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Review Article

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Potential Cancer Chemopreventive Compound Citrus Auraptene

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Abstract: Auraptene is the most abundant prenyloxycoumarin. It has been isolated from plants belonging to many genus of the *Rutaceae* family, comprising several edible fruits and vegetables. Although known for a long time, only in the last decade has auraptene been seen to exert valuable pharmacological effects as an orally active cancer chemopreventive, anti-bacterial, anti-protozoal, anti-fungal, anti-inflammatory and anti-oxidant agent. This review aims to summarize the biological activities, including its cancer chemopreventive ability, and the mechanism of action underlying the observed pharmacological activities of this chemical.

Keywords: Cancer chemoprevention; Anti-inflammatory activity; Citrus fruits; Auraptene; Prenyloxycoumarins

Abbreviations used are: *AOM, azoxymethane; ARE, antioxidant response element; AUR, auraptene; BrdU, 5-bromodeoxyuridine; CD, β-cyclodextrin; COX, cyclooxygenase; DMBA, 7,12-dimethylbenz[a]anthracene; DEN, N,N-diethylnitrosamine; DSS, dextran sodium sulphate; EAF, enzyme-altered foci; EBV, Epstein-Barr virus; ER, endoplasmic reticulum; GST, glutathione-S-transferase; GST-P, placental for of glutathione-S-transferase; IFN, interferon; IGF, insulin like growth factor; IL, interleukin; LPS, lipopolysaccharide; MCP, monocyte chemoattractant protein; MMP, metalloproteinase; MNU, N-methyl nitrosourea; mTOR, mammalian target of rapamycin; NMBA, N-nitrosomethylbenzylamine; iNOS, inducible nitric oxide synthase; NQO1, NADPH quinone oxidoreductase; 4-NQO, 4-nitroquinoline 1-oxide; Nrf2, nuclear factor-erythroid-2-related factor-2; ODC, ornithine decarboxylase; PCNA, proliferating cell nuclear antigen; PG, prostaglandin; PPARs, peroxisome proliferator-activated receptors; QR quinonereductase; ROS, reactive oxygen species; TGF, transforming growth factor; TNF, tumor*

necrosis factor; TPA, 12-O-tetradecanoylphorbol-13-acetate; TRAP, transgenic rat for adenocarcinoma of prostate.

1. INTRODUCTION

Malignant neoplasms originated from either epithelial or non-epithelial cells are one of the largest health threats to human, claiming millions of lives each year. If malignancies can be detected in their eaqrly stage, surgical removal may be applicable as an efficacious therapy. However, many patients with malignancy still need additional treatments, including radiotherapy and/or chemotherapy with or without undesirable adverse effects. Cancer chemoprevention is an ideal and appropriate strategy against cancer development [1, 2]. Cancer chemoprevention is based on a number of experimental and epidemiological evidence that our environment could contain not only carcinogenic compounds but also natural or synthetic substances able to inhibit or reverse the process of carcinogenesis [3-5].

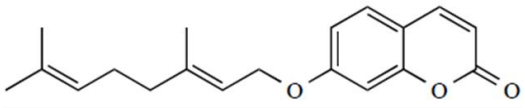
Coumarins represent a large class of natural compounds typically found in the families of Rutaceae, *Apiaceae*, and *Compositae*. Although more than 1,300 natural coumarins have been identified to date [6], most chemical and pharmacological studies were conducted on coumarin itself or structurally simple derivatives. Coumarins can be classified into three groups: i) substituted coumarin, ii) ring-fused coumarins and iii) *C*- and *O*-prenylcoumarins. In particular, the third group comprises compounds in which a terpenyl side chain is attached to the benzopyrone ring via a C-C or a C-O bond respectively. While prenylcoumarins have been well-studied both from a chemical and a pharmacological point of view, prenyloxycoumarins, considered for decades merely as biosynthetic intermediates of linear-, furano- and pyranocoumarins, have only in the last decade been characterized as secondary metabolites exerting valuable biological activities [6].

