A review of the pharmacological and therapeutic effects of auraptene

Abstract:

There is a growing awareness in herbal medicine globally, as they are usually safe and devoid of significant adverse effects. Auraptene is a natural bioactive monoterpene coumarin ether and is consumed all over the world. There is growing evidence of the therapeutic benefits of auraptene. Auraptene, also known as aurapten and 7-geranyloxycoumarin, is a bioactive monoterpene coumarin from Rutaceae family, which is isolated from *Citrus aurantium* (Seville orange) and bael fruit (Aegle marmelos). Auraptene is a highly pleiotropic molecule which can modulate intracellular signaling pathways that control inflammation, cell growth and apoptosis. It potentially has a therapeutic role in the prevention and treatment of various diseases due to its anti-inflammatory and antioxidant activities as well as its excellent safety profile. In the present article, various pharmacological and therapeutic effects of auraptene were reviewed. Different online databases using keywords such as auraptene, therapeutic effects and pharmacological effects were searched until the end of September 2018 for this purpose. Auraptene has been suggested to be effective in the treatment of a broad range of disorders including inflammatory disorders, dysentery, wounds, scars, keloids and pain. In addition, different studies have demonstrated that auraptene possesses numerous pharmacological properties including anti-inflammatory, anti-oxidative, anti-diabetic, anti-hypertensive and anti-cancer as well as neuroprotective effects. The present review provides a detailed survey of scientific researches regarding pharmacological properties and therapeutic effects of auraptene.

Keywords: Auraptene; pharmacological properties; chemopreventive.

1. Introduction:

Herbal compounds are excellent candidates for finding new therapeutic options for the management of various diseases. Auraptene, also known as 7-geranyloxycoumarin, is a prenyloxycoumarin found in plants belonging to Apiacea and Rutaceae families (1). Different pharmacological and medicinal properties have been described for auraptene including anti-diabetic (2), antiprotozoal (3), anti-genotoxic (4), anti-inflammatory (5) and immunomodulatory (6) activities. Auraptene has been shown to have a significant effect on the prevention and treatment of various chronic diseases such as cystic fibrosis, nonalcoholic fatty liver and hypertension (7).

Dietary administration of auraptene had cancer chemo-preventive effects in animal models of oral (8), breast (9), prostate (10), colon (11) and esophagus (12) cancers. The possible mechanism for these effects could be due to its glutathione S transferase inducing activity (13), lipid peroxidation (14), inhibition of key biological targets such as metalloproteinases (MMPs), glycoprotein P, peroxisome proliferator-activated receptors (PPARs), acetylcholinesterase (15) modulation of inflammation (16), suppression of superoxide generation (17), inhibition of microglial activation and inflammatory mediators (18). This article aims to review the effects of auraptene in the prevention and management of various conditions.

1.1.Structural description, bioavailability, and safety of auraptene:

Auraptene is a member of the class of coumarins that is umbelliferone in which the phenolic hydrogen has been replaced by a geranyl group (Figure 1). It is isolated from several edible fruits and vegetables and exhibits a variety of therapeutic properties. Auraptene can be prepared with a reaction between 7-hydroxycoumarin and geranyl bromide in K_2CO_3 solution (19). Auraptene can also be synthesized from umbelliferone by prenylation with NaH and geranyl bromide in

dimethylformamide (DMF) (20). Auraptene can also be synthesized from 7-hydroxycoumarin under alkaline conditions (DBU) using nuclear magnetic resonance (NMR) spectroscopic methods including nuclear magnetic resonance spectroscopy (21).

When the acute and subacute toxicity of orally administrated auraptene in rats was investigated, varying concentrations of auraptene (125, 250, 500, 1000 and 2000 mg/kg body weight) had no effect on mortality for a period of two days. However, administration of auraptene for 28 days showed some differences in the hematological and biochemical parameters of the treated and untreated groups, but all differences were within normal reference ranges. Histopathological investigation showed no toxic effects suggesting that suggested that auraptene is safe (22).

2. Methods:

We searched the literature available in ISI Web of Knowledge, Medline, Pub Med, Scopus and Google Scholar databases for English articles published until September 2018. For this purpose, we used appropriate keywords including auraptene, anticancer, anti-inflammatory, cardioprotective, immunomodulation, anti-diabetic, and neuroprotective. Sixty-five studies were considered eligible for inclusion in this review. Abstracts or unpublished articles and non-English language articles were excluded.

3. Results:

3.1. Auraptene and cancer:

Cancer has high mortality and morbidity worldwide. There are a number of unwanted side effects which occur during chemotherapy and radiotherapy. Natural therapies, including the use of plant-derived compounds, potentially have a better safety profile (23). When the antiangiogenic activity of auraptene was investigated *in vitro*, auraptene (0-500 nM) dose-dependently inhibited vascular

endothelial growth factor (VEGF)-induced human umbilical vein endothelial cell (HUVEC) tube formation, viability, migration and invasion of endothelial cells (24).

Effect of auraptene (0-100 µM) in human gastric cancer cells (SNU-1 cell line) showed that auraptene increased the sub-G1 phase cells and fragmented nuclei. It also induced depolarization of the mitochondrial membrane and regulated apoptotic signaling by downregulating the mammalian target of rapamycin (mTOR) pathway via Akt (protein kinase B) pathway (25).

The synergic effects of auraptene on anticancer drugs (cisplatin, paclitaxel, and 5-fluorouracil (5-FU)) were studied on esophageal carcinoma cells (KYSE30 cell line). Auraptene enhanced the cytotoxicity of cisplatin, paclitaxel and 5-FU, as well as the apoptosis induced by anticancer agents. Auraptene also down-regulated the expression of the cancer stem cell markers (12).

The effect of auraptene was investigated on the growth capacity of cervical cancer cells and ovarian cancer cells. Results revealed that auraptene reduced cell viability and inhibited in vitro migration and invasion, as well as suppressed matrix metalloproteinase (MMP)-2 and MMP-9 enzymatic activity (26). Combinatorial treatment with hyperthermia and auraptene in human colon adenocarcinoma cells resulted in reduced cell viability and up-regulation of P21 expression compared to untreated cells (11).

