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Hitoshi Kojo
Systems Pharma Sciences Research Organization, 2641 Yamazaki, Noda-shi, Chiba, Japan

Yukihiro Eguchi
Systems Pharma Sciences Research Organization, 2641 Yamazaki, Noda-shi, Chiba, Japan

Kimiko Makino
[1] Systems Pharma Sciences Research Organization, 2641 Yamazaki, Noda-shi, Chiba, Japan
[2] Faculty of Pharmaceutical Sciences, Tokyo University of Science, 2641 Yamazaki, Noda-shi, Chiba, Japan

Hiroshi Terada
[1] Systems Pharma Sciences Research Organization, 2641 Yamazaki, Noda-shi, Chiba, Japan
[2] Faculty of Pharmaceutical Sciences, Tokyo University of Science, 2641 Yamazaki, Noda-shi, Chiba, Japan
[3] Niigata University of Pharmacy and Applied Sciences, 265-1 Higashijima, Niigata-shi, Niigata, Japan

Correspondence
Hitoshi Kojo
Systems Pharma Sciences Research Organization, 2641 Yamazaki, Noda-shi, Chiba, Japan

Versatile pharmacological activities of phytochemicals through their effects on nuclear receptors

Hitoshi Kojo, Yukihiro Eguchi, Kimiko Makino and Hiroshi Terada

Abstract
Phytochemicals are well-known to exert versatile pharmacological activities, and these activities had been ascribed to their antioxidative activity and ability to interact with membranes. This review focuses on the activities of phytochemicals against nuclear receptors (NRs) and summarizes recent progress in this area, leading to elucidation of the versatile pharmacological activities of phytochemicals. The *in vitro* modes of action of 94 phytochemicals on 19 NRs and their *in vivo* modulatory activities in regulating the physiological functions of NRs, as well as the modulatory activities of some phytochemicals against NR signaling networks in the regulation of aquaporins and circadian rhythm, are described. These studies have revealed not only that there are phytochemicals capable of modulating multiple NRs but also that NRs perform their physiological roles in co-operation with other NRs through crosstalk between them as well as working independently. Hence, further efforts are needed to clarify the entire picture of the pharmacological activities of phytochemicals against NRs.

Keywords: phytochemicals, nuclear receptors, versatile activity, xenobiotics, signaling networks, circadian rhythm

Introduction
Phytochemicals are well-known to exert versatile pharmacological activities, and the mechanisms behind these activity are increasingly being elucidated. The versatile activities of phytochemicals are caused mainly by their antioxidative activity, ability to interact with membranes, and ability to modulate the activity of nuclear receptors (NRs). First, the antioxidative activity of phytochemicals presumably developed in the course of evolution where plants acquired resistance to the oxidative stresses produced by ultraviolet light and photosynthesis-derived oxygen free radicals. Antioxidant phytochemicals exert pharmacological activities against a broad spectrum of diseases because oxidative stresses induce their onset [1, 2]. Second, the effects of phytochemicals on biomembranes are caused by the interaction of amphiphilic or hydrophobic structures with membrane components, such as phospholipids and cholesterol, resulting in the modification of membrane fluidity, microviscosity, order, elasticity, and permeability. These modifications of membrane properties lead to alterations in both membrane function and the activity of membrane-associated receptors, ion channels, and transporters [3, 4]. Lastly, phytochemicals modulate NR activity as xenobiotics or nutrients because some NRs, such as constitutive androstane receptor (CAR), pregnane X receptor (PXR), and vitamin D receptor (VDR), act as xenobiotic sensors, and others NRs, such as liver X receptors (LXRs), farnesoid X-activated receptor (FXR), and peroxisome proliferator-activated receptors (PPARs), regulate the metabolism of nutrients such as lipids and carbohydrates and also crosstalk with nutrients [5, 6]. As these NRs are also responsible for physiological roles other than regulators of xenobiotic and nutrient metabolism, phytochemicals can exert a broad spectrum of pharmacological activities. This review focuses on the pharmacological activities of phytochemicals against NRs and summarizes recent progress in this area, leading to elucidation of the versatile pharmacological activities of phytochemicals.

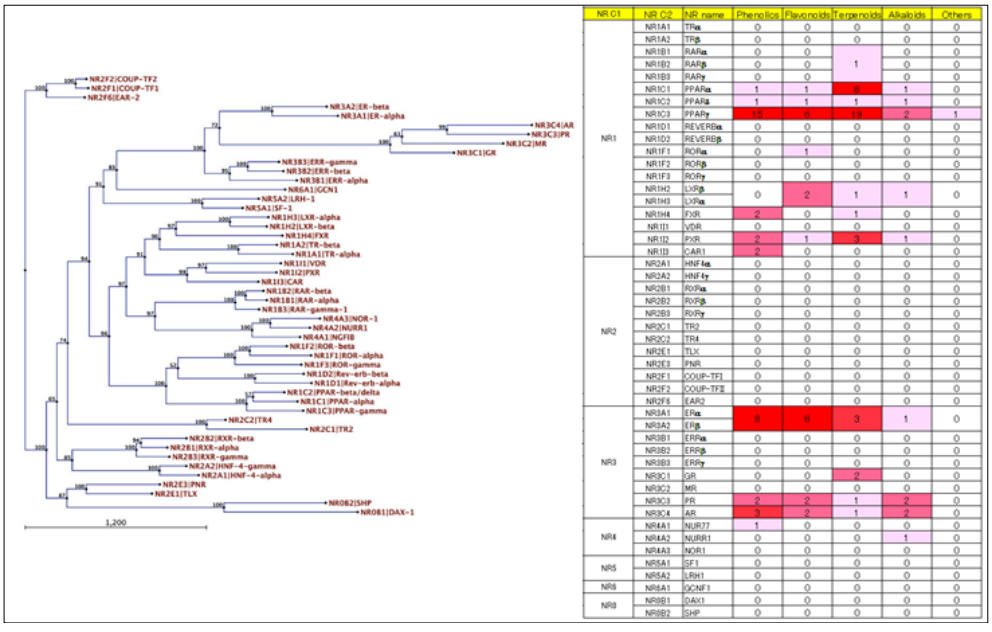
Outline of the NR superfamily
NRs are a type of transcription factor and form a superfamily consisting of 48 members in humans. NRs are composed of several domains, including DNA and ligand binding domains, which show highly homologous DNA and protein sequences among NRs. Endogenous ligands have been identified for most NRs, but those for more than 15 NRs are either unknown or may not exist [7].

NRs induce or repress the expression of their target genes, and the modes of modulation by NRs are classified into the following three categories. 1) NRs bind to NR responsive elements (NREs), which are DNA sequences located upstream of target genes and are recognized by DNA binding domains of NRs after they are activated by the binding of ligands to the ligand binding domains. Then, NRs mobilize coactivators and promote the transcription of their target genes. 2) NRs bind directly to other transcription factors through protein–protein interactions upon ligand activation, leading to the detachment of transcription factors from DNA binding sites and consequently repressing the expression of the transcription factor target genes independently of NREs. 3) Upon ligand activation, DNA-bound NRs interact directly with other transcription factors to detach them from their binding sites in the promoter of their target genes, thereby repressing the expression of the target genes dependently of NREs [8].

To identify NR agonist/antagonists, the following three methods are used. 1) Reporter gene assays using full-length NRs [9, 10]. Host cells are co-transfected with a reporter plasmid containing the NRE upstream of a reporter gene, such as a luciferase gene, and a full-length NR expression plasmid. After incubation of transfected cells with agonist/antagonist candidate compounds, the cells are lysed and the quantity of reporter gene product is measured using an appropriate activity assay to evaluate the agonist/antagonist activity. 2) NR one-hybrid reporter gene assays [11]. This assay is similar to that described above, except that the NRE used in reporter plasmid and full-length NR expression plasmid are substituted by a Gal4 binding DNA sequence and a Gal4-NR ligand-binding domain hybrid expression plasmid, respectively. 3) Binding assays [12]. The ability of the agonist/antagonist to bind to an NR is measured by physical methods using recombinant NR proteins.