The most abundant prenyloxycoumarin found in nature is 7-geranyloxycoumarin, best known as auraptene (AUR) (**Figure 1a**). This natural compound is well-characterized for its interesting and valuable pharmacological properties, in particular with regard to the prevention of degenerative diseases. The main natural sources of the title prenyloxycoumarin and its pharmacokinetic profile were recently reviewed by Epifano and his coworkers [7]. It is interesting to note that the richest plants in AUR comprise several edible plants from the genus Citrus, like grapefruits, lemons, oranges, etc.

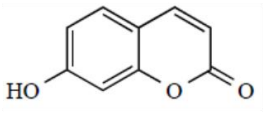
The aim of this article is to examine in detail the in so far reported biological activities ascribed to AUR and what is known about the mechanism of action underlying the observed effects of this secondary metabolite by means providing of a survey of the current literature in which AUR has been reported to be an inhibitor of key biological targets, such as metalloproteinases (MMPs) [8-10], glycoprotein P [11, 12], peroxisome proliferator-activated receptors (PPARs) [13-15] and several others [16, 17].

2. Cancer chemopreventive activity

Although AUR has been identified for eighty years, the first report concerning its anti-cancer activity was published in the literature in only 1997 by Murakami and co-workers [18]. In that study, AUR and its parent compound, umbelliferone (**Figure 1b)** were tested as to whether they act as inhibitors of the tumor



(a)



(b)

Figure 1. Chemical structures of (a) auraptene ($C_{19}H_{22}O_3$) and (b) umbelliferone ($C_9H_6O_3$).

promoter 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced Epstein-Barr virus (EBV) activation in Raji cells, which were lymphoblast-like cells established from Burkitt's lymphoma. The authors found that AUR (IC_{50} = 18.0 μM) was equal in potency to the known inhibitor of TPA-induced EBV activation, genistein [19]. Umbelliferone, which lacks the geranyloxyl group, was by far less active (IC_{50} = 450 μM), suggesting that the *O*-side chain has a key role in targeting a specific, although possibly unknown receptor(s), on the surface of the cell membrane or inside the cell.

2. 1 Skin carcinogenesis

In 1997, Murakami et al. [18] conducted a two-stage mouse skin carcinogenesis experiment to investigate the anti-promoter activity of AUR. ICR mice were topically administered a carcinogen, 7,12-dimethylbenz[*a*]anthracene (DMBA) (0.19 μmol) and then a tumor-promote, TPA (1.6 nmol), was painted on their skin. The application of AUR at a dose of 160 nmol significantly decreased the incidence of skin tumors and number of tumors/mouse by 27% and 23%, respectively. AUR at a concentration of 50 μM also strongly suppressed reactive oxygen species (ROS) generation induced by TPA (100 nM) in differentiated human promyelocytic HL-60 cells. Such protective effects resulted in extensive prevention of DNA H_2O_2 or superoxide anion-induced damage when applied at concentrations over 25 μM [20]. The data showing that AUR exerted an anti-genotoxic effect greater than that of ascorbic acid led to the hypothesis that AUR has specific targets among ROS-detoxifying enzymes inside cells.

2. 2 Digestive tract carcinogenesis

Several studies regarding the capacity of AUR to act as an orally active cancer chemopreventive agent were conducted by our research group [21]. In 1998, we investigated the modifying effects of dietary AUR at dose levels of 100 ppm and 500 ppm during the initiation and post-initiation phases of 4-nitroquinoline 1-oxide (4-NQO)-induced tongue carcinogenesis in male F344 rats. The incidence of tongue lesions (neoplasms and preneoplasms), polyamine levels in the tongue tissue and cell proliferation activity estimated according to the 5-bromodeoxyuridine (BrdU)-labelling index were determined and compared among the experimental groups of animals. In addition, the activities of glutathione-*S*-transferase (GST) and quinone reductase (QR) in the liver and tongue of rats administered at different doses of AUR (0, 200, 400 and 800 mg/kg body weight) in their diet for five days were assessed. Feeding with AUR at 100 and