The effects of auraptene on beta-catenin-T-cell factor (TCF) activity as well as cell cycle expression levels of beta-catenin target genes such as c-myc (a human gene over-expressed in various cancers) were evaluated in human colorectal cancer cells. Treatment with auraptene for 48h inhibited cell growth with G2/M arrest in both caco-2 and DLD-1 cell lines. Auraptene suppressed beta-catenin/TCF activity in caco-2 and enhanced its activity in DLD-1. The modulation of beta-catenin/TCF activity by auraptene was inversely correlated with c-myc

expression levels. This suggests that auraptene induced inhibition of growth in these cells by different mechanisms independent on the modulation of beta-catenin-TCF signaling (27).

The effect of auraptene on the growth and sphere (surrogate tumors) formation of HT-29 (colorectal adenocarcinoma) wild type and FOLFOX (a combination chemotherapy regimen that is used to treat colorectal cancer)-resistant and HT-116 (colorectal carcinoma) wild type and FOLFOX-resistant were studied. Auraptene significantly inhibited the growth of parental and FOLFOX-resistant lines in both types of cells. (28).

Antitumor activity of auraptene was studied against intraperitoneally transplanted azoxymethane (AOM) in mice. Oral administration of (0.01 and 0.05%) of auraptene for 17 weeks significantly reduced the incidences of colorectal adenocarcinomas, the multiplicity of colon adenocarcinomas and colonic inflammation scores as well as increased the apoptotic index in colonic malignancies (29). In another study, where the preventive effect of auraptene (250 ppm) in the diet for 10 weeks on AOM induced colorectal preneoplastic lesions in mice was examined, auraptene significantly reduced the number of aberrant crypt foci, ß-catenin-accumulated crypt, cell proliferation activity but increased apoptotic cells (30). Similarly, administration of auraptene in the diet for 15 weeks on colon carcinogenesis model induced by AOM/dextran sodium sulfate (DSS) in mice showed auraptene suppressed the development of colonic adenocarcinomas. There was a reduction in PCNA-labeling index and survivin-positive rate and increased terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL)-positive rate in colonic adenocarcinomas. Additionally, auraptene reduced the incidence of colonic adenomas, total colonic tumors and expression of pro-inflammatory cytokines. This suggests that auraptene inhibited colitis-related colon carcinogenesis by modulating inflammation in mice (31).

In another study the effect of auraptene (500 ppm) in the diet for 20 weeks on NMBA-induced esophageal tumorigenesis in the rat was examined. Auraptene significantly reduced the incidence and the frequency of tumors as well as the incidence of severe dysplasia. This might be mediated by suppression of cell proliferation in the esophageal epithelium (32).

Auraptene has shown to significantly reduce extracellular signaling-regulated kinase (ERK) 1/2 activation, *H. pylori* adhesion and IL-8 production in human gastric carcinoma cell lines. In addition, the knockdown of CD74 expression led to significant reduction of *H. pylori* adhesion but elevated IL-8 production suggesting this effect is potentially mediated by disrupting ERK1/2 (33).

The effect of administration of auraptene in the diet for 7 weeks on liver carcinogenesis model induced by N, N-diethylnitrosamine (DEN) in the rat was evaluated. Auraptene inhibited the incidence of liver cell carcinoma and cell proliferation in liver cell neoplasms models (34). In a similar study of auraptene on DEN-induced hepatocarcinogenesis cells showed auraptene suppressed the occurrence of mutations in the beta-catenin gene in liver cell adenomas probably by negative selection of mutation harboring neoplastic cells (35).

The effect of auraptene was investigated on the cell cycle and the genes related to the cell cycle in mammary adenocarcinoma (MCF-7) cells line. Auraptene significantly reduced cyclin D1 protein expression in these cell lines, inhibited IGF-1 stimulated S phase of cell cycle and modulated the transcription of various genes involved in the cell cycle (9).

Tang et al. examined the in vivo effects of auraptene (500 ppm) in the diet for 15 weeks on prostate carcinogenesis using transgenic rats with adenocarcinoma of the prostate. Auraptene significantly reduced the epithelial component and high-grade lesions in the prostate. Furthermore, they examined the chemotherapeutic effects of auraptene using human prostate cancer cells *in vitro.*

Auraptene significantly reduced the cell viability in a dose-dependent manner and increased apoptosis in these cell lines (10).

Effect of auraptene (100 and 500 ppm) in the diet for 38 weeks on AOM induced colon carcinogenesis in the rat was examined. Dietary administration of auraptene significantly reduced the incidence and multiplicity of colon adenocarcinoma and the production of aldehydic lipid peroxidation products in the colonic mucosa. Auraptene suppressed the expression of cell proliferation biomarkers in the colonic mucosa. It also increased the activities of phase II drug-metabolizing enzymes in the liver and colon. The protective effects of auraptene in the AOM model of colon carcinogenesis have been suggested to be related to its ability to suppress cell proliferation and lipid peroxidation (14). Similarly, administration of auraptene in the diet after induction of pulmonary metastasis in mice for 2 weeks reduced the numbers of metastatic lung tumors, cross-sectional areas and volumes of the tumors and increased the apoptotic indices compared to the controls (36).

The preventive effect of auraptene in the diet on *N*-methylnitrosourea (MNU)-induced mammary carcinogenesis model in the rat showed auraptene inhibited cell proliferation and reduced the expression of cyclin D1, c-Myc, and ODC in the tumors (37). The effect of auraptene was investigated on cell proliferation in the human breast carcinoma cell line (MCF-7 and MDA-MB-231). It showed auraptene significantly suppressed the proliferation in both the cell lines and reduced insulin-like growth factor1 (IGF-1)-induced cyclin D1 expression in MCF-7 cells. In addition, the in vivo effects of auraptene in the diet on MNU-induced mammary carcinogenesis in the rat showed that auraptene delayed median time to the tumor, reduced incidence of tumor and cyclin D1 expression (38).

Dietary administration of auraptene after induction of oral carcinogenesis in the rat for 22 weeks significantly reduced the frequency and incidences of tongue cancer, 5-bromodeoxyuridine (BrdU)-labelling index and polyamine concentrations in the oral mucosa. It also increased the activities of GST and QR in the tongue which suggests that the mechanism for this action might be related to the suppression of cell proliferation (8).