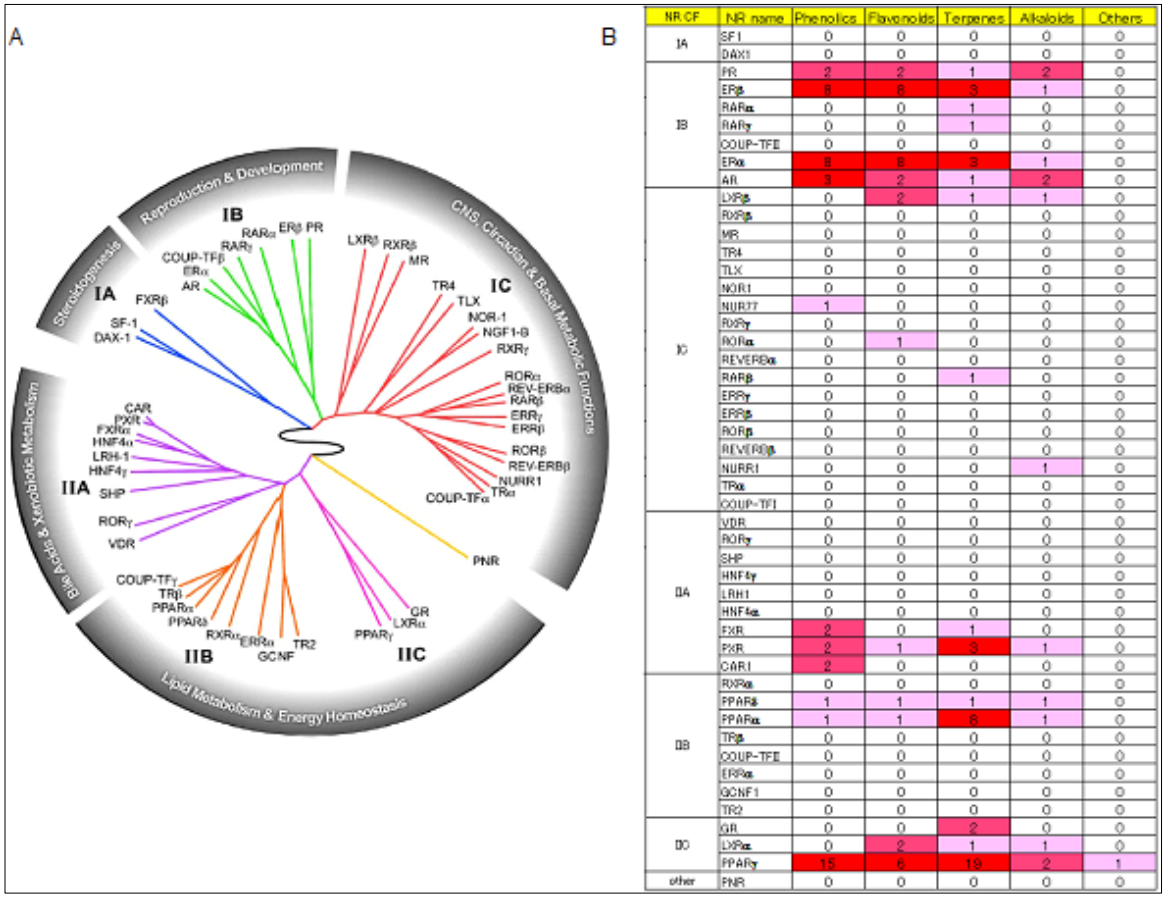
Actions of phytochemicals against NRs

Members of the NR superfamily have been classified by two different criteria, namely, sequence and phylogenetic relationship and physiologic function relationship based on tissue expression distribution profiles [13, 14]. The former classification proposed by NC-IUPHAR divides the NR superfamily into 7 groups: NR1–6 and NR0 [13]. Meanwhile, the latter classification proposed by Mangelsdorf *et al.* divides the superfamily into 2 major groups, each of which is further divided into 3 subgroups [14]. The major groups were identified to play roles in the regulation of physiological functions of reproduction, development, and growth and those of absorption, metabolism, and excretion of nutrition and xenobiotics, respectively. In preparing this review, we determined 91 phytochemicals that have been so far found to act on NRs, and these phytochemicals consist of 34 phenolics (excluding flavonoids), 18 flavonoids, 30 terpenoids, 8 alkaloids, and 1 other compound. We analyzed the relationship between the structural classification of phytochemicals acting on NRs and the classification of the NR superfamily (Fig. 1 and Fig. 2). Notably, the groups in the NC-IUPHAR classification whose member phytochemicals act on were confined to NR1, NR3, and NR4 (Fig. 1). Furthermore, as to physiological function classification, phytochemicals predominantly act on members of subgroups of IB (reproduction and development), IIA (bile acids and xenobiotics metabolism), IIB and IIC (lipid metabolism and energy homeostasis) (Fig. 2). It is also noteworthy that the ratios of phenolics (36%) and terpenoids (32%) are exceedingly high among the phytochemicals that act on NRs, whereas there is no particular difference in the relationship with the NR groups among the structural groups of phytochemicals (Fig. 1 and Fig. 2). The cause of the relationship of phytochemicals with the NR superfamily remains unclear, but part of the causes might be ascribed to some phytochemicals acting as xenobiotics or nutrients on NRs involved in xenobiotic or nutrient metabolism, and also to the chemical structures of some phytochemicals resembling those of endogenous ligands of NRs, such as those involved in reproduction and development. In the following sections, we summarize studies on the actions of phytochemicals against NRs generally in the order of physiological function classification in the NR superfamily.



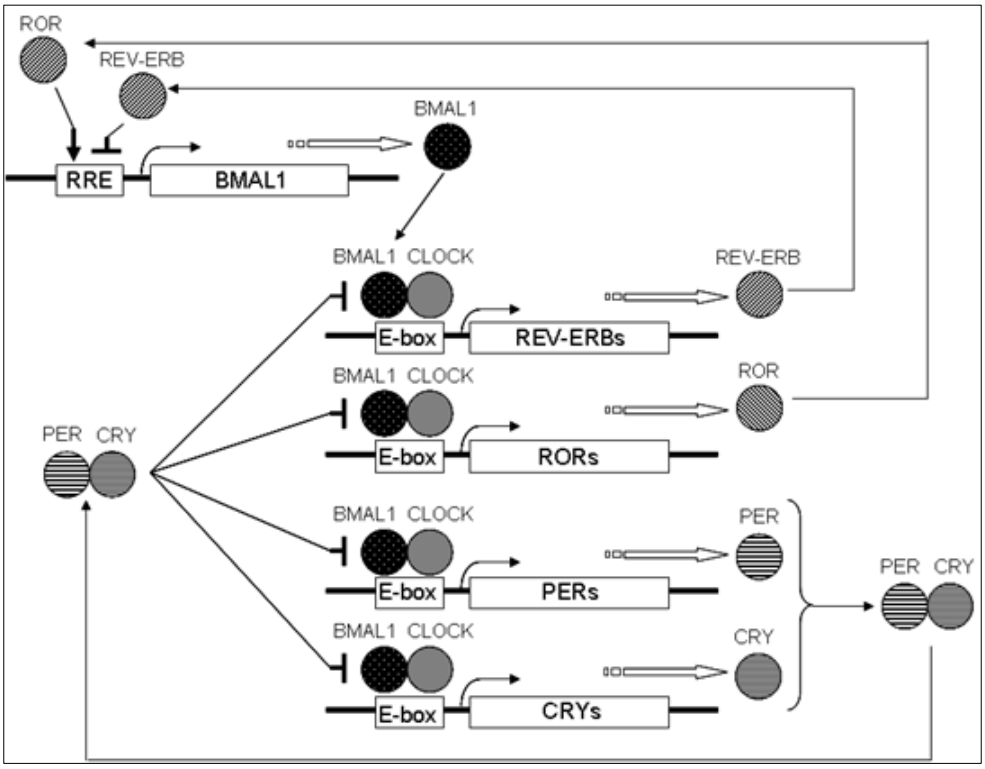
NR 01	NR 02	NR name	Phenolics	Flavonoids	Terpenoids	Alkaloids	Others
NR1	NR1A1	TRα	0	0	0	0	0
	NR1A2	TRβ	0	0	0	0	0
	NR1B1	RARα	0	0	1	0	0
	NR1B2	RARβ	0	0		0	0
	NR1B3	RARγ	0	0	1	0	0
	NR1C1	PPARα	1	1	0	1	0
	NR1C2	PPARβ	1	1	1	1	0
	NR1C3	PPARγ	15	6	19	2	1
	NR1D1	REVERBα	0	0	0	0	0
	NR1D2	REVERBβ	0	0	0	0	0
	NR1F1	RORα	0	1	0	0	0
	NR1F2	RORβ	0	0	0	0	0
	NR1F3	RORγ	0	0	0	0	0
	NR1H2	LXRβ	0	2	1	1	0
	NR1H3	LXRα					
	NR1H4	FXR	2	0	1	0	0
	NR1I1	VDR	0	0	0	0	0
	NR1I2	PXR	2	1	3	1	0
	NR1I3	CAR1	2	0	0	0	0
NR2	NR2A1	HNF-4α	0	0	0	0	0
	NR2A2	HNF-4γ	0	0	0	0	0
	NR2B1	RXRα	0	0	0	0	0
	NR2B2	RXRβ	0	0	0	0	0
	NR2B3	RXRγ	0	0	0	0	0
	NR2C1	TR2	0	0	0	0	0
	NR2C2	TR4	0	0	0	0	0
	NR2E1	TLX	0	0	0	0	0
	NR2E3	PNR	0	0	0	0	0
	NR2F1	COUP-TF1	0	0	0	0	0
	NR2F2	COUP-TF2	0	0	0	0	0
	NR2F6	EAR2	0	0	0	0	0
NR3	NR3A1	ERα	8	6	3	1	0
	NR3A2	ERβ					
	NR3B1	ERRα	0	0	0	0	0
	NR3B2	ERRβ	0	0	0	0	0
	NR3B3	ERRγ	0	0	0	0	0
	NR3C1	GR	0	0	2	0	0
	NR3C2	MR	0	0	0	0	0
	NR3C3	PR	2	2	1	2	0
	NR3C4	AR	3	2	1	2	0
NR4	NR4A1	NUR77	1	0	0	0	0
	NR4A2	NURR1	0	0	0	1	0
	NR4A3	NOR1	0	0	0	0	0
NR5	NR5A1	SF1	0	0	0	0	0
	NR5A2	LRH1	0	0	0	0	0
NR6	NR6A1	GCNF1	0	0	0	0	0
NR0	NR0B1	DAX1	0	0	0	0	0
	NR0B2	SHP	0	0	0	0	0