500 ppm during the initiation phase led to a significant decrease in the frequency of tongue squamous cell carcinoma (100 ppm: 91% reduction and 500 ppm: 63% reduction). When AUR was administered after 4-NQO exposure, the frequency of tongue squamous cell carcinoma was also decreased (100 ppm: 100% inhibition and 500 ppm: 74% inhibition). The incidence of tongue preneoplasia (severe dysplasia) in the groups that received 4-NQO and AUR was significantly smaller than that seen in the control group. Feeding with 500 ppm AUR alone did not cause any pathological alterations in the levels of toxic signs in the rats. The dietary administration of AUR at 100 ppm and 500 ppm significantly decreased the BrdU-labelling index and total polyamine concentrations in the oral mucosa and greatly increased the activities of GST and QR in the liver and tongue. These data indicate that AUR is effective in inhibiting of the development of tongue neoplasms and preneoplasms induced by 4-NQO. The suppression caused by AUR feeding during the initiation phase of carcinogenesis may be related to the increase in the activities of phase II enzymes, such as GST and QR, in the liver and in tongue. The inhibition induced by dietary AUR during the post-initiation stage of carcinogenesis may be related to the suppression of increased cell proliferation caused by 4-NQO in the mucosa of the oral cavity.

Similar results were obtained when the effect of dietary feeding with AUR was investigated in 1998 using a rat model of chemically induced large bowel carcinogenesis initiated by azoxymethane (AOM) [22]. Male F344 rats received diets containing 100 or 500 ppm AUR for four weeks starting one week before the first dosing of AOM. At the end of the study, after 38 weeks, the dietary administration of AUR was shown to exert a dose-dependent inhibition of AOM-induced large bowel carcinogenesis. Feeding during the initiation phase reduced the incidence of colorectal adenocarcinoma by 49% at 100 ppm and 65% at 500 ppm. AUR administration during the post-initiation phase inhibited the incidence of colorectal adenocarcinoma by 58% at 100 ppm and 65% at 500 ppm. Moreover, the degree of multiplicity of colorectal carcinoma was significantly reduced by initiation feeding with AUR at a dose level of 500 ppm and post-initiation feeding with AUR at dose levels of 100 and 500 ppm. AUR feeding also suppressed the expression of biomarkers of cell proliferation, such as the ornithine decarboxylase (ODC) activity and total polyamine content in the colonic mucosa, and reduced the chemical degradation of biomolecules resulting from lipid peroxidation, namely malondialdehyde and 4-hydroxy-2(E)-nonenal. Additionally, as noted in a previous study, AUR increased the GST and QR activities in the liver and colorectal region.

In 2000, the effect of dietary AUR on *N*-nitrosomethylbenzylamine (NMBA)-induced esophageal tumorigenesis was evaluated in male F344 rats [23]. The animals received 15 subcutaneous injections of NMBA (0.5 mg/kg, 3 times per week) for five weeks. At the end of the study (week 29), 75% of the rats treated with NMBA alone developed esophageal neoplasms (squamous cell papilloma), while the rats that received AUR 500 ppm during the initiation phase showed a reduced incidence (39%) of tumors. Dietary exposure to AUR during the post-initiation phase also decreased the frequency of esophageal tumors by 29%. Moreover, the cell proliferation activity in the esophageal squamous epithelium, estimated by counting the number of proliferating cell nuclear antigen (PCNA)-positive squamous cells, was lowered by AUR feeding. The tissue polyamine content in the animals that received NMBA and AUR was also lower than that observed in the rats that received the carcinogen, NMBA.

In 2004, the same scientific research group investigated the effect of AUR on *N*,*N*-diethylnitrosamine (DEN)-induced rat hepatocarcinogenesis in male F344 rats in order to determine the