Antitumor activity of auraptene was studied on the prostate cancer cells (PC3 and DU145 cell line). After 24 h, auraptene significantly exhibited a cytotoxic effect in a time-dependent manner and increased the number of TUNEL-positive cells in a dose-dependent manner. Auraptene activated caspase-9, caspase-3 and pro-apoptotic protein Bax. It also suppressed the expression of anti-apoptotic proteins including Bcl-2 and myeloid cell leukemia 1 (Mcl-1) in these prostate cancer cells. The possible mechanism of chemo-preventive effects of auraptene could be related to Mcl-1-mediated activation of caspases (39).

The effect of auraptene was investigated on human renal cancer cells (RCC4 and RCC4/VHL cell lines). Results indicated that auraptene inhibited glycolytic and mitochondrial metabolism as well as VEGF and tube formation by HUVECs. It also decreased cell motility, induced hypoxia-inducible factor 1α (HIF-1α) degradation in a von hippel–lindau (VHL)-independent manner and promoted HIF-1a protein degradation by inhibition of translation initiation (40).

Topical administration of auraptene (16 nmol and 160 nmol/o.1 ml in acetone) after induction of skin tumor by 12-O-tetradecanoylphorbol-13-acetate (TPA) in the rat twice a week for 20 weeks significantly reduced the incidence and number of tumors (17). Comparison of the cytotoxicity of auraptene and umbelliprenin against some cancerous cell lines such as HeLa (cervical cancer cell line), Jurkat (T cell leukemia cell line), MCF-7 (breast cancer cell line) and KYSE-30 (oesophageal

carcinoma cell line) showed that auraptene is more cytotoxic than umbelliprenin (41). The anticancer effects of auraptene are summarized in Table 1.

3.2. Auraptene and the nervous system:

The effect of auraptene (6.0 mg/day, p.o.) on cognition was studied in healthy volunteers. Cognitive assessments were evaluated using mild cognitive impairment (MCI) screen and mini-mental state examination (MMSE) at baseline and at 24 weeks. Results showed that auraptene did not improve cognitive function after 24 weeks compared to baseline (42).

The effect of auraptene (10 and 25 mg/kg/day, s.c.) was evaluated 5 days before and 3 days after the induction bilateral common carotid artery occlusion in mice. The results indicated that auraptene decreased the numbers of ionized calcium binding adaptor molecule 1 positive cells, glial fibrillary acidic protein positive cells and COX-2-positive cells. The presence of auraptene in the brains of mice following (50 mg/kg, i.p.) administration of auraptene suggests that it has the ability to pass through the blood-brain barrier. Results of *in vitro* study using cultured astrocytes showed that auraptene suppressed the mRNA expression of the inflammatory cytokines (43). Similarly, the effect of administration of auraptene on bilateral common carotid artery occlusion induced cerebral global ischemia in mice showed that auraptene suppressed neuronal loss in the hippocampal regions of CA1, CA2 and CA3, microglia activation by reduction IBA1-positive cells in the hippocampus and COX-2 expression in astrocytes (16). Administration of auraptene intra-peritoneally after induction of demyelination by cuprizone for 21 days increased the immunoreactivity to oligodendrocyte transcription factor 2 (olig2) which is a marker of precursor cells of oligodendrocytes and the number oligodendrocyte lineage precursor cells (OPCs). There was also a reduction in microglial activation (44).

The neuroprotective and memory enhancing effects of auraptene (4, 8 and 25 mg/kg, p.o.) were investigated in bilateral carotid artery occlusion model of cerebral global ischemia. The results showed that auraptene significantly reduced the scape latency time and increased the percentage of time spent and traveled pathway in the target quadrant in the Morris water maze. Auraptene also reduced the MDA concentrations and increased glutathione (GSH) content in the cortex as well as in the hippocampus. Histopathological data showed that auraptene protected cerebrocortical and hippocampus neurons against ischemia (45). In the the rat pheochromocytoma cell line (PC12 cells), which is a model system for studies on neuronal proliferation and differentiation, auraptene induced activation of the extracellular signal-regulated kinases (ERK)1/2. In addition, auraptene promoted neural outgrowth from PC12 cells (46).

The effect of auraptene on the cognitive performance induced by scopolamine showed that auraptene significantly reversed scopolamine-induced avoidance memory retention impairments, 24 and 168 hr after training trial in step-through task (47). The neuroprotective effects of auraptene are summarized in Table 2.

3.3. Auraptene and the cardiovascular system:

The effect of auraptene (5 and 50 mg/kg, orally) once daily for 6 weeks on myocardial infarction (MI) in rats showed improved left ventricular fractional shortening (LVFS) and reduced posterior wall thickness (PWT), myocardial cell diameter and perivascular fibrosis. In addition, auraptene inhibited the activations of atrial natriuretic factor and MCP-1 mRNA levels (48).

When auraptene was administered intraperitoneally in normotensive and desoxycorticosterone acetate (DOCA)-induced hypertensive rats, there was a significant reduction in mean systolic blood pressure in both groups in a dose and time-dependent manner. This suggests that auraptene

had anti-hypertensive properties and dietary supplementation with auraptene would be a potentially beneficial strategy for the management of hypertension (49).

The influence of auraptene on mean arterial blood pressure and heart rate was studied in the rat. Animals were divided to a control group that received single intravenous injections of normal saline/DMSO, auraptene and nifedipine as a positive control. Although auraptene did not have any significant effect on heart rate, it significantly reduced mean arterial blood pressure. This suggests a potential antihypertensive effect of auraptene comparable to established anti-hypertensives such as nifedipine at the used concentrations (50). Auraptene is also potent *in vitro* inhibitor of the spontaneous beating of mouse myocardial cells. The IC_{50} of auraptene was 0.6 µg/ml, which is comparable to that of verapamil, a well-known Ca^{+2} antagonist (51). The cardioprotective effects of auraptene are summarized in Table 3.