Fig 1: Relationship between IUPHAR NR classification and structural classification of phytochemicals acting on NRs. A. Phylogenetic tree of human nuclear receptor quoted from Wikipedia, Nuclear receptor created on 9 June 2007. B. Heatmap depicting the relationship between the IUPHAR NR classification and the structural classification of phytochemicals acting on NRs was created by using Microsoft Excel 2010.

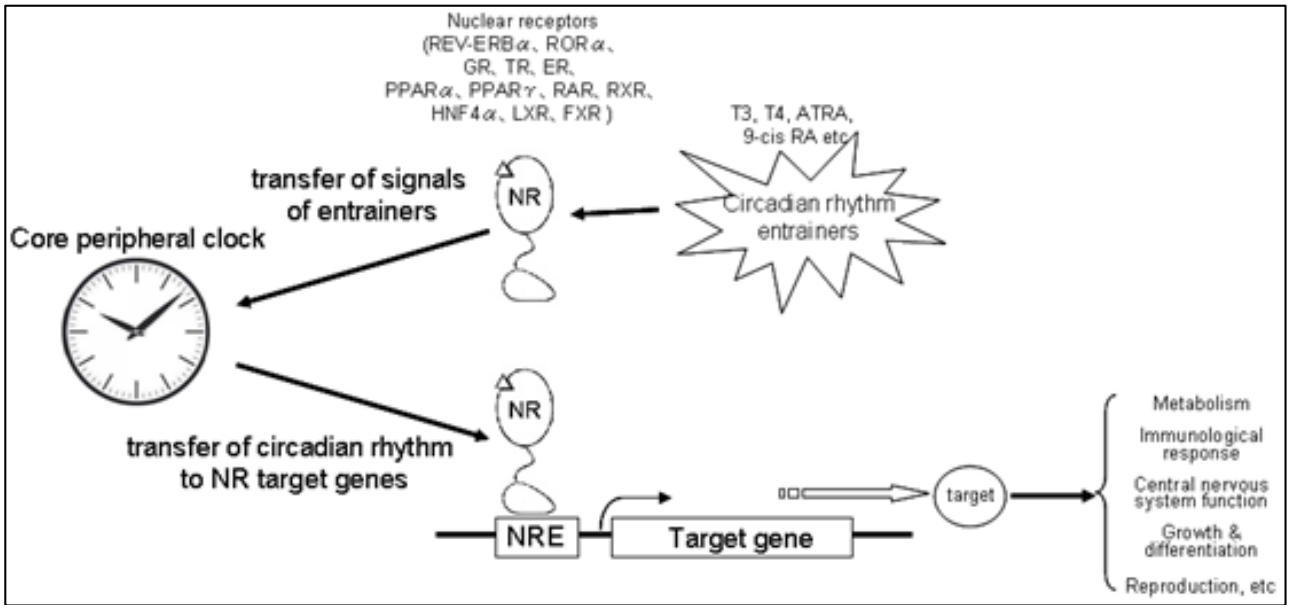


NR CF	NR name	Phenolics	Flavonoids	Terpenes	Alkaloids	Others
IA	SF1	0	0	0	0	0
	DAX1	0	0	0	0	0
IB	PR	2	2	1	2	0
	ERβ	6	6	3	1	0
	RARα	0	0	1	0	0
	RARγ	0	0	1	0	0
	COUP-TFE	0	0	0	0	0
	ERα	6	6	3	1	0
	AR	3	2	1	2	0
IC	LXRβ	0	2	1	1	0
	RXRβ	0	0	0	0	0
	MR	0	0	0	0	0
	TR4	0	0	0	0	0
	TLX	0	0	0	0	0
	NOR1	0	0	0	0	0
	NUR77	1	0	0	0	0
	RXRγ	0	0	0	0	0
	RORα	0	1	0	0	0
	REVERBα	0	0	0	0	0
	RARβ	0	0	1	0	0
	ERRγ	0	0	0	0	0
	ERRβ	0	0	0	0	0
	RORβ	0	0	0	0	0
	REVERBβ	0	0	0	0	0
	NURR1	0	0	0	1	0
	TRα	0	0	0	0	0
	COUP-TF1	0	0	0	0	0
IIA	VDR	0	0	0	0	0
	RORγ	0	0	0	0	0
	SHP	0	0	0	0	0
	HNF4γ	0	0	0	0	0
	LRH1	0	0	0	0	0
	HNF4α	0	0	0	0	0
	FXR	2	0	1	0	0
	PXR	2	1	3	1	0
	CAR1	2	0	0	0	0
IIB	RXRα	0	0	0	0	0
	PPARδ	1	1	1	1	0
	PPARα	1	1	6	1	0
	TRβ	0	0	0	0	0
	COUP-TFE	0	0	0	0	0
	ERRα	0	0	0	0	0
	GCNF1	0	0	0	0	0
	TR2	0	0	0	0	0
IIC	GR	0	0	2	0	0
	LXRα	0	2	1	1	0
	PPARγ	15	6	19	2	1
other	PNR	0	0	0	0	0

Fig 2: Relationship between NR functional classification and structural classification of phytochemicals acting on NRs. A. Circular dendrogram representing hierarchical clustering of NR tissue expression distribution profiles is quoted from Cell 126: 789-799, 2006. B. Heatmap depicting the relationship between the NR functional classification and structural classification of phytochemicals acting on NRs was created by using Microsoft Excel 2010.



A. Role of Red-erb and ROR in circadian oscillators.



B. Roles of NRs in peripheral clocks.

Fig 3: Roles of NRs in circadian rhythm

(1) Actions of phytochemicals on reproduction, development, and growth through NRs

Estrogen receptors (ERs), androgen receptor (AR), glucocorticoid receptor (GR), retinoic acid receptor β (RARβ), nuclear receptor related-1 (Nurr1), and Nur77 are the targets of phytochemicals and are involved in reproduction, development, and growth. The pharmacological actions of phytochemicals on these NRs are described in detail here.

1) Estrogen receptors

Phytochemicals reported to modulate the activity of ERs include: flavonoids, such as icariin, naringenin, 8-prenyl-naringenin (8-PN), 6-(1,1-dimethylallyl)naringenin (6-DMAN), peltogynoid ophioglonin, genistein, daidzein, biochanin A; phenolics, such as phloretin, tschimgine, tschimganidine, ferutinine, glyceollins and carnosol, lindleyin, α-zearalanol, zearalenone, coumestrol, and resveratrol; and an alkaloid, indole-3-carbinol. The modulatory activities of phytochemicals on ERs were evaluated by either reporter gene assays using a reporter plasmid containing the estrogen-responsive element upstream of a reporter gene or quantitative measurement of mRNA or protein products of ER target genes such as lactoferrin, vitellogenin, cathepsin D, oxytocin, or alkaline phosphatase. The modes of action on ERs are classified into three categories: agonistic, antagonistic, and selective ER modulation [15]. Modulators of ERs are also classified according to subtype selectivity because there are two subtypes of ER: ERα and ERβ [16]. Phytochemicals are known to show a variety of activities as their mode of action and subtype selectivity.