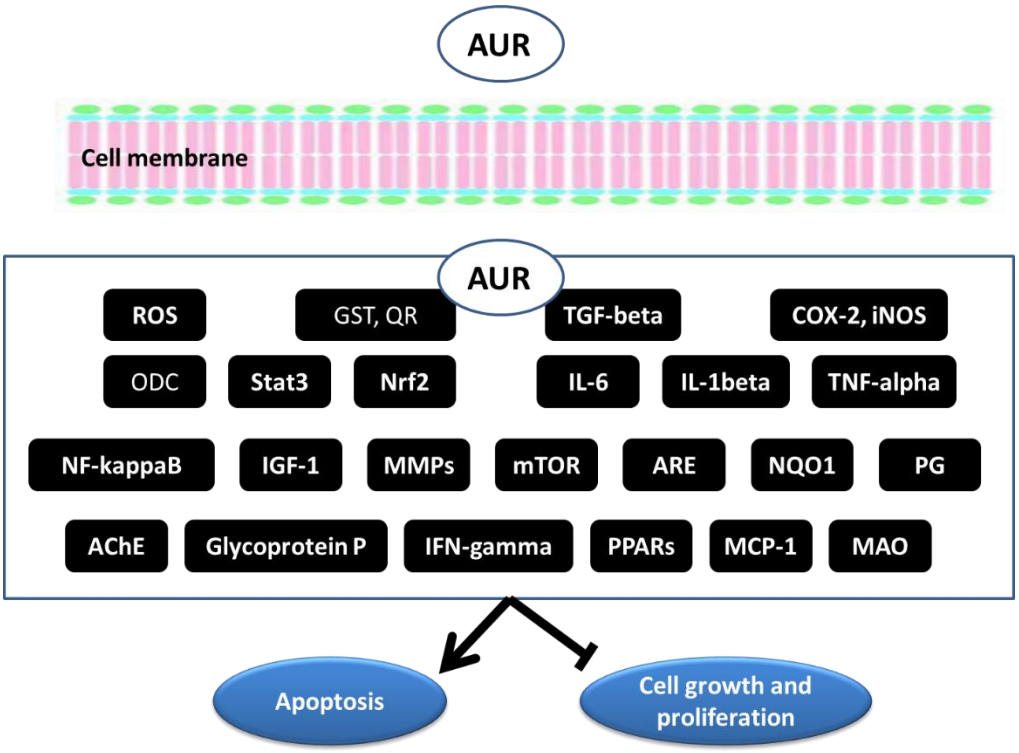


Figure 2. Molecular targets of auraptene.

inhibitory effects of AUR on the development of hepatocellular carcinoma [24]. In the first experiment, the animals were fed diets containing AUR at two dose levels (100 and 500 ppm) for seven weeks: one week before, during and one week after the initial step of liver carcinogenesis induced by DEN (40 ppm in drinking water). The number of hepatocellular enzyme-altered foci (EAF) per unit area (cm^2) was detected based on immunohistochemical staining of the placental form of GST (GST-P) and transforming growth factor (TGF)-α in the sections. In the second experiment, animals undergoing to DEN treatment were fed AUR-containing diets at dose levels of 100 and 500 ppm during either the initiation or post-initiation phase of DEN-induced hepatocarcinogenesis. In the first experiment, feeding with AUR at both doses decreased the mean number of GST-P- and TGF-α-positive EAF/cm^2. In the second experiment, initiation feeding with 500 ppm AUR significantly inhibited the incidence (33% vs. 83%) and multiplicity (0.67 - 1.09 vs. 1.96 - 1.85) of liver cell carcinoma. Moreover, post-initiation feeding with AUR at both doses significantly decreased the rate of development of hepatocellular carcinoma (100 ppm AUR: 15% incidence, 0.25 - 0.64 multiplicity; and 500 ppm AUR: 11% incidence, 0.26 - 0.81 multiplicity) and the dietary administration of AUR reduced cell proliferation and increased the apoptotic index in the liver cell neoplasms.

In 2006, our research group studied the effect of AUR on AOM and dextran sodium sulphate (DSS)-induced colon carcinogenesis in mice [25]. Experimental diets containing AUR at two dose levels (0.01% and 0.05%) were fed for 17 weeks to male CD-1 (ICR) mice treated with a single intraperitoneal injection of AOM (10 mg/kg body weight) and promoted by 1% (w/v) DSS in drinking water. The tumor inhibitory effects were assessed after 20 weeks by recording the incidence and multiplicity of colonic neoplasms and assessing the PCNA-labeling index, apoptotic index and the immunohistochemical expression of