3.5. Auraptene and the immune system:

Auraptene significantly increased the expressions of IL-10, IFN-γ, IFNγ/IL-4 and IL-10/IL-4 ratio in non-phytohaemagglutinin (PHA)-stimulated lymphocytes. After PHA stimulation auraptene significantly reduced the expressions of IL-4, IL-10, IFN-γ, NF-κB and NO and increased IFN-γ/IL-4 and IL-10/IL-4 ratio. This suggests the effects of auraptene on T cell subsets shifting towards Th1 (IFN-γ) and Treg (IL-10) may play a therapeutic role in the management of Th2 cells predominant conditions (52).

The effect of auraptene was evaluated on DNA damage in human peripheral lymphocytes induced by H_2O_2. This demonstrated that auraptene significantly reduced the genotoxicity of H_2O_2. This is most probably due to the prenyl moiety and suppression of superoxide anion (O^{2-}) generation (4).

The effect of oral administration of auraptene on macrophage and lymphocyte functions in mice showed that auraptene significantly increased glucose consumption of peritoneal macrophages, activities of acid phosphatase and beta-glucuronidase as well as the production of IL-1β and TNF-α (6). Studies on the effect of auraptene on T lymphocyte activation using mice CD3/CD28-activated lymphocytes showed that auraptene inhibits the CD3/CD28-activated lymphocyte proliferation by inhibition of cell cycle progression and cell division. Furthermore, auraptene reduced the T cell cytokines (53). The immunomodulatory effects of auraptene are summarized in Table 4.

3.5. Auraptene and gastrointestinal system:

The beneficial effect of auraptene on the lithocholic acid (LCA)-induced cholestatic liver injury was investigated in mice. Different concentrations of auraptene were administered orally once a day for 7 days to mice. Auraptene promoted bile acid efflux from the liver into the intestine via induction of farnesoid X receptor (FXR) target genes canalicular bile salt export pump (Bsep) and multidrug resistance-associated protein 2 (Mrp2) expression. It also promoted liver repair through induction in the liver regeneration-related gene. It reduced hepatic uptake through inhibition in Na^+/taurocholate cotransporting polypeptide (Ntcp) as well as suppressed the liver inflammation through repressing inflammation-related genes. Auraptene reduced bile acid synthesis through repressing FXR-target genes cholesterol 7a-hydroxylase (Cyp7a1) and oxysterol 12a-hydroxylase (Cyp8b1) and increased bile acid metabolism through induction of sulfotransferase 2a1 (Sult2a1) (54).

The effect of auraptene was investigated on azoxymethane (AOM)-induced colonic aberrant crypt foci (ACF) in the male albino mice. Dietary administration of auraptene significantly reduced the frequency of ACF in a dose-dependent manner and suppressed the expression of cell proliferation

biomarkers and increased the activities of phase II enzymes (GST and QR) in the liver and colon. This suggests that the protective effects of auraptene may be related to enhancement in phase II enzymes activity in the liver and colon as well as suppression of cell proliferation in the colonic mucosa (13).

The effect of auraptene in *H. pylori*–infected mice using a feeding needle showed that auraptene inhibited *H. pylori* colonization and resultant gastric mucosal injuries, attenuated expressions of CD74, IL-1β, TNF-α in stomach tissue and level of macrophage inhibitory protein-2 (MIP-2) in the serum (55). In vivo effects of auraptene in the diet on hepatic lipid metabolism using Otsuka Long-Evans Tokushima fatty rats showed that auraptene reduced abdominal white adipose tissue weight and hepatic triglyceride levels. It also increased the activities of carnitine palmitoyltransferase and peroxisomal ß-oxidation and expression of acyl-CoA oxidase in a dose-dependent manner in the liver (56).

Kawada et al., showed that auraptene acts as an agonist of the isoforms peroxisome proliferator-activated receptors (PPAR)α and PPARγ. At a concentration of 50 µM, auraptene activated PPARα and PPARγ while no effects were recorded for PPAR δ. Furthermore, auraptene was also able to enhance the mRNA expression level of adiponectin in 3T3-L1 adipocytes as well as the secretion of adiponectin (57).

The effect of auraptene on thioacetamide (TAA)-induced hepatic fibrosis in mice showed a reduction of liver collagen content. Auraptene also inhibited the activation of hepatic stellate cells by down-regulating the expression of transforming growth factor-ß1 (TGF-β1) and α-smooth muscle actin (α-SMA). There was also a reduction in the expression of NF-κB, TNF-α and IL-1β suggesting potential anti-inflammatory effects. However, the changes in these genes and protein

expression, as well as ameliorative liver histology induced by auraptene were repealed by farnesoid X receptor (FXR) antagonist guggulsterone (a phytosteroid found in the resin of the guggul plant, *Commiphora mukul*) *in vivo* and FXR siRNA *in vitro* (58).

Auraptene when administered through the diet significantly reduced *H. pylori* colonization in *H. pylori*–infected mongolian gerbil but did not have an effect on gastric inflammation (59). Administration of auraptene (0.1% w/w, in diet) after induction of ulcerative colitis by DSS model in mice inhibited the gelatinolytic activity of MMP-7 as well as the expression of MMP-2 and MMP-9 in the mucosa of the colon (60). The protective effects of auraptene on gastrointestinal diseases are summarized in Table 5.

3.6. Miscellaneous effects of auraptene:

Auraptene (0.1 and 0.2%, in diet) significantly reduced lipid accumulation in the liver and skeletal muscle and increased the mRNA expression of the PPARα target genes such as fatty acid translocase (FAT)/CD36, acyl-CoA synthetase (ACS), acyl-CoA oxidase (ACO) and carnitine palmitoyl transferase 1 (CPT1) involved in fatty acid oxidation in high-fat-diet (HFD)-fed KK-Ay diabetic obese mice (2). The therapeutic potential of auraptene was studied in a mice model of diabetes which was induced by streptozotocin. Results indicated that auraptene suppressed astroglial activation and the hyperphosphorylation of tau at 231 of threonine in neurons. It also recovered the suppression of neurogenesis in the dentate gyrus of the hippocampus in the hyperglycemic mice. The potential protective effects of auraptene could be associated with its anti-inflammatory and anti-oxidative action in the hyperglycemic brain (61).

