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Review article

Natural heat shock protein 90 inhibitors in cancer and inflammation

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ABSTRACT

Heat shock protein (HSP)90 is the most abundant HSPs, which are chaperone molecules whose major roles are cell protection and maintenance by means of aiding the folding, the stabilization and the remodeling of a wide range of proteins. A few hundreds of proteins depend on HSP90 chaperone activity, including kinases and transcriptional factors that play essential roles in cancer and inflammation, so that HSP90-targeted therapies have been considered as a potential strategy for the treatment of cancer and inflammatory-associated diseases. HSP90 inhibition by natural, semi-synthetic and synthetic compounds have yield promising results in pre-clinical studies and clinical trials for different types of cancers and inflammation. Natural products are a huge source of biologically active compounds widely used in drug development due to the great diversity of their metabolites which are capable to modulate several protein functions. HSP90 inhibitors have been isolated from bacteria, fungi and vegetal species. These natural compounds have a noteworthy ability to modulate HSP90 activity as well as serve as scaffolds for the development of novel synthetic or semi-synthetic inhibitors. Over a hundred clinical trials have evaluated the effect of HSP90 inhibitors as adjuvant treatment against different types of tumors and, currently, new studies are being developed to gain sight on novel promising and more effective approaches for cancer treatment. In this review, we present the naturally occurring HSP90 inhibitors and analogues, discussing their anti-cancer and anti-inflammatory effects.

Contents

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1. Introduction

Heat shock proteins (HSP) are constitutive and inducible chaperone molecules triggered by the heat shock transcription factor-1 (HSF-1), whose major roles are cell protection against damage and maintenance of vital cellular functions by means of aiding the folding, the stabilization and the remodeling of a wide range of nascent and non-native proteins, referred to as "client proteins" [1,2]. The 90 kDa HSP (HSP90) is the most abundant chaperone that is predominantly active within an intracellular multiprotein complex that includes chaperones, co-chaperones and adaptor proteins, called the HSP90 chaperone machinery. This complex undergoes dynamic conformational cycle during processing of client proteins, which is initiated by the binding of the chaperone HSP70 that, aided by HSP40, plays a central role in the delivery of client proteins to the open state of HSP90 [1]. The co-chaperone HOP [HSP70/HSP90 organizing protein] binds to both chaperones and helps to stabilize the open conformation of HSP90, in order to receive client proteins. Further, while the HSP90 co-chaperone Cdc37 (cell division cycle 37) prevents the closure of the complex, Aha1 (activator of HSP90 ATPase homologue 1) initiates the formation of the closed state, which is stabilized by the p23 cochaperone [3]. Detailed information about HSP90 chaperone machinery can be found in Schopf et al. [2].

Different isoforms of HSP90 have different subcellular localizations. HSP90α and HSP90β isoforms are expressed in the cytoplasm, HSP90β in the nucleus, TRAP1 within the mitochondria, and GRP94/Gp96 in the endoplasmic reticulum. Even though most of HSP90 are localized intracellularly, some can be expressed on cell membranes or, even, be released to extracellular milieu (eHSP90) in response to stress stimuli by active secretion or as a result of cell necrosis [4,5]. Approximately 400 client proteins depend on HSP90 chaperone activity, including kinases and transcriptional factors [6] (For an updated list of HSP90 interactors, see Picard's website [https://www.picard.ch/downloads/Hsp90interactors.pdf]).
Several of these client proteins play essential roles in cancer and inflammatory diseases. Indeed, tumor cells depend on intracellular HSP90 activity to survive and proliferate, since the overexpression of this chaperone supports their high metabolism. Similarly, proteins involved in inflammatory pathways depend on HSP90 chaperone activity, supporting HSP90 as a cornerstone for cancer and inflammatory-associated diseases. Hence, HSP90-targeted therapies have been considered a potential strategy for treating these conditions. Even though there is no current HSP90-targeted drug approved for clinical use, promising results obtained in pre-clinical studies are paving the way to the evaluation of HSP90 inhibitors in clinical trials for several types of cancers (www.clinical trials.gov).

The first HSP90 inhibitor described, geldanamycin, was isolated from the bacteria *Streptomyces hygroscopicus* [7], and it is currently known that naturally occurring HSP90 inhibitors can be produced by bacteria, fungi and vegetal species. These substances inhibit HSP90 activity by binding to different functional regions of the chaperone, as well as by binding to its co-chaperones, impairing the proper activation of the HSP90 machinery [3]. Biologically active compounds obtained from natural products have been widely used in drug development and medicine [8]. HSP90 natural inhibitors, such as geldanamycin, have served as scaffolds for novel synthetic or semi-synthetic entities with reduced unwanted adverse effects and improved efficacy [9,10], including 17-AAG, the first HSP90 inhibitor that entered a clinical trial [11].

On the basis of the aforementioned *i*) central role of HSP90 in the regulation of cellular proteins, *ii*) biological effects of natural products, and *iii*) the growing number of reports on new identified natural HSP90 inhibitors, in this review we present the current knowledge on the natural compounds that inhibit HSP90 activity and its effects on cancer and inflammation.

1.1. Modulation of HSPs in cancer

Tumor cells highly depend on the activity of oncogenes to survive, which has been designated as "oncogene addiction" [12]. Several proteins involved in oncogenic processes are HSP90 client proteins, including the human epidermal growth factor receptor 2 (HER2/neu), B-rapidly accelerated fibrosarcoma homologue B (B-Raf), tyrosine-protein kinase Src (Src), protein kinase B (AKT/PKB), breakpoint cluster region/Abelson murine leukemia virus (BCR/ABL), tumor protein 53 (P53) and octamer-binding transcription factor 4 (OCT4) [2,13]. Considering that HSP90 chaperone activity is essential for oncoprotein maturation and for the maintenance of the high rates of protein synthesis and metabolism (required for tumor cell high rates of proliferation, cytoskeletal organization and cell motility), HSP90 activity is essential for tumor development.

Indeed, HSP90 is overexpressed in tumor and serum of patients with a variety of cancer types, such as those of the breast, skin, blood, colon, prostate, lung, pancreas and liver. Moreover, HSP90 expression positively correlates with tumor malignancy and poor prognosis [14–24].

Extracellular HSP90 also favors tumor development. The interaction of extracellular HSP90 with matrix metalloproteinase (MMP)-2 and MMP-9 disrupts extracellular matrix and contributes to invasiveness and metastasis of different tumor types, including breast cancer, melanoma, fibrosarcoma and anaplastic lymphoma [22,25–29]. In addition, HSP90 promotes actin re-arrangement and cell migration by binding to the extracellular domain of tumor cell receptors HER2/ErbB2 and, consequently, inducing downstream signaling kinases such as phosphatidylinositol (PI) 3-kinase-AKT, MEK and ERK [5]. HSP90 also binds to low density lipoprotein receptor 1 (LRP1)/CD91, triggering the activation of AKT and NFκB, consequently promoting lamellipodia formation, increased integrin expression and cell migration of glioblastoma and colon cancer cells [30,31]. The binding of HSP90 to CD91 has also been shown in prostate tumor cells, which leads to ERK activation and contributes to cell migration [32]. In addition, HSP90 binding to TLR4 expressed on glioblastoma transactivates epidermal growth factor receptor (EGFR)/ErbB1 and also triggers cell mobility [33] (Fig. 1).