cyclooxygenase (COX)-2, inducible nitric oxide (iNOS) and nitrotyrosine in colorectal adenocarcinoma tissues. Feeding with AUR, at both doses, significantly inhibited the occurrence and multiplicity of colorectal adenocarcinoma by 42.6% and 68.5% for AUR 0.01% and 0.05% respectively. In addition, feeding with AUR significantly lowered the positive rates of PCNA, COX-2, iNOS and nitrotyrosine in the adenocarcinomas and increased the apoptotic index in the colonic malignancies. Our group recently reported the colon cancer strong chemopreventive effects of AUR, which was included in β-cyclodextrin (CD), with oral administration [26]. Using the chemically-induced colorectal carcinogenesis model (AOM-DSS model), the complex AUR-CD decreased the incidence of both benign (adenoma) and malignant (adenocarcinoma) types of colonic neoplasms by 10% (100 ppm AUR-CD) and 39% (100 ppm AUR-CD), respectively, in comparison to the control group. Moreover, dietary AUR favorably modulated the expression of several pro-inflammatory cytokines, all induced in adenocarcinomas, such as tumor necrosis factor (TNF)-α, NF-κB, Stat3, nuclear factor-erythroid-2-related factor-2 (Nrf2), IL-6 and IL-1β.

2.3 Carcinogenesis in the lung, prostate and breast

In 1999, our research group investigated the effect of AUR on lung metastasis of B16BL6 murine melanoma [27]. In that study, male C57BL/6 mice were fed a basal diet supplemented with AUR at dose levels of 250, 500 or 1,000 ppm, two weeks before and after the intravenous injection of $1x10^5$ viable melanoma cells. At the end of the study (week 4), the incidence and apoptotic indices of lung metastatic tumors were recorded. The mean number of metastatic lung tumors was significantly lower in the mice fed AUR (500 and 1000 ppm) than in the controls. Additionally, apoptotic indices in the mice fed the diets mixed with AUR (500 and 1000 ppm) were significantly greater than those noted in the control group.

Another study showed that AUR also exerts effects as a dietary cancer chemopreventive agent against prostate adenocarcinoma [28]. The influence of AUR on prostate carcinogenesis was investigated using transgenic rats, who developed adenocarcinoma of the prostate (TRAP) bearing the SV40 T antigen transgene under control of the probasin promoter and human prostate cancer cells. Starting at 5 weeks of age, male TRAP rats received a powder diet containing 500 ppm AUR or the basal diet for 15 weeks. Since all animals developed prostate carcinomas, the tumor cells were semiquantitatively measured and expressed as the relative proportion of prostate epithelial cells. Feeding with AUR effectively reduced the epithelial component ($P<0.05$) and high-grade lesions ($P<0.05$) in the lateral prostate. A subsequent experiment demonstrated that the growth of androgen-sensitive LNCaP and androgen-insensitive DU145 and PC3 human prostate cancer cell lines was slightly suppressed by AUR with a significant increase in apoptosis.

Studying the effects of AUR on breast cancer prevention by AUR, Kleiner-Hancock et al. investigated the effect of this prenyloxycoumarin *in vitro* on the cell proliferation of MCF-7 and MDA-MB-231 human breast carcinoma cell lines [29]. The authors also investigated the dietary effects of AUR on the tumor incidence, multiplicity an

d latency *in vivo* in the *N*-methyl nitrosourea (MNU)-induced mammary carcinogenesis model in female Sprague-Dawley rats [29] and further determined the expression of cyclin Dl in MCF-7 cells [29]. AUR suppressed MDA-MB-231 cell proliferation by 50% at 12 μM and up to 85% at 25 μM. Meanwhile, the effect of AUR on MCF-7 cells was not as high as that observed in the MDA-MB-231 cells, although a significant decrease in MCF-7 cell proliferation was recorded at doses ranging between 20 and 50 μM (26-49%). AUR (500 ppm) significantly delayed the median time to tumor development by 39 days compared to that seen in the MNU-treated group of animals. Finally, AUR (10 μM) decreased the insulin like growth factor (IGF)-1 (10 ng/mL)-induced cyclin Dl expression by 40% in MCF-7 cells and *in vivo* by 49%,

compared to that observed in the group treated with MNU alone.

3. Mechanism of action by which AUR exerts cancer chemopreventive effects

Potential mechanisms by which AUR exerts its cancer chemopreventive action are illustrated in **Figure 2**.