Marquis and his colleagues evaluated the effect of auraptene on *Porphyromonas gingivalis* (*P. gingivalis*). It showed that auraptene inhibited the adherence of *P. gingivalis* to oral epithelial cells

and reduced the secretion of cytokines and MMP by LPS-stimulated macrophages. It also inhibited MMP-9 activity (62). The effects of auraptene on the secretion of inflammatory mediators and chemokine by LPS-stimulated oral epithelial cells showed that auraptene reduced the secretion of MMP-2, IL-6, IL-8 and chemokine (C-C motif) ligand (CCL)-5 secreted by *Aggregatibacter actinomycetemcomitans* lipopolysaccharide-stimulated oral epithelial cells. Furthermore, the effect of auraptene as a wound healing agent was examined using a gingival fibroblast model. Auraptene improved wound closure by promoting cell migration (63).

The effect of auraptene on lipopolysaccharide (LPS)-stimulated murine macrophage line (RAW 264.7) showed that auraptene had better biocompatibility and lower cytotoxicity compared to aspirin. In addition, it significantly reduced the production of PGE2, levels of mRNA expression and protein of COX-2 (5). Auraptene significantly suppressed the expression of monocyte chemoattractant protein-1 (MCP-1), COX-2 and iNOS as well as TNF-α release from the RAW 264.7 cell line (64, 65).

Auraptene inhibits Ba^{+2}, acetylcholine or histamine-induced contractions of smooth muscles in accordance with its spasmolytic activity. Studies of structure-activity relationship performed with synthetic analogs of auraptene suggest that the observed spasmolytic activity is closely associated with the presence of both the geranyl chain and the benzopyrone ring (66).

The effect of auraptene on the growth and viability of *Leishmania major* (*L. major*) Friedlin cells showed auraptene (2, 5, 7, 10 and 15 µg/ml) significantly inhibited growth of *L. major* promastigotes at the used concentrations (3). The miscellaneous effects of auraptene are summarized in Table 6.

4. Conclusions:

There is growing evidence on the multiple health benefits of auraptene. Studies suggest that auraptene has potential therapeutic benefits in a wide range of conditions ranging from diabetes to cancer. These effects are mediated via a variety of mechanisms including anti-inflammatory, anti-oxidant and anti-tumor activities through its regulatory impacts on various molecular targets.

This review showed a wide spectrum of effects of auraptene on different disorders both in experimental and clinical studies (Figure 2). With respect to the effects in cancer, auraptene has chemo-preventive and inhibitory effects on all stages of tumorigenesis, growth and proliferation of cancer cell lines. In experimental studies, auraptene had inhibitory effects on the proliferation of several cancer cell lines, the formation of DNA adducts, an increase of glutathione S-transferase activity and reduction of the number of aberrant crypt foci (precursors of colon cancers).

Auraptene showed improved effects on memory and behavioral deficits, motor incoordination and short-term memory as well as decreased cerebral infarct size. In cardiovascular system, auraptene treatment reduced high blood pressure, cardiac hypertrophy and vasodilation in experimental research. On the gastrointestinal system, auraptene reduced abdominal white adipose tissue weight as well as H. pylori colonization and resultant gastric mucosal injuries. It also increased the activities of carnitine palmitoyltransferase, phase II enzymes and peroxisomal ß-oxidation as well as expression of Acyl-CoA oxidase in the liver and colon.

In experimental studies, auraptene caused a significant reduction on blood glucose levels and dietary glucose absorption, an increase of serum insulin levels and protection of pancreatic islets. In experimental models of periodontal disease, auraptene reduced the adherence of *P. gingivalis* to oral epithelial cells as well as the secretion of cytokines (IL-8 and TNF-α) and MMP. Auraptene also has anti-inflammatory effects as well as reduction of immunological markers such as IL-4 and IL-10 and an increase of IFN-γ in experimental studies.

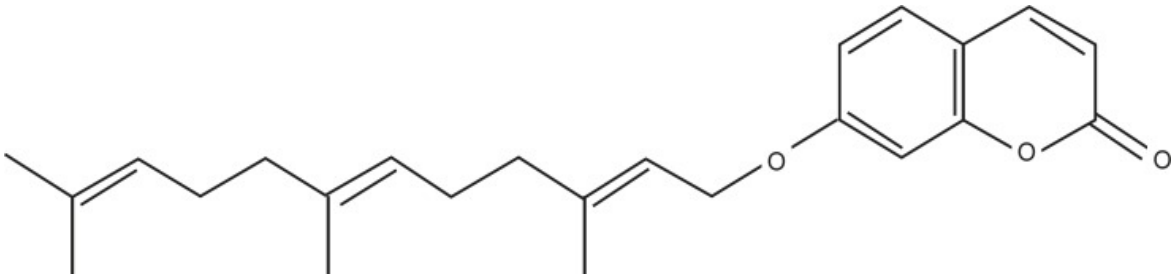
Auraptene due to its ability to affect a wide range of molecular targets with an excellent safety profile could potentially be a potential candidate for the prevention and/or management of a number of diseases. A wide range of pharmacological effects was reported for auraptene in the published studies so far mainly in experimental studies. However, more clinical trials are needed regarding the effects of auraptene before it could be translated in clinical practice.

Conflict of interest:

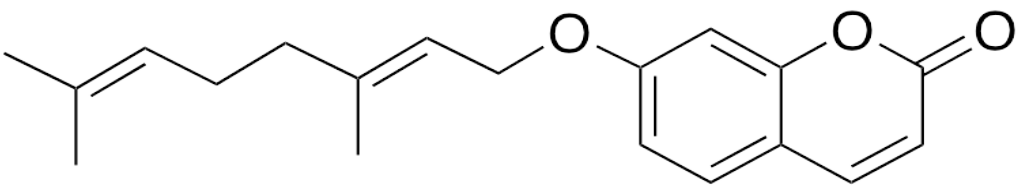
None.

Figure Legend

Figure 1. Chemical structures of umbelliprenin (a) and auraptene (b).



(a)



(b)

Figure 2. Various effects of auraptene.