Most phytochemicals, including icariin [17], naringenin [18, 20], 8-PN [18], peltogynoid ophioglonin [19], genistein [20], daidzein [20], biochanin A [20], phloretin [21], tschimgine [22], tschimganidine [22], lindleyin [23], α-zearalanol [20], zearalenone [20], coumestrol [20], and resveratrol [24] were classified as agonists, whereas glyceollins [25], carnosol [26], and indole 3-carbinol [27] were shown to exhibit antagonistic activities. Furthermore, ferutinine [22] acts as an agonist for ERα whereas it acts as a selective estrogen receptor modulator (SERM) for ERβ. 6-DMAN was shown to be a SERM for ERα [18]. Only a proportion of phytochemicals have had their ER subtype selectivity reported. Naringenin exhibits agonistic activity on both ERα and ERβ, whereas 8-PN shows agonistic activity only for ERα [18]. Tschimgine is an agonist for both ERα and ERβ, but tschimganidine is an agonist only for ERα [22]. Glyceollins were shown to exert antagonistic activity on ERα much more potently than on ERβ [25].

The most closely examined pharmacological activities of phytochemicals acting on ERs are 1) effects on estrogen-dependent carcinogenesis, such as those of breast, uterine, and ovarian cancers and 2) protective effects on osteoporosis and osteopenia. Among the effects on carcinogenesis, indole 3-carbinol, with antagonistic activity on ERα, was reported to prevent the development of estrogen-enhanced cancers including breast, endometrial, and cervical cancers as well as to induce expression of growth arrest in response to DNA damage (GADD) [27]. Although 8-PN increased the uterine wet weight of ovariectomized (OVX) rats, 6-DMAN, a naturally occurring SERM, did not alter uterine wet weight or the level of expression of proliferation markers. Furthermore, 8 phytochemicals with ER agonistic activity, including genistein, daidzein, coumestrol, α-zearalanol, zearalenone, naringenin, taxifolin and biochanin A, all gave some measure of estrogenicity when sensitive morphological and biochemical parameters such as uterine gland number increased and the induction of the estrogen-responsive protein lactoferrin were used; however, when an *in vivo* immature mouse uterotrophic assay was used, naringenin, taxifolin, daidzein, and biochanin A did not cause an increase in uterine wet weight whereas genistein, coumestrol, α-zearalanol, and zearalenone caused an increase [20]. These results aroused our attention that there is a range of estrogenicities among phytochemicals with ER agonistic activity when phytoestrogens were evaluated for their effects on estrogen-dependent carcinogenesis. As to the effect of phytochemicals on osteoporosis and osteopenia, icariin, which exerts ER agonistic activity, was clarified to restore the osteogenic differentiation and mineralization capacity of bone marrow stromal cells in OVX rats. Icariin was also shown to enhance the expression in OVX-bone marrow stromal cells of ERα, PR, PS-2, which are involved in the estrogen signaling

pathway, but this effect was abrogated when an ER antagonist was added. These results indicated that icariin restores osteogenic differentiation and mineralization by acting through the estrogen pathway [17].

2) Androgen receptor

Phytochemicals acting on AR (and progesterone receptor (PR)) were identified by quantitatively measuring prostate-specific antigen (PSA) secreted from breast cancer cells after the cells were incubated with either phytochemical alone or together with an AR antagonist (RU56187) or a PR antagonist (mifepristone) because the secretion of PSA was shown to be AR/PR dependent. Using this method, naringenin [28] was identified as an AR/PR agonist and taxifolin [28], chlorogenic acid [28], β-carotene [28], α-tocophenol [28], chlorophyllin [28], and homocysteine [28] were identified as AR/PR antagonists although the effective concentrations of these phytochemicals were high (around 10^{-5} M). Isosilybin B was also identified as an AR antagonist by measuring the quantity of PSA secreted from prostate cancer cells incubated with isosilybin and an AR agonist, R1881, together [29].

The phytochemicals acting on AR are expected to exhibit anticancer activity against androgen-dependent prostate cancer. Isosilybin, an AR antagonist, was shown to enhance the formation of a complex between Akt kinase, E3 ubiquitin ligase (Mdm2), and AR, which promoted phosphorylation-dependent AR ubiquitination and its degradation by the proteasome. Furthermore, isosilybin was shown to inhibit synthetic androgen R1881-induced growth of prostate cancer cells by causing G1 arrest [29].

3) Glucocorticoid receptor

18β-Glycyrrhetinic acid (GE) and glycyrrhizic acid (GI) [30] were reported to be GR agonists. GE and GI were shown to bind directly to GR in a competitive receptor binding assay and their affinities for GR were five orders of magnitude lower than dexamethasone, a GR agonist. GE and GI also bind to the mineralocorticoid receptor (MR) with affinities four orders of magnitude lower than aldosterone, an MR ligand [31]. GE and GI were shown to activate the glucocorticoid transcription element. Furthermore, GE was confirmed to lead to the dissociation of a GR-HSP90 complex [32].

Anti-inflammatory activity was examined as a candidate of the pharmacologic action of GE and GI through their GR agonistic activities. Glucocorticoid resistance is one of the most serious problems in the treatment of inflammatory diseases. GE and GI were shown to restore glucocorticoid sensitivity by following mechanism. A phosphoinositide 3-kinase (PI3K) other than GR was identified as the target of GE and GI, the activation of which led to the simultaneous activation of transcription elements such as AP1, cyclic AMP responsive element, and NFAT, which are all members of the PI3K signaling pathway. GE and GI were shown to induce the expression of dual specificity protein phosphatase 1 and HO-1 by coordinated activation of GR and PI3K signaling, the former of which inhibits inflammatory reactions and the latter removes glucocorticoid resistance by depleting reactive oxygen species [30].

4) Retinoic acid receptor

All trans retinoic acid (ATRA), one of the retinoids that are metabolites of the phytochemical carotene, is known as an RAR/ retinoid X receptor (RXR) agonist [33].

One of the pharmacological activities of ATRA is anti-proliferative and pro-differentiating activity against cancers such as acute promyelocytic leukemia (APL) and melanoma. However, most metastatic melanoma exhibits ATRA resistance, the cause of which is supposed to be decreased expression of RARs, and the methylation of the RAR-β2 promoter was elucidated to be responsible for silencing of RAR-β2.

Furthermore, because the reactivation of RAR-β2 expression in melanoma was achieved by inhibition of DNA methylation with 5-aza-2'-deoxycytidine, treatment of melanoma sequentially with DNA methylation inhibitors and ATRA was suggested to have a possible therapeutic benefit [33].

5) Nuclear receptor related-77 (NGFI-B, NR4A1)

Nur77 is involved in the survival and apoptosis of cancer cells. The expression of Nur77 is induced by tumor necrosis factor α (TNFα), and Nur77 plays a role in antagonizing the apoptosis of cancer cells in TNF signaling [34, 35].

No phytochemicals that can interact directly with Nur77 have been found until now, but cytosporone B, an octaketide isolated not from plants but from endophytic fungi, was found to be a Nur77 agonist [36] and honokiol was reported to have the ability to modulate Nur77 signaling [37]. Honokiol was shown to interfere with the interaction of TNFR1 with receptor-interacting protein 1 (RIPK1), which inhibited TNFα-induced Nur77 mRNA expression and consequently led to the apoptosis of cancer cells. Honokiol is considered to be an effective sensitizer of TNF-α.

6) Nuclear receptor related-1 (NR4A2)

Nurr1 plays a pivotal role in the differentiation of Th17 cells involved in immunoregulation as well as both the homeostasis and development of dopamine neurons [34, 38, 39].

C-DIM12, a synthetic derivative of the phytochemical indole-3-carbinol was reported to be a Nurr1 agonist [40]. C-DIM12 induced the expression of Nurr1-regulated genes that was abolished by Nurr1 knockdown in dopaminergic neuronal cell lines. C-DIM12 also induced Nurr1 expression in primary dopaminergic neurons and increased the expression of transfected Nurr1.

C-DIM12 enhanced neuronal survival after exposure to neurotoxic 6-hydroxydopamine (6-OHDA) and prevented loss of dopaminergic neurons in an MPTP model of Parkinson's disease (PD) in mice. Decreased expression of Nurr1 is suggested to cause the degeneration of dopaminergic neurons in PD. C-DIM12 was concluded to enhance neuronal survival by inducing the expression of Nurr1-regulated and neuroprotective genes [40].