HSP90 machinery has been increasingly considered as a potential target for cancer treatment, since HSP90 simultaneously modulates multiple pathways, implicating in all the hallmarks of cancer (including proliferation, invasion, metastasis, angiogenesis and resistance to apoptosis) [34]. Promising pre-clinical data have been obtained with HSP90 inhibitors from both natural and synthetic sources in innumerous types of tumor cells and in animal models, such as lymphoma, melanoma, glioblastoma, breast, stomach, ovarian, pancreas, thyroid, colon and lung cancer [35–42]. Ansamycins, N-terminal binding HSP90 inhibitors from natural origin, were the first evaluated on clinical trials in 1999 in patients with unspecific solid tumors (www.clinicaltrials.gov; identifier NCT00003969). Since then, the range of cancer types included in clinical trials with HSP90 inhibitors from natural, semi-synthetic and synthetic origin has been increasing. Worthy of note, HSP90 inhibitors are less likely to induce resistance, as commonly observed with the use of chemotherapic agents that target individual proteins [43]. Prevention of resistance to HSP90 inhibitors is believed to result from the high dependence of tumor cells on HSP90 chaperone activity combined to the fact that the inhibition of HSP90 affects multiple targets and pathways.

Considering the fact that HSP90 is essential and abundantly expressed by normal cells, a major concern would be the selectivity of HSP90 inhibitors. However, there are some unique characteristics that make HSP90 inhibitors to preferentially target HSP90 expressed by tumor cells. In tumors, HSP90 is presented in tightly integrated multichaperone complexes (also called “chaperome complexes” or “epichaperome”) that have around 100-fold higher affinity for HSP90 inhibitors than the HSP90 expressed by non-tumor cells [3,44,45]. Consequently, HSP90 inhibitors accumulate for longer periods in tumors, whereas they are rapidly cleared from normal tissues [46,47]. The high affinity of tumoral HSP90 for inhibitors combined with the “oncogene addition” warrants the selective disruption of malignant cell cycle, supporting the high potential of HSP90 inhibitors in anti-cancer therapy.

1.2. Modulation of HSPs in inflammation

Besides the anti-tumor effect of HSP90 inhibitors, compelling data indicate that HSP90 modulation also reduces inflammation. To date, the study of anti-inflammatory effects of HSP90 inhibitors are restricted to preclinical research. *In vivo* experiments demonstrated that HSP90 inhibition negatively modulates the inflammatory response associated to allergy [48], arthritis [49,50], gastric ulceration [51], colitis [52], uveitis [53], atherosclerosis [54], lung inflammation [55] and sepsis [56], among others. The basic anti-inflammatory mechanism of HSP90 inhibitors relies in the impairment of NFκB activation, inhibition of inflammatory mediators and increased expression of HSP70. HSP90 activity also contributes to neuroinflammation and neurodegeneration. For example, HSP90 mediates the aggregation of amyloid-β and of phosphorylated tau, which are major features of Alzheimer’s disease [57–59]. The aggregation of α-synuclein and the resulting citotoxicity, hallmarks of Pakinson’s disease, also depends on HSP90 chaperone activity [60]. HSP90 inhibition prevents α-synuclein assembly, upregulates HSP70 expression and reduces α-synuclein-induced toxicity [60,61].

Several HSP90 client proteins are key signaling factors involved in inflammation, including transcription factors (such as NFκB and signal transducer and activator of transcription [STAT]), kinases (such as mitogen-activated protein kinases [MAPK], ERK, AKT, PI3K, p38) and the pattern recognition receptors TLR 9, TLR3 and TLR4/MD-2. The inhibition of HSP90 chaperone activity results in the arrest of inflammation; however, the anti-inflammatory effect of HSP90 inhibitors also results from the induction of HSF1 activation and consequent induction of HSP70 expression. Unlike in cancer, in inflammatory conditions, the induction of HSP70 is a desired effect of the HSP90 inhibitors. The HSP70 anti-inflammatory actions have been demonstrated in different experimental models, including sepsis [62], arthritis [63] and colitis [64] by inhibiting NFκB activation and inducing IL-10 production [62,63,65–70] (Fig. 2).

There is still much to be learned about the anti-inflammatory effects of HSP inhibitors; however, the available data strongly demonstrate promising effects. Inasmuch, given the recognized role of chronic inflammation in cancer development, the dual role of HSP90 inhibitors as anti-inflammatory and anti-tumor represents a promising therapeutic approach to the treatment of cancer and inflammatory diseases.

2. Natural inhibitors of HSP90

Natural products comprise a plethora of biologically active compounds that have been used with different applicability in medicine. Great part of current marketed drugs is derived from natural products, and approximately one third of new molecular entities approved by the Food and Drug Administration (FDA) are derived from natural sources [8,71]. Natural HSP90 inhibitors have been isolated from fungi, bacteria and vegetal species. Off-target toxicity is one of the worst limitations of natural HSP90 inhibitors, and, therefore, they have predominantly served as scaffolds for the development of the current synthetic or semi-synthetic HSP90 inhibitors with reduced unwanted adverse effects and improved efficacy. A remarkable example is the naturally occurring geldanamycin, the first HSP90 inhibitor described, which served as a prototype for more efficacious and safer antitumor drug analogues that have advanced to clinical trials [7,72] indicated in Table 1.

There are different mechanisms by which HSP90 inhibitors impair HSP90 activity. Most natural inhibitors modulate HSP90 activity by blocking ATP binding site in N-terminal domain and impairing ATPase activity, which is required for HSP90 effect. Other inhibitors bind to ATP binding site in C-terminal domain, and some bind to co-chaperones, impairing the formation of the functional HSP90 multimeric complex and, thus, indirectly blocking the HSP90 conformational cycle.

Even though the anti-tumor effect of N-terminal binders is well established, an undesirable side effect concerns the upregulation of

