Chi, K. N., Gleave, M. E., Fazli, L., Goldenberg, S. L., So, A., Kollmannsberger, C., et al. (2012). A phase II pharmacodynamic study of preoperative figitumumab in patients with localized prostate cancer. *Clinical Cancer Research, 18*(12), 3407–3413. https://doi.org/10.1158/1078-0432.CCR-12-0482

539. Hor, S., Lee, S., Wong, C., Lim, Y., Lim, R., Wang, L., et al. (2008). PXR, CAR and HNF4α genotypes and their association with pharmacokinetics and pharmacodynamics of docetaxel and doxorubicin in Asian patients. *The Pharmacogenomics Journal, 8*(2), 139–146.

540. Chew, S.-C., Lim, J., Singh, O., Chen, X., Tan, E.-H., Lee, E.-J., et al. (2014). Pharmacogenetic effects of regulatory nuclear receptors (PXR, CAR, RXRα and HNF4α) on docetaxel disposition in Chinese nasopharyngeal cancer patients. *European Journal of Clinical Pharmacology, 70*(2), 155–166.

541. Deeken, J. F., Cormier, T., Price, D. K., Sissung, T. M., Steinberg, S. M., Tran, K., et al. (2010). A pharmacogenetic study of docetaxel and thalidomide in patients with castration-resistant prostate cancer using the DMET genotyping platform. *Pharmacogenomics Journal, 10*(3), 191–199. https://doi.org/10.1038/tpj.2009.57