(2) Actions of phytochemicals on the absorption, metabolism, and excretion of nutrients and xenobiotics through NRs

LXRs, FXR, CAR, PXR, and PPARs are the targets of phytochemicals and are involved in the absorption, metabolism, and excretion of nutrients and xenobiotics. Pharmacological actions of phytochemicals on these NRs are described in detail here.

1) Liver X receptors

LXRs include two subtypes, LXRα and LXRβ, both of which play important roles in the regulations of metabolism and transport of cholesterol and the regulation of metabolism of sugar [41].

Hespertin [42] and paxillin [43] isolated from a fungus were reported to be LXR agonists, whereas geranylgeranyl pyrophosphate was reported to be an LXR antagonist [44]. An anthocyanin, cyanidin-3-O-beta-glucoside (C3G), was also found to induce the expression of LXR, although it did not interact directly with LXR [45]. Hespertin was identified as an LXR agonist from a phytochemical library using a reporter gene assay with a vector including a combination of the ABCA1 promoter and LXR response element. Hespertin was also shown to have PPARγ agonistic activity.

LXR is responsible for regulation of the expression of ATP-binding cassette (ABC) transporter family proteins, including ABCA1, ABCC2, ABCG1, ABCG5, and ABCG8, whose expression was induced after LXR activation. ABCA1 is involved in regulation of the metabolism of high-density lipoprotein and transport of cholesterol, whereas ABCC2 plays crucial role in the hepatobiliary transport of sulfate-, glucuronide-, and glutathione-conjugated metabolites as well as a variety of amphiphilic organic anions derived from hepatic metabolism. Hespertin induces ABCA1 expression by activating LXRα and PPARγ, which leads to promotion of the excretion of cholesterol via ApoA1. This effect of hespertin is expected to contribute to the prevention and treatment of atherosclerosis [42]. Paxillin was also confirmed to induce ABCC2 production [43].

LXRα exerts anti-inflammatory effects other than the regulatory effects on cholesterol and sugar metabolism. The mechanism of this effect was suggested to involve LXRα inhibiting the expression of lipopolysaccharide (LPS)-induced inducible nitric oxide synthase (iNOS) and cyclo-oxygenase 2 (COX2) through the suppression of activation of nuclear factor kappa B (NF-κB). LXRα activation was suggested to play an essential role in the anti-inflammatory effect of C3G [45].

2) Farnesoid X-activated receptor

When activated by ligand (bile acids) binding, FXR 1) down-regulates the transcription of genes for bile acids synthetic enzymes, cholesterol 7α-hydroxylase (CYP7A1) and cholesterol 12α-hydroxylase (CYP8B), 2) induces the expression of ABCB11 and ABCC2 transporters involved in bile acids excretion, 3) down-regulates the transcription of ileal bile acid-binding protein (I-BABP) involved in reabsorption of conjugated bile acids. The mechanism of down-regulation of the transcription of genes for CYP7A1, CYP8B, and I-BABP by FXR was elucidated as follows. The transcription of these genes is induced by the activation of another NR named liver receptor homolog-1 (LRH). FXR induces the expression of its target, small heterodimer partner (SHP), which forms a heterodimer with LRH and represses the expression of LRH-targeted genes [46]. FXR is responsible for protecting liver cells from bile acids toxicity by repressing bile acids synthesis and enhancing bile acids excretion [47].

Marchantin A and marchantin E were reported to be FXR agonists [48], whereas the phytosterol guggulsterone was reported to be a highly efficacious FXR antagonist [49, 50]. Guggulsterone treatment was shown to decrease hepatic cholesterol in wild-type mice fed a high-cholesterol diet but it was not effective in FXR-null mice. Accordingly, the cholesterol-lowering effect of guggulsterone was clarified to be caused by its action on FXR.

3) Constitutive androstane receptor

CAR is responsible as a xenobiotics sensor for inducing the expression of drug metabolizing enzymes such as CYP1A2, CYP2B6, CYP2C19, and CYP3A4 as well as regulating the expression of genes involved in energy metabolism [51]. Ellagic acid and trans-resveratrol were identified as CAR agonists using a reporter gene assay with a combination of recombinant CAR and CAR-response element [52].

4) Pregnane X receptor

PXR is a xenobiotics sensor similar to CAR for inducing the expression of phase I drug-metabolizing enzymes, such as CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4, phase II drug metabolizing enzymes, such as uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), and drug transporters such as ABCB1 and ABCC2, and thus PXR is responsible for detoxifying xenobiotics. Additionally, PXR was also reported to be responsible for other physiological functions, including: anti-inflammation, owing to its inhibition of NF-κB; inhibition of TNFα production and inhibition of toll-like receptor 4 production; anti-proliferation including the induction of expression of cell cycle regulatory factor, p21; promotion of cell motility owing to its promotion of GADD45β production and inhibition of hepatocyte nuclear factor 4 (HNF4) production; and promotion of cell apoptosis owing to the promotion of Bcl-2 production. All these functions of PXR appear to contribute to maintaining homeostasis against invasion by xenobiotics, which is in effect the same as detoxification [53].

A phytochemical library was explored for PXR agonists by applying a reporter gene assay with recombinant PXR and the UGT1A1 transcriptional regulatory sequence, which resulted in the discovery of 50 positives out of 101 compounds. This result indicated that a broad spectrum of phytochemicals can act as PXR agonists [54]. Terpenoids ginkgolide A and ginkgolide B and the flavonoid tangeretin were found to be potent PXR agonists among phytochemicals [55, 56], whereas sulforaphane was identified as a PXR antagonist [57]. Lignans showed low PXR agonistic activity, but lignan metabolites produced by colonic bacteria showed medium PXR activity. For example, enterolactone, a metabolite of secoisolariciresinol, increased PXR agonistic activity by 80% [58].

The triterpene ginsenoside was reported to protect benzo[a]pyren-induced DNA damage by detoxifying benzo[a]pyren through activation of PXR and the Nrf2 signaling pathway [59].

5) Peroxisome proliferator activated receptor α

PPARα is expressed in tissues with high oxidative rates such as muscle, heart, and liver. Upon activation by ligand binding, PPARα induces the expression of genes involved in metabolism of fatty acids and lipoproteins as well as repressing the expression of genes involved in inflammatory reactions. Through these actions, PPARα contributes to improving steatosis, inflammation, and fibrosis in non-alcoholic fatty liver disease [60].

Phytol [61] and hederagenin (*Kalopanax pictus*-derived triterpenoid 5) [62] as PPARα agonists, dehydroabietic acid [63], farnesol, geranylgeraniol [64], caulophyllogenin (*K. pictus*-derived triterpenoid 4) [62] and 4-(2-hydroxypropan-2-yl)-1-methylcyclohex-3-ene-1,2-diol (*Asarum sieboldii*-derived phytochemical 7) [65] as PPARα/γ agonists and genistein [66], pseudolaric acid B [67], veratryl glycerol (*A. sieboldii*-derived phytochemical 10) and N-(2-methylpropyl)deca-2,4,8-trienamide (*A. sieboldii*-derived phytochemical 11) [65] were identified as PPARα/δ/γ agonists.

Phytol, a branched-carbon-chain alcohol and a component of chlorophylls, was confirmed to be a PPARα-specific agonist using a reporter gene assay and *in vitro* binding assay that measured the increase in binding of coactivator SRC-1 to GST-PPARα. Because phytol was confirmed to induce the expression of PPARα-target genes, it was suggested to have an ability to manage abnormalities in lipid metabolism [61]. Dehydroabietic acid, a PPARα/γ agonist, was found to markedly repress the production of proinflammatory mediators such as monocyte chemoattractant protein-1 (MCP-1), TNF-α, and nitric oxide (NO) in activated macrophages or macrophages co-cultured with adipocytes [63]. Isoprenols, farnesol, and geranylgeraniol were confirmed to be double PPARα/γ agonists using a reporter gene assay and was shown to increase the expression of several target genes of lipid metabolism in fat and liver cell lines [64]. These results suggested that dehydroabietic acid, farnesol, and geranylgeraniol are efficacious for the treatment of abnormalities of lipid metabolism associated with diabetes mellitus [63, 64]. Genistein, a PPARα/δ/γ agonist, was found to increase the expression of carnitine palmitoyltransferase 1 involved in fatty acid metabolism through the activation of PPARα and was suggested to be a possible hypolipidemic agent [66]. Pseudolaric acid B, a diterpenoid, was found to increase the activation of PPARα and the phospholipase C signaling pathway and to stimulate peroxisomal fatty acyl-CoA oxidase activity in a liver cell line. These effects of pseudolaric acid B were blocked by staurosporine, which suggests that the action of pseudolaric acid B on PPARα is mediated by a protein kinase C-dependent phosphorylation [67].