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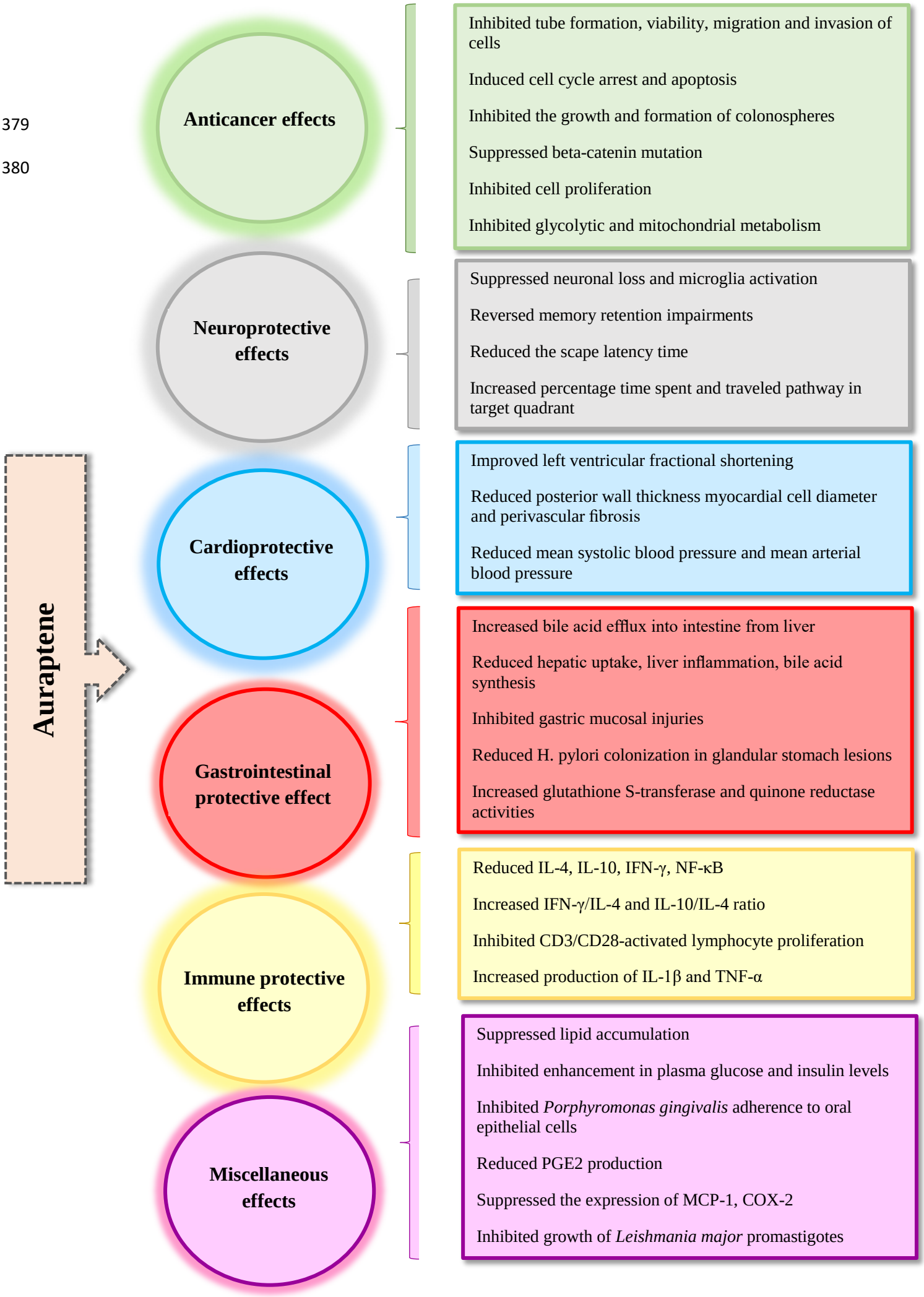
Auraptene
Anticancer effects
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Cardioprotective effects
Improved left ventricular fractional shortening
Reduced posterior wall thickness myocardial cell diameter and perivascular fibrosis
Reduced mean systolic blood pressure and mean arterial blood pressure
Gastrointestinal protective effect
Increased bile acid efflux into intestine from liver
Reduced hepatic uptake, liver inflammation, bile acid synthesis
Inhibited gastric mucosal injuries
Reduced H. pylori colonization in glandular stomach lesions
Increased glutathione S-transferase and quinone reductase activities
Immune protective effects
Reduced IL-4, IL-10, IFN-γ, NF-κB
Increased IFN-γ/IL-4 and IL-10/IL-4 ratio
Inhibited CD3/CD28-activated lymphocyte proliferation
Increased production of IL-1β and TNF-α
Miscellaneous effects
Suppressed lipid accumulation
Inhibited enhancement in plasma glucose and insulin levels
Inhibited Porphyromonas gingivalis adherence to oral epithelial cells
Reduced PGE2 production
Suppressed the expression of MCP-1, COX-2
Inhibited growth of Leishmania major promastigotes

381 **Table 1**. Summary of studies reporting anticancer effects of auraptene.

Dose	Exp. model	Effect	Ref.
0-500 nM, *In vitro*	VEGF-induced HUVEC growth stimulation	Inhibited tube formation, viability, migration and invasion of HUVEC	(24)
0-100 μM, *In vitro*	Human gastric cancer cell line	Induced cell cycle arrest and apoptosis in SNU-1 cells via activation of p53 and inhibition of mTOR signaling	(25)
5, 10, and 20 ug/ml, *In vitro*	Human esophageal carcinoma cell line	Reduced the expression of CD44, BMI-1 markers	(12)
6.25, 12.5, 25, 50, and 100 μM, *In vitro*	Human ovarian and cervical cancer cell line	Inhibited migration and invasion capacity of human ovarian and cervical and ovarian cancer by decreasing MMP-2, MMP-9 activity	(26)
10 and 20 ug/ml, *In vitro*	Human colon adenocarcinoma cell line	Reduced cell viability Up regulated of P21 expression	(11)
75 μM, *In vitro*	Human colorectal cancer cell line	Induced growth inhibition	(27)
2.5, 5, 10, 20 and 40 μM, *In vitro*	Human colorectal adenocarcinoma and carcinoma cell lines	Inhibited the growth and formation of colonospheres	(28)
0.01 and 0.05%, p.o.	AOM-induced colon carcinogenesis in mice	Inhibited the occurrence of colonic adenocarcinoma	(29)
250 ppm, p.o.	AOM-induced colonic preneoplastic lesions in mice	Reduced the number of ACF, BCAC, cell proliferation activity Increased apoptotic cells	(30)
100 and 500 ppm, p.o.	AOM/ DSS induced colon carcinogenesis in mice	Suppressed the development of colonic adenocarcinomas and colonic inflammation	(31)
500 ppm, p.o.	NMBA-induced esophageal tumorigenesis in rat	Inhibited the development of esophageal tumors	(32)
0-50 μM, *In vitro*	Human gastric carcinoma cell lines	Suppressed CD74 expression, *H. pylori* adhesion and IL-8 production	(33)
100 and 500 ppm, p.o.	DEN-induced hepatocarcinogenesis in rat	Reduced the development of hepatocellular carcinoma	(34)