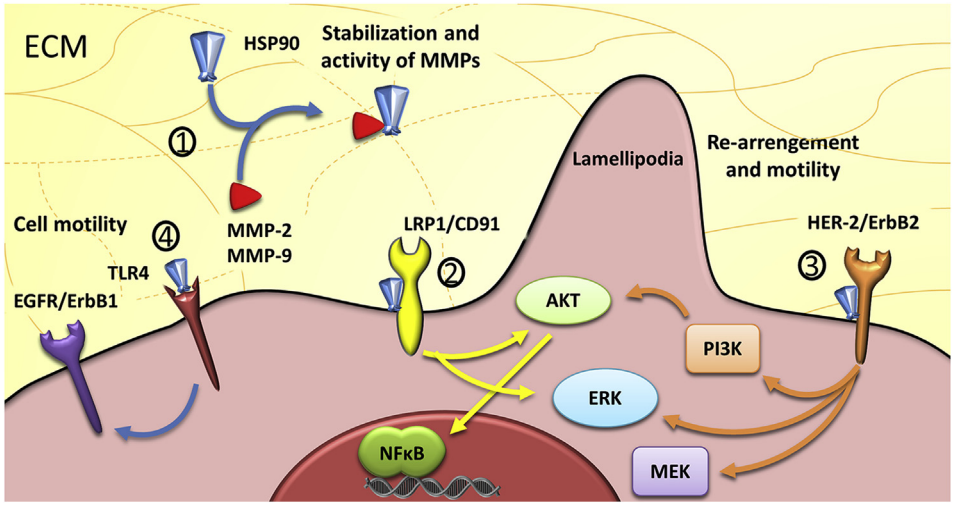


Fig. 1. HSP90 effect on tumor promotion. (1) Extracellular HSP90 complexes with MMP-2 and MMP-9, enhancing metalloproteinase activity, disrupting extracellular matrix (ECM), and facilitating invasion and metastasis. Surface HSP90 interacts with (2) LRP1/CD91 and (3) HER2, inducing ERK, PI3kinase, AKT and NFκB activation, promoting actin re-arrangement, lamellipodia formation and enhanced motility. (4) HSP90 interacts with TLR4 and transactivates epidermal growth factor receptor (EGFR) to promote cell migration. LRP1/CD91: low density lipoprotein receptor 1/cluster of differentiation 91; MMP: metalloproteinase; TLR4: toll-like receptor 4; VEGF: vascular endothelial growth factor.

HSP70 due to increased heat shock response via HSF1 activation, which favors tumorigenesis [73–75]. Increased heat shock response correlates with resistance and poor prognosis [76,77]. In this sense, the combined inhibition of HSP90 and HSP70 has been proposed as an alternative to overcome the effects of HSP70 expression in cancer [78–80]. Other alternative is the silencing of SIRT, a histone deacetylase required for the activation of HSF1 [37]. A third option is targeting either the HSP90 C-terminal domain (e.g. novobiocin) or the co-chaperones (e.g. gedunin), which do not induce heat shock response [81–85]. Binding to co-chaperones has an additional benefit, which is the sensitizing of tumor cells to HSP90 inhibition [83,86]. On the other hand, in the context of cancer defense, membrane bound and extracellular HSPs can be beneficial to the host by inducing anti-tumor immune responses. Surface HSP70 can upregulate antigen presentation by antigen presenting cells (APC) and augment recognition of tumor cells by cytotoxic T lymphocytes, leading to enhanced killing. Chaperokine activity of extracellular HSPs stimulates immune cells to produce cytokines, which can result in protection against tumors and serves as a tool for HSP-based anti-cancer immunotherapy [87–89].

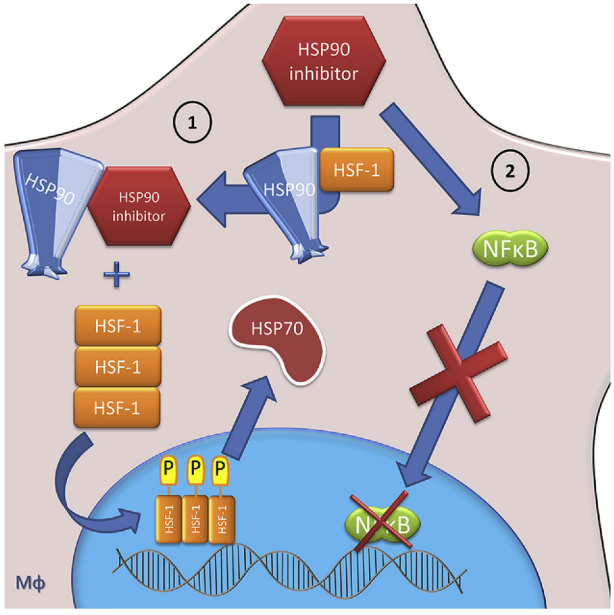


Fig. 2. HSP90 inhibition on inflammation. (1) HSP90 inhibitors bind to HSP90, displacing HSF-1 (Heat Shock Factor-1), which translocates into the nucleus and initiates HSP70 translation. (2) Inhibition of HSP90 impairs NFκB nuclear translocation and binding to DNA. NFκB: nuclear factor κB; DNA: deoxyribonucleic acid.

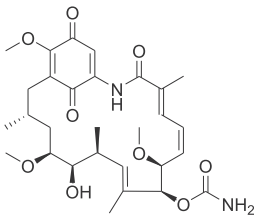
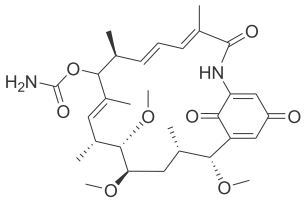
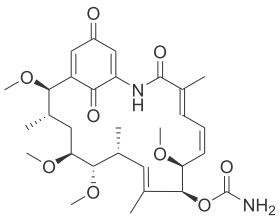
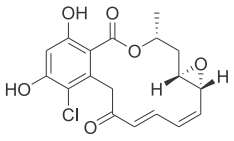
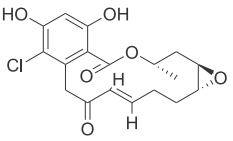
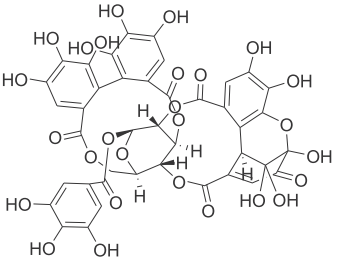
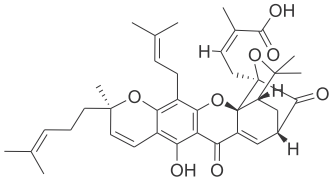
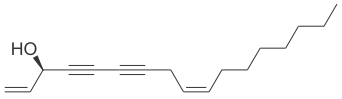
Another undesirable effect related to the induction of heat shock response by compounds that bind to N-terminal domain is the propensity to develop resistance. It is proposed that resistance can be avoided by the use of HSP90 inhibitors that selectively bind to co-chaperones and, therefore, fairly induce heat shock response. Other way to overcome the development of resistance is through combination therapies using HSP90 inhibitors and anti-tumor chemotherapeutics, claimed to be more promising, since it employs a combination of drugs with different targets [43]. Examples of combination therapies evaluated in clinical trials include ganetespib (a second generation resorcinol-triazole HSP90 inhibitor) with docetaxel [90], and tanespimycin (IPI504, geldanamycin analog) with trastuzumab [91]. In spite of the promising results obtained in clinical trials, some N-terminal HSP90 inhibitors have induced undesirable side effects such as ocular toxicity and hepatotoxicity [92,93].

2.1. N-terminal domain binders

2.1.1. Ansamycins

Ansamycins comprise a family of macrocyclic antibiotics that includes geldanamycin, herbimycins and macbecin. Geldanamycin is the most studied and has served as a prototype for natural product-based drug discovery in the last decades. Geldanamycin was discovered in 1970 in culture filtrates of the bacteria *Streptomyces hygroscopicus*, and inhibited the growth of bacteria, protozoa and fungi. Besides its antimicrobial activity, geldanamycin strongly inhibited the growth of human epithelial carcinoma and murine lymphocytic leukemia cells [7]. The first evidence that geldanamycin binds to HSP90 occurred in 1994 [94], but only in 1997 it was demonstrated that geldanamycin binds to the ATP binding site of the N-terminus of HSP90 [95]. Since then, several geldanamycin analogues have been developed aiming to improve efficacy and reduce toxicity, which results from a reactive quinone ring that forms a

Table 1
Inhibitors of HSP90 from natural source.