6) Peroxisome proliferator activated receptors γ

PPARγ has two isoforms, PPARγ1 and PPARγ2, which arise from differential splicing. PPARγ2 is expressed primarily in adipocytes, whereas PPARγ1 is expressed relatively highly in macrophages and large intestine epithelial and endothelial cells, but less in liver and muscle. PPARγ plays roles in: 1) primarily in the induction of differentiation of adipocytes; 2) in the regulation of lipid metabolism in mature adipocytes, including the promotion of expression of the genes involved in uptake of blood fatty acids such as lipoprotein lipase and fatty acid transport protein, promotion of expression of genes involved in the synthesis of triacylglyceride, such as glycerol kinase and phosphoenolpyruvate carboxykinase, and promotion of β-oxidation of fatty acids through the induction of expression of coactivator PGC-1α, which contributes to preventing hypertrophy of adipocytes; 3) in ameliorating insulin resistance by reducing the production of the insulin-resistance factor cortisol and reducing another insulin-resistance factor blood free fatty acids through promoting the uptake of free fatty acids into adipocytes; 4) in ameliorating atherosclerosis by preventing the conversion of macrophages to foam cells through promoting cholesterol removal, which results from PPARγ inducing the production of cholesterol transporter ABCA1 via LXR in spite of promoting the uptake of oxidized low-density lipoprotein; 5) in both preventing inflammatory reactions and ameliorating atherosclerosis by repressing the production of pro-inflammatory proteins such as iNOS, TNFα and matrix metalloproteinase 9 (MMP9) through inhibiting actions of the transcription factors NF-κB, activator protein 1 (AP-1), and signal transducer of activation (STAT); and 6) repressing carcinogenesis of most of cancers although promoting carcinogenesis of some cancers [68, 69].

The following phytochemicals were identified as PPARγ-specific agonists; 1,7-bis(4-hydroxyphenyl)hept-4-en-3-one (*Renealmia thyrsoidea* phytochemical 17), 1,7-bis(4-hydroxyphenyl)hept-4,6-dien-3-one (*R. thyrsoidea* phytochemical 18) [70], odoratin (*Chromolaena odorata* phytochemical 6) [71], (9S,13R)-12-oxo-phytodienoic acid (*C. odorata* phytochemical 1) [72], auraptene (7-geranyloxycoumarin) [73], resveratrol [74], methyl 2-cyano-3,11-dioxo-18β-olean-168,12-dien-30-oate (β-CDODA-Me), methyl 2-cyano-3,11-dioxo-18α-olean-1,12-dien-30-oate (α-CDODA-Me) [75], abscisic acid [76], ginsenoside 20(S)-protopanaxatriol [77], capsaicin [78], ajulemic acid (AJA) (synthetic derivative of tetrahydrocannabinol [THC]-11-oic acid, a metabolite of THC) [79], abietic acid [80], glycycoumarin, glycyrin, dehydroglyasperin C, dehydroglyasperin D [81], saurufuran A [82], dehydrotrametenolic acid [83], apigenin, chrysin, kaempferol [84], *A. sieboldii*-derived phytochemicals 1–3 & 6 [65], *Kalopanax pictus*-derived triterpenoids 2, 6, and 9 [62], cinnamic acid [85], tanshinone IIA, and cryptotanshinone [85]. As phytochemicals that promote the expression of PPARγ, curcumin [86] and gallic acid [87] were identified.

Chalcones, odoratin, and (9S,13R)-12-oxo-phytodienoic acid isolated from *C. odorata* [71, 72] and furanoditerpene, saurufuran A isolated from *Saururus chimenesis* [82] were shown to be PPARγ agonists. Diarylheptanoids, 1,7-bis(4-hydroxyphenyl)hept-4-en-3-one and 1,7-bis(4-hydroxyphenyl)hept-4,6-dien
-3-one isolated from *R. thyrsoidea* were shown to be PPARγ agonists and to induce the expression of CD36, Dectin-1 and mannose receptor in macrophages, which suggested that these phytochemicals have the ability to regulate immunological reactions [70]. Prenylflavonoids, glycycoumarin, glycyrin, dehydroglyasperin C, and dehydroglyasperin D isolated from *Glycyrrhiza uralensis* Fisher were shown to be PPARγ agonists using a GAL4-PPARγ chimera reporter gene assay [81]. 2-Cyano derivatives of triterpene, glycyrrhetinic acid, methyl 2-cyano-3, 11-dioxo-18β-olean-1, 12-dien-30-oate (β-CDODA-Me) and methyl 2-cyano-3, 11-dioxo-18α-olean-1, 12-dien-30-oate (α-CDODA-Me) isolated also from *G. uralensis* were found to be PPARγ agonists [75]. However, these compounds were shown using two-hybrid assay to exhibit different effects on the interaction of activated PPARγ with coactivators. Furthermore, β-CDODA-Me but not α-CDODA-Me induced the expression of caveolin-1, a proapoptotic protein in an SW480 colon cancer cell line, whereas both compounds induced the expression of caveolin-1 in HT-29 and HCT-15 colon cancer cell lines. Meanwhile, both isomers of CDODA-Me induced the expression of KLF-4, another proapoptotic protein in SW480 and HT-29 cells but had minimal effect on KLF-4 expression in HCT-15 cells. These isomers are the first PPARγ agonists that induce gene expression gene- and cell type-selectively [75]. Auraptene (7-geranyl-oxycoumarin), a PPARα/γ agonist that is abundant in citrus fruits, was shown to induce the expression of adiponectin but to repress the expression of MCP-1 in adipocytes. These effects were confirmed to be caused by PPARγ activation because they were abolished by a PPARγ antagonist. These results suggested that auraptene is efficacious for preventing lipid and glucose metabolism abnormalities [73]. Resveratrol, which is present in wines, was shown to have a PPARγ agonistic activity using a reporter gene assay. Resveratrol markedly inhibited extracellular matrix metalloproteinase inducer (EMMPRIN) expression and MMP9 activity, both of which were greatly up-regulated