100 and 500 ppm, p.o.	DEN-induced hepatocarcinogenesis in rat	Suppressed beta-catenin mutation	(35)
10 μM, *In vitro*	Human breast cancer cell line	Reduced cyclin D1 protein expression Inhibited IGF-1 stimulated S phase of cell cycle Modulated the transcription of many genes	(9)
0, 1×10^{-5}, 5×10^{-5}, 1×10^{-4}, 5×10^{-4} and 1×10^{-3} mol/L	Human prostate carcinoma cell lines	Reduced cell viability Increased apoptosis	(10)
500 ppm, p.o.	Prostate carcinogenesis using TRAP	Reduced the epithelial component and high grade lesions in the lateral prostate lobe	
100 and 500 ppm, p.o.	AOM-induced colon carcinogenesis in rat	Reduced the incidence and multiplicity of colon adenocarcinoma, MDA and 4-HNE Suppressed ODC and polyamine content Increased GST and QR	(14)
250, 500, and 1000 mg/kg, p.o.	Experimental metastasis mouse model using B16BL6 melanoma cells	Decreased the numbers of metastatic lung tumors, cross-sectional areas and volumes of the tumors Increased apoptotic indices	(36)
200 and 500 ppm, p.o.	MNU induced mammary carcinogenesis in rat	Inhibited cell proliferation Reduced the expression of cyclin D1, c-Myc, and ODC	(37)
1–50 μM, *In vitro*	Human breast cancer cell line	Suppressed proliferation Reduced IGF-1-induced cyclin D1 expression	(38)
200 and 500 ppm, p.o.	MNU induced mammary carcinogenesis in rat	Delayed median time to tumor Reduced cyclin D1 expression and incidence and multiplicity	
100 and 500 ppm, p.o.	4-NQO-induced oral carcinogenesis	Reduced the frequency and incidences of tongue carcinoma, BrdU-labelling index and polyamine Increased the activities of GST and QR	(8)
0, 15, 30, 60, 90, and 120 μM, *In vitro*	Human prostate cancer cell line	Increased TUNEL-positive cells, sub-G1 population Cleaved poly (ADP-ribose) polymerase, activated pro-apoptotic protein Bax, caspase-3 and caspase-9 Suppressed the expression of anti-apoptotic proteins	(39)

0, 25, 50, 75 and 100 µM, *In vitro*	Human renal cancer cell line	Inhibited glycolytic and mitochondrial metabolism, VEGF, and tube formation HUVECs	(40)
16 nmol and 160 nmol/o.1 ml in acetone, p.o.	TPA-induced skin tumor	Reduced tumor incidence and the numbers of tumors	(17)
10, 20, 40 µg/ml, *In vitro*	Cervical cancer, breast cancer, oesophageal carcinoma and T cell leukaemia cell lines	Cytotoxic effect	(41)

Abbreviations: VEGF: vascular endothelial growth factor, HUVEC: human umbilical endothelial cells, AOM: azoxymethane, ACF: aberrant crypt foci, BCAC: ß-catenin-accumulated crypt, DSS: dextran sodium sulfate, NMBA: N-nitrosomethylbenzylamine, DEN: N,N-diethylnitrosamine, TRAP: transgenic rats developing adenocarcinoma of the prostate, MDA: malondialdehyde, 4-HNE: 4-hydroxy-2(E)-nonenal, ODC: ornithine decarboxylase activity, GST: glutathione S-transferase, QR: quinone reductase, MNU: *N*-methylnitrosourea, IGF-1: insulin like growth factor1, 4-NQO:4-nitroquinoline 1-oxide, BrdU: 5-bromodeoxyuridine, VEGF: vascular endothelial growth factor, TPA: 12-O-tetradecanoylphorbol-13-acetate, p.o.: oral administration,

Table 2. Summary of studies reporting neuroprotective effects of auraptene.

Dose	**Exp. model**	**Effect**	**Ref.**
10 and 25 mg/kg/day, s.c.	2VO induced cerebral global ischemia in mice	Reduced the numbers of IBA1-positive cells, GFAP-positive cells and COX-2-positive cells	(43)
25 and 50 mg/kg, s.c.	2VO induced cerebral global ischemia in mice	Suppressed neuronal loss, microglia activation, and COX-2 expression	(16)
6.0 mg/day, p.o.	Healthy volunteers	No effect on cognitive function	(42)
17 and 50 mg/kg, i.p.	Cuprizone-induced demyelination in mice	Increased olig2 and the number OPCs Reduced the microglial activation	(44)
4, 8 and 25 mg/kg, p.o.	2VO induced cerebral global ischemia in rat	Reduced the scape latency time Increased percentage time spent and traveled pathway in target quadrant	(45)
10, 30 and 50 µM, *In vitro*	Rat pheochromocytoma cell line	Induced the activation of ERK1/2 Promoted neurite outgrowth	(46)
50, 75, and 100 mg/kg, s.c.	Scopolamine-induced avoidance memory retention impairments in mice	Reversed memory retention impairments induced by scopolamine	(47)

Abbreviations: 2VO: 2-vessel occlusion, IBA1: ionized calcium binding adaptor molecule 1, GFAP: glial fibrillary acidic protein, olig2: oligodendrocyte transcription factor 2, OPCs: oligodendrocyte lineage precursor cells, ERK: extracellular signal-regulated kinases,

Table 3. Summary of studies reporting cardioprotective effects of auraptene.