N-TERMINAL BINDERS HSP90 Inhibitor	Analogues	Source	Class	Structure
Geldanamycin	17-AAG 17-DMAG IPI-504 IP-493	*Streptomyces hygroscopicus*	Benzoquinone ansamycin	
Macbecin		*Nocardia* sp.	Benzoquinone ansamycin	
Herbimycin A		*Streptomyces hygroscopicus*	Benzoquinone ansamycin	
Radicicol (Monorden)	KF25706 KF58333	*Monosporium bonorden*	Macrocyclic lactone antibiotic	
Pochonin A	Pochoxime A Pochoxime B Pochoxime C	*Pochonia chlamydosporia*	Macrocyclic lactone antibiotic	
Geraniin (ellagitannin geraniin)		*Geranium thunbergii*	Tannin	
Gambogic Acid	NG-18	*Garcinia hanburyi*	Xanthonoid	
Panaxynol		*Panax ginseng*	Polyacetylene	

(*continued on next page*)

Table 1 (*continued*)

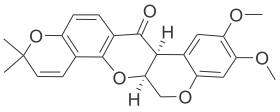
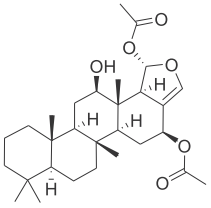
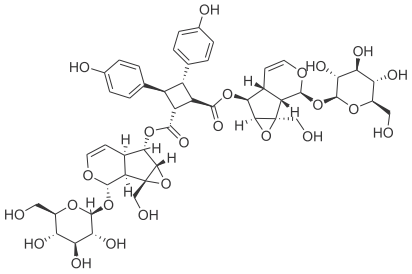
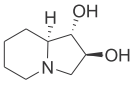
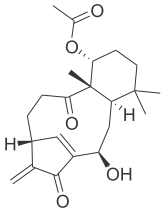
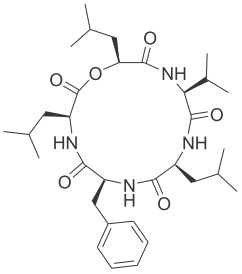
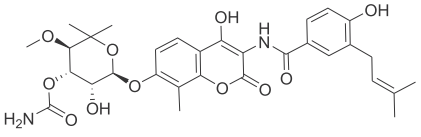
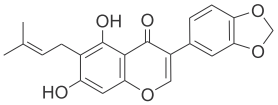
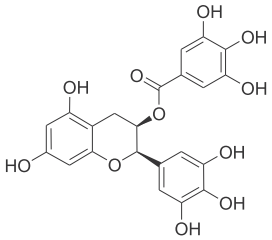
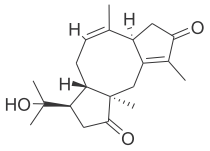
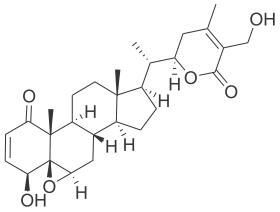
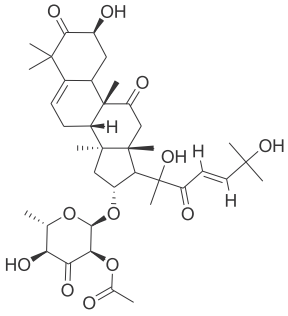
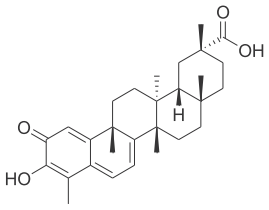
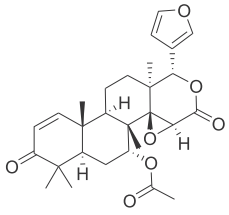
Deguelin		Fabaceae (Leguminosae) plants	Rotenoid	
Heteronemin		Marine sponges	Sesterpene	
Argenteoside A	C_9-type iridoids	Bignoniaceae plants	C_9-type iridoids	
MIDDLE DOMAIN BINDERS				
HSP90 Inhibitor	**Analogues**	**Source**	**Class**	**Structure**
(+)-lentiginosine	(−)-lentiginosine	*Astragalus lentiginosus*	Dihydroxyindolizidine alkaloid	
Kongensin A		*Croton kongensis*	Diterpene	
Sansalvamide A	Di-Sansalvamide A	*Fusarium* sp	Cyclic pentadepsipeptide	
C-TERMINAL DOMAIN BINDERS				
HSP90 Inhibitor	**Analogues**	**Source**	**Class**	**Structure**
Novobiocin (Cathomycin, Albamycin)	DHN1 DHN2	*Streptomyces niveus*	Aminocoumarin	
Derrubone		*Derris robusta*	Isoflavone	

Table 1 (*continued*)

Epigallocatechin-3-gallate		*Camellia sinensis*	Catechins	
18-hydroxyhypoestenone	Brassicicene S Fusicomycin B	*Alternaria brassicicola*, *Hypoestes forsskaolii* (Vahl)	Fusicoccane diterpene	
CO-CHAPERONE BINDERS				
HSP90 Inhibitor	**Analogues**	**Source**	**Class**	**Structure**
Withaferin A	withanolides	Solanacea plants	Steroidal lactones	
Cucurbitacin D	Cucurbitacins	Cucurbitacea plants	Tetracyclic triterpenes	
Celastrol		*Tripterygium wilfordii*; *Celastrus regelii*	Triterpene	
Gedunin		Meliaceae plants	Triterpene	

All chemical structures were drawn by Chemdraw 8.0 software.

semiquinone, releasing toxic superoxide radicals [96]. The anti-tumor effects of geldanamycin and its analogues have been largely demonstrated in *in vitro* and *in vivo* pre-clinical studies against different tumor types, such as colon adenocarcinoma, ovarian, breast cancer cells [97,98] and in xenograft model of prostate cancer [99,100]. Geldanamycin reduced the expression and activity of HER-2/ErbB2, inducing its ubiquitination and proteasomal degradation in tumor cells *in vitro*, as well as impaired subcutaneous growth of cells transfected with ErbB2 in nude mice [97,101,102]. The positive outcomes obtained with geldanamycin supported the first clinical trials in 1999, when the effect of 17-AAG was evaluated against unspecific solid and hematological tumors (www.clinicaltrials.gov; *identifiers NCT00003969* and *NCT00004065*). In the past two decades, progress has been made within the clinical evaluation of geldanamycin derivatives in cancer. According to the US National Institutes of Health, geldanamycin analogues 17-AAG, 17-DMAG, IPI-493 and IPI-504

(retaspimycin) have been tested in more than fifty phase I, II and III clinical trials since 1999 in the USA, either as monotherapy or as combined therapy. The clinical limitations obtained with 17-AAG were partially overcome by 17-DMAG, which is more potent and induce reduced side effects. IPI-493 was tested in a few terminated clinical trials, and following researches focused on the analogue IPI-504, which was well tolerated by patients with gastrointestinal tumors and non-small-cell lung cancer [103,104] The evident anti-tumor effect of these substances has greatly contributed to establish HSP90 as a target for anti-cancer therapy. A detailed review on clinical studies of HSP90 inhibitors is provided by Hong et al., 2013 [105].