during phorbol-12-myristate-13-acetate-induced macrophage differentiation from THP-1 monocytes. The effects were confirmed to result from the activation of PPARγ by resveratrol because they were abolished by a PPARγ agonist [74]. Abscisic acid, a sesquiterpene, was confirmed to have a PPARγ agonistic activity in 3T3-L1 pre-adipocytes, and the effect of abscisic acid on a diabetic model, *db/db* mice fed high-fat diets, was evaluated. Abscisic acid supplementation for 36 days at a dose of 100 mg/kg/day reduced fasting blood glucose levels, ameliorated glucose tolerance, and increased the expression of PPARγ and its target genes such as adiponectin, aP2, and CD36 in white adipose tissue, and, furthermore it significantly attenuated adipocyte hypertrophy, TNF-α expression, and macrophage infiltration in white adipose tissue. These results suggested that dietary abscisic acid could be used for the treatment of type II diabetes and obesity-related inflammation [76]. Ginsenoside 20S-protopanaxatriol (PPT), a triterpene, was ascertained to be a PPARγ agonist using a Gal4-PPARγ chimera reporter gene assay. PPT enhanced adipogenesis by increasing the expression of adipocyte-fatty acid binding protein (aP2), lipoprotein lipase (LPL), phosphoenolpyruvate carboxykinase (PEPCK) and, furthermore, increased the expression of glucose transporter 4 (GLUT4), which suggested that PPT could ameliorate insulin resistance associated with diabetes [77]. Capsaicin, a major ingredient of hot pepper, was found to be a PPARγ agonist using a GAL4-PPARγ chimera or full-length PPARγ reporter gene assay. Capsaicin inhibited markedly the production of TNFα, a pro-inflammatory cytokine, by LPS-stimulated RAW264.7 macrophages. This inhibition was confirmed to be mediated by PPARγ activation because it was abrogated by a specific PPARγ antagonist. The anti-inflammatory action of capsaicin was suggested to be mediated by PPARγ activation [78]. Capsaicin was also shown to induce apoptosis in HT-29 human colon cancer cells. Because capsaicin-induced apoptosis was abrogated by a specific PPARγ antagonist but not by an antagonist of the other capsaicin target, vanilloid receptor-1, capsaicin-induced apoptosis in HT-29 was ascertained to be mediated by PPARγ activation [88]. AJA, a synthetic derivative of THC, is a major active ingredient of marijuana and has potent analgesic and anti-inflammatory activities without the psychotropic action of THC. Unlike non-steroidal anti-inflammatory drugs, AJA is not ulcerogenic at therapeutic doses, making it a promising anti-inflammatory drug. AJA was revealed to be a PPARγ agonist by showing that AJA directly and specifically bound to PPARγ and increased the transcriptional activity of PPARγ at pharmacological concentrations. Furthermore, AJA was shown to inhibit interleukin-8 promoter activity in a PPARγ-dependent manner, suggesting that the anti-inflammatory activity of AJA results from the PPARγ activation [79]. Abietic acid, a terpenoid, was found to be a PPARγ agonist using a reporter gene assay and was also shown to induce the expression of PPARγ target genes in RAW264.7 macrophages or 3T3-L1 adipocytes. Abietic acid suppressed the protein expression of pro-inflammatory proteins TNFα and COX2 in LPS-stimulated macrophages. Because this effect resembled that of synthetic PPARγ agonists, thiazolidinediones, the anti-inflammatory effect of abietic acid was suggested to be mediated by PPARγ activation [80]. Dehydrotrametenolic acid, a triterpene isolated from *Poria cocos*, a traditional Chinese medicinal plant, was found to be a PPARγ agonist. Dehydrotrametenolic acid promoted adipocyte differentiation, reduced hyperglycemia in obese hyperglycemic *db/db* mice, a non-insulin-dependent diabetes mellitus model, and acted as an insulin sensitizer as indicated by the results of the glucose tolerance test [83]. Flavonoids apigenin, chrysin, and kaempferol were confirmed to be PPARγ agonists using a reporter gene assay. These flavonoids strongly inhibited promoter activity of inducible COX and iNOS genes in LPS-activated macrophages that contained PPARγ expression plasmids. These flavonoids exhibited weak ability to compete with the binding of a synthetic PPARγ agonist rosiglitazone to PPARγ in an *in vitro* binding assay. However, limited protease digestion of PPARγ suggested that the flavonoids produced a change in conformation of PPARγ different from that produced by rosiglitazone. These three flavonoids were speculated to act as allosteric effectors that bound to a site in PPARγ different from that bound by rosiglitazone [84]. Curcumin, a diarylheptanoid derived from *Curcuma longa* was found to increase the expression of PPARγ. Protective effects of curcumin against sepsis were was evaluated using a cecal ligation and puncture (CLP) male SD rat model. Intravenous administration of curcumin attenuated tissue injury, reduced mortality, and decreased the expression of TNFα in septic rats. Furthermore, the administration of curcumin markedly improved the down-regulation of PPARγ in the liver after CLP. Meanwhile, concurrent administration of curcumin and a specific PPARγ antagonist abolished the beneficial effect of curcumin. Curcumin also inhibited endotoxin-induced increases in TNFα expression and markedly up-regulated PPARγ expression in RAW264.7 macrophages. These results suggested that the beneficial effect of curcumin on sepsis is mediated by up-regulation of PPARγ [86]. Gallic acid isolated from *Punica granatum* flower was shown to enhance PPARγ mRNA and protein expression levels and increase PPARγ-dependent mRNA expression and activity of LPL in THP-1 human differentiated macrophage cells. Administration of a methanol extract of *P. granatum* flower inhibited the glucose loading-induced increase in plasma glucose levels, enhanced cardiac PPARγ mRNA expression, and restored the down-regulated cardiac GLUT4 mRNA in Zucker diabetic fatty rats, a genetic animal model for type 2 diabetes. These results suggested that the anti-diabetic action of *P. granatum* flower is mediated by the up-regulation of PPARγ by gallic acid [87].

Effect of phytochemicals on NR signaling networks

It has become apparent that NRs are not only responsible for individual specified physiological functions but also for the cooperative regulation of common physiological functions through cross-talk between them. This review focuses on the regulation of aquaporins (AQPs) and circadian rhythm as a typical example of NR signaling networks and summarizes recent studies on the effect of phytochemicals on NR signaling networks.

(1) NR signaling networks in the regulation of aquaporins

AQPs are transmembrane proteins responsible for the transport of water molecules. The human AQPs superfamily consists of 13 members, which are classified into three subtypes. The first subtype called classical AQPs includes AQP0, AQP1, AQP2, AQP4, and AQP5, which are water-selective channels and transport water molecules only. The second subtype includes AQP3, AQP7, AQP9, and AQP10, termed aquaglyceroporins, which are permeated by small uncharged molecules such as glycerol and urea in addition to water. The third subtype called unorthodox AQPs includes AQP6, AQP8, AQP11, and AQP12 whose functions are still unknown. AQPs are membrane-bound proteins consisting of

250–290 amino acid residues and share a structure with 6 α-helical transmembrane spanning domains, 5 loop domains, and N- and C-terminal ends both in the cytoplasm. AQPs form a functional tetramer whereas water molecules cross through a water pore formed within each AQP protein. Osmotic pressure differential between the two sides of the membrane drives water molecules to traverse the membrane, and water molecules are able to move through the pore in both directions [89]. The most important mechanism to regulate the water content of the body is the excretion of urine from the kidney. Many AQPs (AQP1, 2, 3, 4, 6, 7, 8, and 11) are expressed in the kidney. Among these AQPs, AQP2 is the most responsible for water reabsorption in the renal collecting ducts, which is the major mechanism of determining urine volume. The anti-diuretic hormone vasopressin, which is released from the pituitary in response to increased plasma osmolarity and decreased blood volume, binds to the V2 receptor located in the basolateral membrane of principal cells of the collecting ducts and triggers the classical cAMP-PKA signaling pathway, which acutely increases the phosphorylation of AQP2 and chronically upregulates AQP2 gene transcription. The phosphorylation of AQP2 induces apical membrane insertion of AQP2 and increases the water permeability of AQP2, promoting water reabsorption together with up-regulation of AQP2 [90].

It has become evident that NRs are responsible for the regulation of water and sodium ion homeostasis and are involved in the regulation of AQP2 gene transcription. The NRs involved in the above-mentioned regulation were reported to be PPARγ, GR, MR (aldosterone receptor), FXR, LXRβ, and ERα [89]. Thiazolidinediones, PPARγ agonists, have been known to exert serious adverse effects, including water retention, edema, and congestive heart failure. These adverse effects were clarified to be due to the enhancement of water reabsorption in kidney collecting ducts and its mechanism was shown by several research groups to involve PPARγ activated by thiazolidinediones promoting AQP2 gene transcription, then, AQP2 products move to the apical membrane and enhance water reabsorpton. GR activated by glucocorticoids was shown to enhance water reabsorption by promoting the expression and localization of AQP2 to the apical membrane in collecting ducts. FXR is expressed in the kidney in addition to the liver and intestine, and it was also shown to be involved in water reabsorption by promoting AQP2 transcription. In contrast, an LXR non-selective agonist was shown to inhibit water reabsorption by repressing the expression of AQP2 through repressed expression of the prorenin receptor in the kidney. ERα is expressed in kidney collecting ducts, and estradiol-activated ERα was shown to repress the expression of AQP2 and consequently block the action of vasopressin. There are contradictory reports on the activity of MR toward AQPs, which were speculated to result from time-dependent changes in the effect of MR. Aldosterone was shown to reduce AQP2 mRNA and protein levels when administrated with arginine vasopressin (AVP) for a short time (≤24 h), whereas aldosterone incubation for 48 h was shown to increase AQP2 protein expression by increasing AQP2 mRNA translation.

In summary, expression of AQP2 responsible for water reabsorption in the kidney collecting ducts is regulated by several NRs, including PPARα, GR, and FXR that promote the expression of AQP2, whereas LXRβ and ERα repress AQP2 expression, and regulation of AQP2 expression by MR changes in a condition-dependent manner. These NRs contribute cooperatively to maintain the homeostasis of body fluid volumes and osmolarity [91].