3.1 Cytotoxicity

In 2007, Jun et al. [30] investigated the cytotoxic effects of AUR on Jurkat T cells. Cell viability was seen to rapidly decline after the treatment with AUR to 92% (10 μg/mL), 62% (15 μg/mL) and 35% (20 μg/mL), resulting in an IC_{50} of 16.5 μg/mL. AUR induced apoptotic DNA fragmentation of Jurkat T cells. After treatment of the Jurkat T cells with AUR, the endoplasmic reticulum (ER) stress-mediated activation of pro-apoptotic enzymes, caspase-12 and caspase-8, followed by a series of events ending with DNA fragmentation, was induced in a dose-dependent manner. The application of a series of antibodies and enzyme inhibitors of biological targets involved at different levels in the caspase cascade did not block the cytotoxicity of AUR. Taken together, these data suggest that the toxicity of AUR towards Jurkat T cells is due to the ER-stress-mediated activation of caspase 8 and the subsequent induction of mitochondria-dependent or -independent activation of the caspase cascade.

3.2 Suppression of MMPs expression

Kawabata et al. [8, 9] studied the relationship between AUR and MMPs, in particular MMP-2, MMP-7 (matrilysin) and MMP-9. These enzymes are known to be key targets in cancer therapy. The effects of AUR on the expression of MMP-2, -7 and -9 were investigated in the colonic mucosa of mice that received DSS to induce ulcerative colitis. As a result, AUR strongly inhibited the production of proMMP-7 proteins without affecting the mRNA expression. As rapamycin, an inhibitor of mammalian target of rapamycin (mTOR), a Ser-Thr kinase regulating protein translation signaling, showed similar results, AUR may suppress mTOR-dependent proMMP-7 translation. Moreover, AUR suppressed the DSS-induced gelatinolytic activity of MMP-7 as well as the expression of MMP-2 and MMP-9. AUR could prevent the adherence of P. gingivalis to oral epithelial cells, dose-dependently reduced the secretion of cytokines (IL-8 and TNF-α) and MMP-8 and MMP-9 by lipopolysaccharide (LPS)-stimulated macrophages, and inhibited MMP-9 activity [10].

3. 3 Effects of β-catenin expression and glycoprotein P

Dietary feeding with AUR was recently reported to inhibit β-catenin mutation in DEN-induced hepatocellular carcinoma in rats [31]. AUR also increases the intracellular accumulation of known anti-cancer drugs, such as daunorubicin, by inhibiting glycoprotein P [12].

3. 4 Modification of xenobiotic metabolizing enzymes

The modulation of xenobiotic metabolizing enzymes, such as cytochrome P450 and GST, is a main factor contributing to favorable cancer chemoprevention. When administered orally to C57BL/6 mice at a dose of 100 mg/kg, AUR induces the GST activity in the liver [32]. In order to investigate the mechanism of action underlying this activation, Kleiner et al. studied whether Nrf2, a cytoplasmic sensor system for enzyme induction by electrophiles and oxidants [33], and the antioxidant response element (ARE) may be involved [34]. AUR enhanced the activation of ARE in HepG2 cells up to 30%. Subsequently, using $Nrf2^{+/-}$ and $Nrf2^{-/-}$ mice, prenyloxycoumarin selectively increased the activity of cytosolic liver GST in the range of 121 - 145%, although it did not affect NADPH quinine oxidoreductase (NQO1). Based on these findings,

Kleiner's group hypothesized that the induction of liver cytosolic GST must be attributed to the AUR-promoted activation of the Nrf2/ARE mechanism.

3. 5 Anti-inflammatory effects

The first study describing the anti-inflammatory properties of AUR was reported by Murakami et al. [35]. AUR is a potent suppressor of TPA-induced ROS generation in differentiated human promyelocytes. Moreover, the authors examined the anti-inflammatory activities of AUR and its parent compound, umbelliferone, using a TPA-treated mouse skin model. Double pre-treatment of the animals with AUR suppressed to a large extent edema formation, H_2O_2 production, leukocyte infiltration and the number of PCNA-positive cells. Such inhibitory effects could be attributed to the selective blockade by AUR of the activation stage of the whole inflammatory process. In a murine macrophage cell line, RAW 264.7, AUR greatly diminished the LPS-induced expression of inducible isoforms of NOS and COX, with a consequently decreased production of nitrite anion, nitric oxide and prostaglandin (PG) E_2 and also abolished the release of TNF-α. Under the same experimental conditions, umbelliferone did not exert any kind of inhibitory activity. These contrasting effects between AUR and umbelliferone might be due to differences in their respective cellular uptake, with the geranyloxy side chain playing a key role in the incorporation of AUR inside the target cells. Employing the same cell line, the mechanism of action by which food phytochemicals attenuate the inflammatory response was recently investigated [36, 37]. AUR also suppresses the expression of COX-2, but not the biosynthesis of the corresponding mRNA, implying that it targets the translation of this pro-inflammatory enzyme [36, 37]. Moreover, the effects of AUR on the iNOS expression were recently reviewed by Murakami et al. [38].