Inhibition of HSP90 by ansamycins also impairs inflammation in pre-clinical studies *in vitro* and *in vivo*. Geldanamycin and its derivatives reduced the production of inflammatory mediators, such as NO, PGE_2, TNF-α, IL-1β, IL-6 and IL-10, in LPS-stimulated murine macrophage cell line (RAW 264.7) *in vitro* [106]. Geldanamycin also attenuated symptoms of collagen-induced arthritis in mice reducing cartilage destruction and bone erosions, impairing the production of inflammatory mediators, the infiltration of inflammatory cells and synovial hyperplasia [107]. Another effect of geldanamycin was the prevention of NLRP3 inflammasome activation, caspase-1 activity and IL-1β, as shown in a model of age-related macular degeneration in human retinal pigment epithelial cells, a disease that leads to blindness among the elderly [108]. In a rat model of endotoxin-induced uveitis, 17-AAG reduced leukocyte adhesion, vascular leakage, NFκB, hypoxia-inducible factor (HIF)-1α, p38 and PI3K activity, and the levels of pro-inflammatory mediators vascular endothelial growth factor (VEGF), TNF-α and IL-1β [53].

Macbecin is another ansamycin, identified in the culture broth of *Nocardia* sp., which binds to HSP90 N-terminal and displays anti-tumor activity *in vitro* and *in vivo*. Macbecin is cytotoxic against leukemia and colon cancer cells, and impairs the development of murine prostate carcinoma xenograft tumors [109]. Herbimycin A, B and C, identified in *S. hygroscopicus* fermentation broth, were named according to their herbicidal activity [110]. A moderate anti-tumor activity of herbimycin A was observed in mouse Ehrlich ascites carcinoma [111]; however, its derivatives presented improved effect. In spite of these findings, the anti-tumor activity of herbimycins does not yield effects robust enough to justify further studies. The anti-inflammatory effect of herbimycin A was shown in human intestinal epithelial cells (HT-29) stimulated with enterotoxin of *Bacteroides fragilis in vitro*. HSP90 inhibition by hebimycin A decreased IKK and NFkB activation, reducing the expression of IL-8 and COX-2 [112].

2.1.2. Radicicol and pochonins

Radicicol is a fungal metabolite with fungistatic properties originally identified in *Monosporium bonorden* [113], that binds to HSP90 N-terminal domain and impairs the growth of several tumor cell lines [114,115]. Radicicol has a chemical instability hindering its efficacy in animal models. A series of radicicol analogues was developed, aiming at increasing metabolic stability. The analogue 14,16-dipalmitoyl-radicicol reduced tumor size in mice models of mammary carcinoma, and suppressed the secretion of VEGF, impairing angiogenesis [116]. Its anti-inflammatory activity was shown *in vitro*, by protecting bovine pulmonary arterial endothelial cell permeability [117], and impairing IL-8 gene expression via the blockade of ERK1/2 and p38 pathway on THP1 human macrophage cell line [118]. Radicicol administration *in vivo* impaired intestinal inflammation in a murine model of sepsis [119].

Pochonins A-F are radicicol-related metabolites, identified in *Pochonia chlamydosporia* that also have anti-tumor activities [120]. Their first biological activities were described as inhibitors of herpes simplex virus 1 and of the protozoan *Eimeria tenella*. Later, it was shown that pochonins A and D directly bind to HSP90 with slightly lower affinity than radicicol [121]. Several pochonins and pochonin analogues, including pochoximes, have been completely synthesized, and have high affinity and efficacy against tumor cells [121,122]. Of special note, pochoxime A is highly toxic to breast cancer cell lines that overexpress HER2, and reduced tumor development in an *in vivo* breast tumor xenograft model [122].

2.1.3. Geraniin

Geraniin is a tannin present in the roots of the vegetal species *Geranium thunbergii* [123] shown to have several biological activities, including anti-inflammatory [124] and anti-tumor effects. The latter has been demonstrated against several tumor cell lines *in vitro*, such as human melanoma, osteosarcoma and glioma [125–127]. Recently, it has been demonstrated that the anti-tumor action of geraniin relies on the inhibition of HSP90 activity [128]. Noteworthy, geraniin inhibited glioma growth in mouse xenograft models *in vivo*, via STAT-3 impairment [126].

Anti-inflammatory activity of geraniin was shown in the murine macrophage cell line RAW264.7 *in vitro* and in acute lung injury model *in vivo*, by reducing the levels of pro-inflammatory cytokines (IL-6, TNF-α and IL-1β). This effect is correlated with the suppression of Akt phosphorylation and the consequent impairment of NFκB translocation. Still, geraniin suppressed the activation of antioxidant genes, by up-regulating Nrf2/HO-1 pathway, playing a protective role in inflammation [129,130].

2.1.4. Gambogic acid

Gambogic acid is a major xanthonoid constituent of gamboge, a resin obtained from *Garcinia hanburyi* (Clusiaceae) [131]. The cytotoxic effect of this compound was initially shown on HeLa cells [132], and further against different cancer types *in vitro* and *in vivo*, including gastric carcinoma, glioblastoma and colorectal cancer. Recent reports have shed light on the anti-tumor mechanisms of gambogic acid, demonstrating that it induced apoptosis, as well as impaired migration, invasion of tumor cells [133,134], and angiogenesis [135]. Gambogic acid also has anti-inflammatory effects *in vitro* and *in vivo*, impairing rheumatoid and antigen-induced arthritis [136,137] and psoriasis [138], by reducing the levels of TNF-α and IL-1β, and the nuclear translocation of NFκB.

The interaction of gambogic acid with HSP90 has been shown to occur via the N-terminal domain, resulting in the inhibition of its chaperoning activity [139]. However, it has been recently reported that gambogic acid binds to the middle domain of the HSP90β isoform, decreasing the client proteins ErbB2, AKT and cyclin dependent kinase 4 (CDK4) in breast cancer cells [140]. Noteworthy, these authors state that this xanthonoid does not bind to GRP94 and TRAP1 HSP90 isoforms, but specifically to different conformational states of HSP90β. Further studies on this interaction are necessary to elucidate the mechanism by which gambogic acid inhibits HSP90 machinery.

2.1.5. Panaxynol

Panaxynol, also known as carotatoxin or falcarinol, is a polyacetylene compound found in Apiaceae and Araliaceae families [141]. Biological activities of panaxynol include anti-tumor and anti-inflammatory [142,143]. Panaxynol anti-tumor activity is due to the reduction of cyclin E mRNA expression, resulting in decreased cell proliferation [144]. Panaxynol interacts with both N- and C-terminal domains of the ATP-binding pocket of HSP90 homodimer, impairing angiogenesis, as well as proliferation and viability of cancer stem cells (CSC) and non-CSC populations from non-small cell lung cancer (NSCLC), without induction of HSP70 expression [145].