Kampo medicines, which are mainly composed of phytochemicals, include prescriptions as hydrostatic modulators to regulate the excretion of body fluids and to treat water poisoning: regulatory disorder of water metabolism. The pharmacological characteristics of hydrostatic modulators seems to overlap with those of medicines acting on AQPs. Actually, Goreisan and its ingredient herb Sojutsu (*Atractylodes lancea*) was found to exert inhibitory activity against AQP3, AQP4, and AQP5, and another herb Keigai (*Schizonepeta tenuifolia*) to exert inhibitory activity against AQP3 [92]. Studies on the activity of herb component phytochemicals against AQPs have made progress lately. 1) Bacopaside I, a triterpene saponin derived from *Bacopa monnieri*, was shown to inhibit the activity of AQP1 through binding to the intracellular loop D region [93]. 2) Spilanthol, a fatty acid amide derived from *Acmella oleracea*, was clarified to exhibit a diuretic effect by inhibiting vasopressin-induced AQP2 expression through a mechanism involving increases in intracellular $[Ca^{2+}]$ [94]. 3) Tannins derived from Rhubarb was elucidated to exhibit antidiarrhoeal effects by inhibiting AQP2 and AQP3 expression in apical and lateral mucosal epithelial cells in the colons of diarrhea mice through down-regulation of the PKA/p-CREB signaling pathway [95]. 4) Curcumin, was shown to reduce neuroinflammation and neurological injury in a brain edema animal model, reduce cerebral edema in a traumatic brain injury model, and improve motor dysfunction and attenuate spinal cord edema in a spinal cord injury model through downregulating AQP4 expression. In contrast, curcumin was shown to worsen brain atrophy and increase the edematous cell size through increasing AQP4 expression in a lupus erythematosus model. The protective effect of curcumin against spinal cord injury was elucidated to result from curcumin inhibition of the Janus kinase/STAT signaling pathway, which is activated during spinal cord injury [96]. 5) Epigallocatechin, a member of cathechin family, was clarified to reduce spinal cord edema by down-regulating AQP4 expression that was elevated in a spinal cord injury model [96]. 6) Pinocembrin, one of the most abundant flavonoids in propolis, was indicated to protect the brain from ischemia injury partly by inhibiting AQP4 expression [96]. 7) Quercetin, a flavonol, and hesperetin, a flavanone glycoside, were shown to prevent retinal edema by inhibiting AQP4 expression in Mueller cell end-feet and the perivascular space in a diabetic retinopathy model [96]. 8) Resveratrol, a stilbenoid, was clarified to inhibit the proliferation of epidermal keratinocytes by reducing AQP3 expression. The reduction in AQP3 expression by resveratrol was suggested to be caused by the inhibition of ERK phosphorylation via increased SIRT1 and AH receptor expression [96]. 9) Chrysin, a flavonoid, was clarified to prevent skin dehydration by exerting a protective effect on AQP3 downregulation induced by ultraviolet light [96]. The action mechanism of phytochemicals that affect AQPs remains largely unclear. However, there is some possibility that these phytochemicals regulate AQP expression through modulating the activity of NRs, because some NRs were revealed to play a role in regulating AQP2 expression and, furthermore, the phytochemicals regulating AQP expression overlapped with those affecting the activity of NRs. Further studies are required to conclude this issue.

(2) NR signaling networks in the regulation of circadian rhythm

Circadian rhythm control is defined as maintaining homeostasis dynamically by aligning internal physiology with the 24-h rotation of the earth. Circadian rhythms are controlled by a central clock located in the suprachiasmatic nucleus of the hypothalamus and peripheral clocks residing in most tissues of the body. Peripheral clocks are synchronized by neural and humoral signals from the central clock. The central clock is entrained directly by light whereas the peripheral clocks are entrained by other external cues such as feeding and ambient temperature in addition to synchronizing cues from the central clock. The framework of the molecular mechanism of circadian oscillators has been elucidated, and NRs were found to play a pivotal role in circadian oscillators (Fig.3A). Both the central and peripheral clocks consist of two interlocked feedback loops. In the primary negative feedback loop, BMAL1/CLOCK heterodimers activate the transcription of period (PER) and cryptochrome (CRY) genes by recognizing E-box cis elements in their promoters. The PER/CRY complex in turn inhibits the transcription of their own genes by blocking BMAL1/CLOCK activity. The second feedback loop involves ROR and REV-ERB, which recognize similar cis-regulatory elements (ROREs) in target genes. ROR acts as a transcriptional activator, and REV-ERB as a repressor. BMAL1/CLOCK binds to E-box elements present in Ror and Rev-erb genes and activate their transcription. ROR and REV-ERB in turn drive rhythmic transcription of the Bmal1 gene by alternately binding to RORE in its promoter. The second feedback loop was found to make an oscillator robust and tunable [97]. In peripheral clocks, NRs such as REV-ERBα, RORα, GR, TR (thyroid hormone receptor), ER, PPARα, PPARγ, RAR, RXR, HNF4α, LXR, and FXR play dual roles in transferring signals of circadian rhythm entrainers to core peripheral clocks and transferring circadian rhythms from the core peripheral clocks to their target genes (Fig. 3B). For example, glucocorticoid, thyroid hormones (T3, T4), ATRA, 9-cis retinoic acid, oleylethanolamide, and 15-deoxy-delta-12, 14-prostaglandin J2 are circadian rhythm entrainers and transfer circadian rhythms to core peripheral clocks through rhythmically activating their receptors, namely GR, TR, RAR, RXR, PPARα, and PPARγ, respectively. Conversely, because transcription of the PPARα gene is directly regulated by BMAL1/CLOCK, the circadian rhythm produced by the core peripheral clock is transferred to target genes of PPARα.

Thus, NRs contribute to harmonizing the peripheral circadian clocks with a diverse array of physiological processes such as metabolism, immune responses, central nervous system functions, growth and differentiation, and reproduction in peripheral tissues. NRs appear to integrate the control of multiple physiologic processes through crosstalk between each other, and responding to circadian rhythm entrainers such as feeding cycles [98]. Disorders of circadian rhythms are known to provoke diseases such as neuropsychiatric, metabolic, cardiovascular, and immune/inflammatory diseases, and even cancers. Phytochemicals affecting NRs are expected to ameliorate circadian rhythm-related diseases by controlling circadian rhythms via modulation of NRs.

Studies on phytochemicals affecting circadian rhythms are only just beginning, but this review briefly summarizes a few studies on phytochemicals and a PPARα agonist, a synthetic hypolipidemic agent, which affect circadian rhythms. 1) Administration of proanthocyanidins, flavonoids, to obese rats was found to normalize the acrophase of circadian rhythms of clock genes (CLOCK, BMAL1, CRY, PER2, RORα, and REV-ERBα) in obese rat livers. Proanthocyanidins were also shown to modulate the amplitude of circadian rhythms of clock genes and to affect BMAL1 expression most-strongly among clock genes. The increase in BMAL1 expression by administration of proanthocyanidins was suggested to result from the activation of RORα transcriptional activity [99, 100]. 2) Administration of resveratrol to obese mice fed a high-fat diet was shown to significantly decrease body weight, and ameliorate the rhythmicity of plasma leptin, lipid profiles, and whole body metabolic status, such as the respiratory exchange ratio. Resveratrol was also shown to modify the rhythmic expression of clock genes (Clock, Bmal1 and Per2) and clock-controlled lipid metabolism-related genes (Sirt1, Pparα, Srebp1c, Acc1, and Fas). Furthermore, the response pattern of mRNA expression of Acc1 was similar to that of the plasma triglyceride level. These results suggested that resveratrol reduces lipogenesis and normalizes the rhythmic expression of plasma lipids via its action on clock machinery [101]. 3) Administration of epigallocatechin to obese mice fed a high-fat and high-fructose diet (HFFD) was shown to normalize a diet-dependent decline in the amplitude of the circadian rhythm, and this normalization was suggested to be caused by influencing the Sirt1-PGC1α loop. Epigallocatechin was suggested to ameliorate diet-induced metabolic misalignment such as increased fatty acid synthesis, decreased β-oxidation in the liver, and adipocyte hypertrophy by regulating the rhythmic expression of the circadian clock genes in the liver and adipocytes [102]. 4) Administration of bezafibrate, a PPARα agonist used as a hypolipidemic agent, was found to phase-advance circadian locomotor activity of mice as well as the circadian expression of clock genes such as period2, BMAL1, and Rev-erbα in various tissues (cortex, liver, and adipocytes). Furthermore, bezafibrate was shown to phase-advance the activity phase that is delayed in model mice with delayed sleep phase syndrome caused by a Clock gene mutation. These results suggested that PPARα could be a potent target of drugs to treat circadian rhythm sleep disorders including delayed sleep phase syndrome [103]. Because phytochemicals with PPARα agonistic activity are known as described previously, the results with bezafibrate raised our interest in whether these phytochemicals affect circadian rhythms and whether there are any differences in the effect on circadian rhythms between bezafibrate and these phytochemicals.

Conclusion

Recent studies have revealed not only that there are some phytochemicals capable of modulating multiple NRs but also that NRs play their physiological roles in co-operation with other NRs through crosstalk between them as well as doing independently. Hence, further efforts are needed to clarify the entire picture of the pharmacological activities of phytochemicals against NRs. Studies on the pharmacological activity of phytochemicals against NRs are expected to contribute to 1) developing phytochemicals for use in drugs or functional food materials, 2) elucidating the action mechanisms of Kampo formulations that contain multiple phytochemicals, and 3) exploring chemical seeds of small molecule drugs.

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