3-6. Effects on pro-inflammatory cytokines

Our research group studied the effect of AUR on macrophages and lymphocytes in mice by measuring certain physiological parameters, such as glucose consumption, the biosynthesis of interleukins (IL), TNF-α and interferon (IFN)-γ and the activities of some key-enzymes, including acid phosphatase, β-glucuronidase and lactate dehydrogenase, which are known to increase their activity after mitogen stimulation of macrophages [39]. The mice were gavaged with AUR at a dose of 100, 200 or 400 mg/kg once a day for 10 days. Glucose consumption in peritoneal macrophages was markedly higher in the AUR-treated animals at all doses (24, 48 and 72 hours of incubation) than in the control group. Additionally the activity of acid phosphatase was significantly increased in the mice given AUR at a dose level of 100 mg/kg, and the activity of β–glucuronidase in the mice given AUR at all doses was significantly higher than that seen in the control group. There were no significant differences between the treated and untreated groups in terms of the lactate dehydrogenase activity of peritoneal macrophages at any dose. Meanwhile, IL-1β production in peritoneal macrophages in the AUR-treated mice at all doses was significantly greater than that noted in the control group. In contrast, TNF-α production in the mice gavaged with AUR at a dose of 200 mg/kg was significantly higher than that observed in the control group, whereas AUR did not affect the proliferation of splenic lymphocytes in mice at any dose. Finally, IL-2 and IFN-γ production stimulated by concanavalin A were significantly increased in the mice fed AUR at dose levels of 100 and 200 mg/kg, while this treatment did not stimulate the spontaneous IL-4 production by splenocytes.

3. 7 Effects on PPARs expression

PPARs are ligand-activated transcriptions factors that play a key role in the regulation of glucose and lipid metabolism and in associated syndromes [40]. In two studies both published in 2008, AUR was

reported to act as an agonist of the isoforms PPARα and PPARγ [13, 14]. In the first report, in a luciferase ligand assay system, treatment with AUR at a concentration of 50 μM activated the levels of PPARα by 4.1-fold and PPARγ by 2.7-fold of the control levels, while no effects were recorded for PPARδ. As an agonist of PPARγ, AUR also enhanced, in a dose-dependent manner, the mRNA expression levels of adiponectin in 3T3-L1 adipocytes and the secretion of adiponectin itself. Moreover, AUR increased the formation of high molecular weight multimers of adiponectin, the total amount of which is reported to positively correlate with an improvement in insulin sensitivity [41]. At non-toxic concentrations, AUR decreased the monocyte chemoattractant protein (MCP)-1 level of both mRNA and proteins in 3T3-L1 adipocytes. In the same cell line, the regulation of both the expression and secretion of adiponectin and expression of MCP-1 was due to PPARγ activation caused by AUR. In the second study, AUR regulated the gene expression acting as a PPARα agonist in the HepG2 cell line by inducing the upregulation of PPAR-targeted genes, such as acylCoA oxidase, carnitine-palmitoyl transferase 1A and acylCoA synthetase. Moreover, AUR led to a marked increase in the cellular uptake of fatty acids.

4. Conclusion

From the data described in this review, AUR may be a potential drug for many kinds of therapeutic areas, including chemoprevention for several types of cancer [42], in particular those of the gastrointestinal tract, as well as inflammation, metabolic disorders and others. Indeed, AUR is an effective modulator of key biological targets, such as MMPs, glycoprotein P, and PPARs. AUR is widely and easily available in large amounts as a result of chemical synthesis accomplished by the geranylation of commercially available umbelliferone with geranyl bromide [7]. Prenyloxycoumarin and its structurally related natural and semi-synthetic compounds will hopefully become a topic of current and growing interest. It is likely that, in the future, more studies aiming to further characterize these pharmacological properties will be reported in the literature.

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The authors declare no conflict of interest

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