Panaxynol anti-inflammatory effect has been demonstrated in *in vivo* models of intestinal inflammation and inflamed macrophage-induced cardiomyocyte hypertrophy, by upregulating Nrf2/HO-1, reducing the levels of inflammatory cytokines, lipid peroxidation and inflammatory cell infiltration [146,147].

2.1.6. Deguelin

Deguelin is a rotenoid, which is a natural occurring insecticide found in Fabaceae (Leguminosae) vegetal family [148]. Oh and collaborators [149] have demonstrated that deguelin directly binds to the N-terminal HSP90 ATP-binding pocket and impairs HSP90 chaperone function *in vitro* and *in vivo*. This rotenoid reduces the expression of HSP90 client proteins, such as HIF-1 and PI3K-Akt, in lung, gastric and prostate cancer cell lines and in subcutaneous xenograft mouse model. Recently, the anti-tumor activity of deguelin has been described against Head and Neck Squamous Cell Cancer (HNSCC) cell line, via the downmodulation of IGF1R-Akt and EGFR-Akt pathways, and apoptose induction [150]. Deguelin also reduces p38 MAPK expression in colorectal cancer cells, leading to apoptosis and reduced tumor size on subcutaneous xenograft mouse model [151].

The anti-inflammatory effect of deguelin was shown in an *in vivo* model of allergic airway inflammation by inhibiting NFκB nuclear translocation and leukocyte infliltration to inflamed tissue [152]. Deguelin also played a protective role in a model of inflammation-mediated bone loss by impairing NFκB activation osteoclastogenesis [153].

2.1.7. Heteronemin

Heteronemin is a sesterpene isolated from marine sponges [154]. Docking studies revealed that heteronemin binds to the ATPase HSP90 site with a better affinity than 17-AAG [155]. Biological evidence of heteronemin HSP90 inhibitory activity was confirmed on LNcap prostate cancer cell line, in which it led to heat shock response increasing HSP70 expression, tubulin acetylation and HSF-1 phosphorylation. Accordingly, HSP90 client proteins such as IRAK1, pAkt, XIAP, Rb2, HDAC1, PCNA, CDK4 and STAT3 phosphorylation were downregulated *in vitro*. Together, *in silico* and biological data provide strong evidence of HSP90 inhibitory activity of heteronemin. In addition, it has been shown that heteronemin inhibits Ras farnesylation, consequently inhibiting the downstream MAPK signaling, as well as proliferation and survival of acute myeloid leukemia cells [156].

2.1.8. C_9-type iridoids

Dal Piaz and collaborators (2013) [157] performed an HSP90 target-oriented screening testing natural compounds, including iridoids. Among them, verminoside, a C_9-type iridoid inhibited HSP90 ATPase activity. This finding motivated further analysis of new phytochemicals from Bignoniaceae family, known to be rich in C_9-type iridoids. Among the Bignoniaceae C_9-type isolated iridoids, Argenteoside A had very high affinity towards HSP90α chaperone and binds to its N-terminal domain, as demonstrated by surface plasmonic resonance and molecular docking analysis. The impairment of HSP90 ATPase activity and the consequent downregulation of the expression of client proteins, such as p-Akt and ERK1/2, suggest a potential antitumor effect of Argenteoside A against HeLa (epithelial carcinoma) cells.

2.2. Middle-domain binders

2.2.1. Lentiginosine

Lentiginosine is a dihydroxyindolizidine alkaloid present in the leaves of the vegetal species *Astragalus lentiginosus* (Fabaceae), which inhibits fungal amyloglucosidase [158]. Recently, it has been shown that this alkaloid (and a series of synthetic derivatives) interacts with the HSP90 middle-domain and impairs HSP90 ATPase activity, without interacting with the N-terminal ATP binding site [159]. Since the middle domain directly interacts with the co-chaperone Aha1 (and with its yeast homologue Hch1) [160], it might be a promising binding site for HSP90 inhibitors. However, this effect, as well as the biological activity of lentiginosine remains to be studied.

2.2.2. Kongensin A

Kongensin A is a diterpene first isolated from the aerial parts of the Chinese plant *Croton kongensis* [161]. The antitumor effect of this diterpene was recently described against epithelial carcinoma (HeLa), osteosarcoma (U-2 OS) and colon cancer (HT-29) [162]. Kongensin A inhibit the phosphorylation of the receptor-interacting protein (RIP)1/RIP3 signaling pathway, resulting in anti-necroptotic and pro-apoptotic activities. These activities rely on the inhibition of HSP90-Cdc37 complex, since this compound covalently binds to the amino acid Cys420 of the HSP90β middle domain and, therefore, reducing the expression of the client proteins ErbB2, AKT, EGFR and B-Raf.

2.2.3. Sansalvamide

Sansalvamide is a cyclic pentadepsipeptide antibiotic originally obtained from the marine fungus *Fusarium* sp., which is cytotoxic against colon carcinoma and melanoma cells [163]. This compound has also been described as a topoisomerase inhibitor of the pathogenic poxvirus *Molluscum contagiosum* [164]. There are only a few studies on the biological activity of the naturally occurring sansalvamide, since it has a depsipeptide moiety that is unstable *in vivo*, being inactivated by esterase enzymes that break its ester linkage [165]. To overcome this drawback, many derivatives were designed to enhance stability, selectivity and potency against several tumor cell lines, including colon and pancreatic cancer [166,167]. The anti-tumor effect of sansalvamide A derivatives has been associated with the inhibition of HSP90 chaperone activity, by its binding to the HSP90 middle domain, which impairs the coupling of co-chaperones [168].

2.3. C-terminal domain binders

2.3.1. Coumarin antibiotics

Novobiocin and coumermycin are natural antibiotics isolated from *Streptomyces* species [169,170] that belong to the aminocoumarin class, which is known to inhibit bacterial cell division by inhibiting the ATPase activity of DNA gyrase [171]. Pre-clinical data revealed their potential anti-tumor activity by destabilizing oncogenic protein kinases. It was revealed that novobiocin binds to the ATP-binding site of HSP90 C-terminal, inhibiting HSP90-p23 and HSP90-HSP70 interactions; however, with weak affinity [172]. Efforts have been made to develop more efficacious analogues by means of structure-affinity relationships, resulting in specific HSP90 inhibitors [173]. Since these analogues led to client protein degradation and anti-proliferative effects against tumor cell lines, including breast cancer and prostate carcinoma, they were considered promising for further evaluation *in vivo*. The anti-inflammatory effect of novobiocin has been demonstrated in a murine model of inflammatory bowel disease, inhibiting leukocyte infiltration, production of inflammatory mediators and activation of NFκB [174].

In spite of the lack of reports on the co-crystal structure of the HSP90 C-terminus bound to inhibitors, different techniques have been used to confirm their binding site at HSP90 C-terminal domain. Novobiocin binds to the C-terminal domain of HSP90, through truncation studies using solid-phase binding assays [172].