Dose	Exp. model	Effect	Ref.
5 and 50 mg/kg, p.o.	Myocardial infarction in rats	Improved LVFS Reduced PWT myocardial cell diameter and perivascular fibrosis	(48)
2, 4, 8 and 16 mg/kg/day, i.p.	DOCA-induced hypertensive in rats	Reduced MSBP	(49)
125, 250 and 500 mg/kg, i.v.	Normetensive rats	Reduced MABP	(50)
0.6 ug/ml, *In vitro*	Myocardial cells of rat	Inhibited spontaneous beating of mouse myocardial cells	(51)

Abbreviations: LVFS: left ventricular fractional shortening, PWT: posterior wall thickness, DOCA: desoxycorticosterone acetate, MSBP: mean systolic blood pressure, MABP: mean arterial pressure, p.o.: oral administration, i.p.: intraperitoneal, i.v.: intravenous,

Table 4. Summary of studies reporting immunomodulatory effects of auraptene.

Dose	Exp. model	Effect	Ref.
10, 30 and 90 µM, *In vitro*	PHA-stimulated human lymphocytes	Reduced IL-4, IL-10, IFN-γ, NF-κB and NO Increased IFN-γ/IL-4 and IL-10/IL-4 ratio	(52)
50, 100, 200 and 400 mM, *In vitro*	H_2O_2-induced DNA toxicity in human lymphocytes	Reduced H_2O_2 genotoxicity	(4)
100, 200 or 400 mg/kg, p.o.	Peritoneal macrophages and splenic lymphocytes in mice	Increased glucose consumption, activities of acid phosphatase and beta-glucuronidase and production of IL-1β and TNF-α No effect on proliferation of spontaneous splenic lymphocytes	(6)
0, 5, 10, 20 and 40 µM, *In vitro*	CD3/CD28-activated lymphocytes isolated from mice	Inhibited CD3/CD28-activated lymphocyte proliferation Reduced IL-2, IFN-γ and IL-4	(53)

Abbreviations: PHA: phytohemagglutinin, H_2O_2: hydrogen peroxide.

Table 5. Summary of studies reporting protective effects of auraptene on gastrointestinal diseases.

Dose	Exp. model	Effect	Ref.
7.5, 15 and 30 mg/kg, p.o.	LCA-induced cholestatic liver injury	Increased bile acid efflux into intestine from liver Reduced hepatic uptake, liver inflammation, bile acid synthesis Increased bile acid metabolism	(54)
100 and 500 ppm, p.o.	AOM-induced colonic ACF in mice	Reduced ACF frequency Reduced expression of cell proliferation indices Increased GST and QR activities	(13)
100 and 500 ppm, p.o.	*H. pylori*–infected mice	Inhibited gastric mucousal injuries due to *H. pylori* colonisation Attenuated expressions of CD74, IL-1β, TNF-α, and level MIP-2	(55)
0.5 and 1 g/kg, oral.	OLETF rats	Reduced abdominal white adipose tissue weight and TG Increased carnitine acyl-CoA oxidase, palmitoyltransferase and peroxisomal ß-oxidation	(56)
1-100 µM, *In vitro*	Human hepatocarcinoma cell line	Increased PPARα and PPARγ levels Increased mRNA expression of adiponectin in 3T3-L1 adipocytes and adiponectin secretion	(57)
7.5, 15 and 30 mg/kg, oral	TAA-induced hepatic fibrosis in mice	Inhibited activation of HSCs Reduced expression of TNF-α, IL-1β, NF-κB	(58)
5, 10 and 20 µM, *In vitro*	Hepatocyte	Increased cell viability	
100 and 500 ppm, p.o.	*H. pylori*–infected Mongolian gerbils	Reduced *H. pylori* colonization in glandular stomach lesions	(59)
0.1% w/w, p.o.	DSS-induced ulcerative colitis in mice	Suppressed gelatinolytic activity of MMP-7 as well as MMP-2 and -9 expression	(60)

Abbreviations: LCA: lithocholic acid, AOM: azoxymethane, ACF: aberrant crypt foci, MIP-2: macrophage inhibitory protein-2, TG: hepatic triglyceride, OLETF: Otsuka Long-Evans Tokushima fatty, TAA: thioacetamide, HSCs: hepatic stellate cells, DSS: dextran sulfate sodium, MMP: matrix metalloproteinase,

Table 6. Summary of studies reporting miscellaneous effects of auraptene.

Dose	Exp. model	Effect	Ref.
0.1 and 0.2%, p.o.	HFD-fed KK-Ay obese diabetic mice	Suppressed lipid accumulation Inhibited enhancement in plasma glucose and insulin levels Increased mRNA expression of PPARα target genes	(2)
50 mg/kg, p.o.	STZ-induced diabetes in mice	Suppressed astroglial activation and neuronal hyper phosphorylation of tau at 231 of threonine Reversed suppression of neurogenesis in hippocampal dentate gyrus	(61)
0, 12.5, 25, 50 and 100 µg/ml, *in vitro*	LPS-stimulated human macrophages	Inhibits *P. gingivalis* adherence to oral epithelial cells Reduced TNF-α, IL-8, MMP	(62)
0, 0.2, 1, 5, and 20 µM, *In vitro*	LPS-stimulated epithelial cells from oral cavity	Reduced secretion of chemokine (C-C motif) ligand (CCL)-5, IL-6, IL-8, MMP-2	(63)
200, 250, 300 µM, *In vitro*	Murine macrophage cell line	Reduced PGE2 production, mRNA expression and COX-2 protein	(5)
5, 10 and 20 µM, *In vitro*	Murine macrophage cell line	Suppressed the expression of MCP-1, COX-2, iNOS and TNF-α	(64, 65)
2, 5, 7, 10 and 15 µg/ml, *In vitro*	*Leishmania major* cells	Inhibited growth of *L. major* promastigotes	(3)

Abbreviations: HFD: high-fat-diet, STZ: streptozotocin, *P. gingivalis*: *Porphyromonas gingivalis*, MMP: matrix metalloproteinase, LPS: lipopolysaccharide, CCL-5: chemokine (C-C motif) ligand-5, TNF-α: tumor necrosis factor, PGE2: prostaglandin E2, COX-2: cyclooxygenase-2, iNOS: inducible nitric oxide synthase, MCP-1: monocyte chemoattractant protein-1, *L. major*: *Leishmania major*,

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