It was further confirmed by point mutation analysis that novobiocin competitively inhibited the binding of ATP-sepharose to HSP90 C-terminal fragment [175]. Novobiocin disrupts HSP90 interaction with p23 and HSP73 [175], as well as impairs HSP90 dimerization [176]. Blagg and co-workers have elucidated the HSP90 C-terminal domain as the binding site and also confirmed the binding of novobiocin at this site by an integrated approach that employs protease fingerprinting, photoaffinity labeling and bioinformatics assays [177]. The enthusiasm with the discovery of novobiocin was short lived due to its poor HSP90 inhibitory activity (IC_{50} around 700 μM) [178]. However, many attempts are still being made to improve the activities of coumarin antibiotics [179].

2.3.2. Derrubone

Derrubone, an isoflavone originally identified in the vegetal species *Derris robusta* (Fabaceae) [180], was discovered to inhibit HSP90 activity by high throughput screening assays [181]. Derrubone and its synthetic analogues have been shown to degrade the HSP90 client protein HER2 and impair *in vitro* proliferation of breast carcinoma and colon cancer cell lines [181,182]. Chimeric analogues of novobiocin and derrubone have been developed; however the anti-proliferative effect of these substances was not improved [183].

2.3.3. Epigallocathechin

Epigallocatechin-3-galate is also an HSP90 modulator that binds to C-terminal ATP binding site. Epigallocatechin-3-galate is a polyphenol from the green tea species *Camellia sinensis* [184] shown to inhibit proliferation and to induce apoptosis of adrenal, pancreatic and breast cancer cells *in vitro* [185,186]. A recent report describes the anti-tumor effect of orally administered epigallocatechin-3-galate *in vivo*, by reducing tumor and metastasis in a mouse xenograft model of human prostate cancer [187]. Like novobicion, epigallocatechin-3-gallate binds to the C-terminal domain, which was demonstrated by truncation studies of the immobilized epigallocatechin-3-gallate with HSP90 [188]. Epigallocatechin-3-galate reduces the levels of several HSP90 client proteins associated with cancer, such as ErbB2, Raf-1, phospho-AKT, pERK and Bcl-2, through the inhibition of HSP90 chaperone dimerization and function. Recently, series of semi-synthetic and synthetic analogues of epigallocatechin-3-gallate have been developed aiming at overcoming its poor drug-like properties accounted by the multiple phenolic hydroxyl moieties and a metabolically labile ester in its structure. In fact, such molecular modifications showed improved HSP90 inhibition and anti-tumor efficacy *in vitro* [189].

Epigallocatechin-3-gallate attenuates microglial inflammation by inhibiting both canonical and non-canonical NLRP3 inflammasome activation via TLR4 in murine BV2 microglial cell line [190]. It also impaired inflammasome activation in macrophages, the release of inflammatory cytokine and the articular infiltration of neutrophil in a mouse model of gout [191].

2.3.4. Fusicoccane diterpenes

Fusicoccanes are diterpenes with the dicyclopenta[a,d]cyclooctane ring system. Its biological activities include anti-bacterial [192] and anti-plasmodium activity [193]. In 2018, Li and collaborators [194] reported and anti-inflammatory effect of a fusicoccane-type diterpenoid (Brassicicene S) isolated from the phytopathogenic fungus *Alternaria brassicicola*. Brassicicene S inhibited nitric oxide (NO), TNF-α and IL-1β production in LPS stimulated RAW264.7 macrophage cell line. Moreover, this compound reduced iNOS expression and abolished NFκBp65 nuclear translocation. Fusicoccane diterpenes also have anti-tumor activity, as demonstrated by the treatment of five human cancer cell lines with fusicoccane diterpene fusicomycin B [195]. It also inhibited migration and invasion, as well as reduced MMP-2 and MMP-9 expression and activity in human hepatocellular carcinoma SMMC7721 cells. Another fusicoccane diterpene, 18-hydroxyhypoestenone, isolated from *Hypoestes forskaolii* (Acanthaceae) was recently reported to inhibit HSP90 activity [196]. This compound reduced the proliferation and induced apoptosis of the HeLa and Jurkat cancer cells, downregulating pAkt and pERK expression. Interestingly, no heat shock response was observed, once HSP70 or HSP90 expressions were not increased. This phenomenon was associated to the binding of 18-hydroxyhypoestenone to the C-terminal domain of HSP90, demonstrated by molecular docking. Surface Plasmon Ressonance results demonstrated a good interaction between 18-hydroxyhypoestenone and HSP90.

2.4. Co-chaperone binders

2.4.1. Withaferin A

Withanolides are natural occurring steroidal lactones present in plants from Solanaceae family. These compounds have a well described anti-tumor activity, inhibiting *in vivo* tumor growth and metastasis of ovarian cancer stem cells [197]. They also induce apoptosis of breast cancer cells and have the HSP90 chaperone as a target [198]. Withaferin A, the most studied withanolides, has anticancer activity against a number of tumor types presenting a pleiotropic role such as pro-apoptotic, anti-proliferative, anti-migratory, anti-invasiveness. Withaferin A inhibits HSP90 by disrupting HSP90-Cdc37 interaction [199]. According to Wang and collaborators (2012) [198], withanolides trigger oxidative insults to HSP90, inducing HSP90 oxidation and aggregation, resulting in loss of chaperone function. Withaferin A has been considered as an IκB kinase inhibitor, since it prevents IκB phosphorylation, NFκB nuclear translocation, DNA binding and transcription, also acting as an anti-inflammatory compound [200].

Withaferin A anti-inflammatory effect was demonstrated in macrophage-like cells, by downregulating NFκB nuclear translocation and reducing pro-inflammatory cytokine release upon LPS stimulus [201–203]. Still, withaferin A reduced inflammasome signaling by reducing caspase-1, IL-1β and IL-18 production by THP-1 cells [201]; reduced COX-2 expression and PGE_2 production on BV2 cells [202], as well as repolarized RAW 264.7 cells from M1 pro-inflammatory-type macrophage towards M2-type macrophages [203]. Withaferin A also has anti-inflammatory effects *in vivo*, as demonstrated in a rat model of adjuvant-induced arthritis [204], in a mouse model of pulmonary fibrosis and in a mouse model of traumatic spinal cord injury [205,206].

2.4.2. Cucurtabicin D

Cucurbitacins are tetracyclic triterpenes present in Cucurbitaceae family plants. Cucurbitacin D displays anti-tumor activity by inhibit CDK1 and CDK4, inducing cell cycle arrest. It inhibits STAT3 and Akt signaling, as well as NFκB nuclear translocation, inhibiting proliferation. Curcubitacin D also reduces MMP2 and MMP9 production reducing migration and metastasis [207–210]. In addition to these activities, Cucurtabicin D modulates glucose metabolism by reducing the expression of GLUT1 receptor. A molecular docking suggests that cucurbitacin D directly binds to GLUT1, reducing glucose uptake by prostate cancer cell line, reducing migration and, leading to a cell cycle arrest and apoptotic cell death [211]. Hall and collaborators (2015) [212] reported, by immunoprecipitation, that cucurbitacin D disrupts HSP90 interaction with both co-chaperones Cdc37 and p23, without inducing heat shock response, resulting in HSP90 client protein degradation. No anti-inflammatory effect has been reported for curcubitacin D. Curcubitacin B and E play anti-

tumor and anti-inflammatory activities; however, the mechanism has not been correlated to HSP90 inhibition.

2.4.3. Celastrol

Celastrol (also named tripterine or tripterin) is a pentacyclic triterpenoid from the vegetal species *Tripterygium wilfordii* (Celastraceae), commonly used in popular Chinese medicine for the treatment of several inflammatory conditions [213]. Celastrol is a multitarget compound that has a wide range of biological activities. Its potent anti-inflammatory effects have been long demonstrated in several pre-clinical data obtained by using different animal models, including rheumathoid arthritis [214] and airway inflammation [215]. Celastrol impairs NFκB activation by directly targeting the cysteine 179 in the IKK, which supports both anti-inflammatory and anti-tumor effects [216].

The anti-tumor effect of celastrol has been originally demonstrated *in vitro* against epidermoid nasopharyngeal carcinoma, glioblastoma, breast, lung, ileocecal and ovarian cancer cell lines [217]. Further reports showed that celastrol has cytotoxic effects against a wider variety of cell lines, such as prostate carcinoma and leukemia cell lines, in which the inhibition of HSP90 decreased the levels of client proteins, including BCR-ABL and EGFR, by an interaction independent of N-terminal ATP-binding pocket [218]. The administration of celastrol significantly impaired the development of breast, prostate and pancreatic tumor xenografts *in vivo*. Moreover, it decreased metastasis and increased survival [219]. It was described that celastrol disrupts HSP90-Cdc37 and HSP90-p23 complexes [220,221], leading to the degradation of the HSP90 client proteins AKT and CDK4, as well as increased levels of HSP70. Celastrol has also been shown to decrease the expression of MMP-2 and MMP-9, impairing the invasion of hepatocellular carcinoma cells [222].

2.4.4. Gedunin

Gedunin is a limonoid constituent of the vegetal species *Azadirachta indica* and *Carapa guianensis*, and other members of the Meliaceae family, which has a wide range of biological activities [223]. For more than a decade, the antimalarial properties of gedunin were the best studied [224]; however, its anti-tumor, anti-allergic and anti-inflammatory activities were subsequently demonstrated in different experimental models [48,49,225].

The anti-inflammatory activity of gedunin and its related limonoids have been primarily demonstrated in a mouse model of airway inflammation, in which the oral administration of these compounds impaired NFκB activation and the production of the eosinophilotactic mediators interleukin (IL)-5 and eotaxin/CCL11 [226]. Subsequent studies demonstrated that the intraperitoneal administration of gedunin also impaired allergic lung response and articular inflammation, inhibiting leukocyte infiltration and the production of chemokines, cytokines and lipid mediators [48,49]. Gedunin also directly modulates neutrophil, macrophage and T lymphocyte activation, by inhibiting migration, production of inflammatory mediators and activation of the transcription factors NFκB and NFAT, among others [48,49,227]. Even though the anti-inflammatory activity of gedunin has been demonstrated in different animal models *in vivo*, its anti-tumor *in vivo* activity has only been recently published. Orally given gedunin reduced the development of oral carcinoma in hamsters, inhibiting PI3K/Akt and NFκB pathways, as well as diminished VEGF levels [228]. Another evidence of gedunin *in vivo* activity was reported in mouse pancreatic xenograft model, in which the intraperitoneal administration of gedunin impaired tumor growth and metastasis via the negative modulation of the hedgehog signaling pathway [42].

Gedunin was first identified as a HSP90 inhibitor by means of connectivity map [229]. Later, it was demonstrated that gedunin impairs HSP90 activity by an indirect mechanism, impairing the interaction of HSP90 with the co-chaperone Cdc37 and, consequently, disrupting client proteins in MCF-7 breast cancer cells [84]. In 2013, Patwardhan and co-workers demonstrated that gedunin binds to another HSP90 co-chaperone, the p23 protein, leading to the apoptosis of several tumor cells, including breast and cervical carcinoma [85]. Gedunin binding site on p23 (pdb code: 1EJF) was mapped by molecular docking studies [230]. The anti-HSP90 activity strongly supports both anti-inflammatory and anti-tumor effects of this limonoid.

Recently, our group has revealed that gedunin is a multitarget compound, which might contribute to the modulation of the inflammatory response induced by pathogen-associated molecular patterns (PAMPs). By using *in silico* analysis, we have shown that gedunin binds to caspase-1, TLR2, TLR3 and to the LPS-binding component myeloid differentiation factor-2 (MD-2) of the MD-2/TLR4 complex [231,232]. Interestingly, crystal structures of MD-2 and p23 revealed that these two proteins possess a similar anti-parallel β-sandwich fold, with a well-defined hydrophobic pocket, implying that gedunin binds to MD-2 in a similar binding site. The binding of gedunin to MD-2 was further confirmed by surface plasmon resonance. *In vitro* and *in vivo* assays demonstrated that gedunin treatment impaired TLR2, 3 and 4 signaling, inhibiting the expression of nucleotide-binding domain and leucine-rich repeat protein-3 (NLRP3) inflammasome, caspase-1 activation and the production of IL-1β by macrophages. Worthy of note, gedunin is capable to elicit anti-inflammatory mechanisms *in vitro* an *in vivo* in both resting and stress conditions, via the production of heme oxigenase (HO-1) and IL-10, which enhances the therapeutic potential of this compound.

It is important to note that the inhibition of the co-chaperones p23, Cdc37 and Aha1 leads to the sensitization of tumor cells to HSP90 inhibitors, such as 17-AAG [83,86]. Therefore, the molecular mechanism of celastrol and gedunin to inhibit HSP90 represents a potential therapeutic strategy to increase sensitivity to HSP90 inhibitors and overcome resistance.

3. Conclusion

HSP90 is a promising target for the treatment of cancer and inflammatory diseases, which is supported by the central role displayed by HSP90 machinery in chaperoning oncoproteins, kinases and transcriptional factors involved in cancer and inflammation. Advances in pre-clinical and clinical studies are paving the way for the use of HSP90 inhibitors in the clinic as monotherapy or as combined therapy, as a strategy to avoid the development of drug resistance. Another strategy to avoid drug resistance is the indirect inhibition of HSP90 activity by silencing co-chaperones, a common mechanism of the natural inhibitors celastrol and gedunin. Considering HSP90 pleiotropic effects and the wide range of HSP90 client proteins involved in homeostatic processes, the selectivity of HSP90 inhibitors for “tumoral HSP90” is one of the great benefits of these compounds, which supports HSP90 as a druggable target. Natural HSP90 inhibitors have highly contributed to the knowledge concerning HSP90 involvement in cancer and inflammation, as well as to the identification and the development of new semi- or full-synthetic HSP90 inhibitors. Although off-target toxicity is one of the biggest limitations of natural HSP90 inhibitors, safety is being improved with the development of derivatives based on natural scaffolds, which aims at high efficacy and low toxicity of novel HSP90 inhibitors.

Declaration of competing interest

The authors declare to have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmech.2020.112063.

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