European Journal of Medicinal Chemistry 298 (2025) 118027

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: www.elsevier.com/locate/ejmech

Review article

Targeting the HGF/MET axis in cancer: therapeutic promise for natural compounds

Pouya Goleij [a,b,*], Mohammad Mahdi Heidari [c,d], Hossein Motevalli [e], Sajad Abolfazli [f], Mohammad Amin Khazeei Tabari [g], Aryan Rezaee [h], Danaé S Larsen [i], Maria Daglia [j,k], Michael Aschner [l], Haroon Khan [m,n,**]

[a] USERN Office, Kermanshah University of Medical Sciences, Kermanshah, 6715847141, Iran
[b] PhytoPharmacology Interest Group (PPIG), Universal Scientific Education and Research Network (USERN), Tehran, Iran
[c] Department of Pediatrics, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
[d] Aliasghar Clinical Research Development Center, Department of Pediatrics, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
[e] School of Medicine, Babol University of Medical Sciences, Babol, Iran
[f] Student Research Committee, School of Pharmacy, Mazandaran University of Medical Science, Mazandaran, 4815733971, Iran
[g] Student Research Committee, School of Medicine, Mazandaran University of Medical Sciences, Mazandaran, 4815733971, Iran
[h] School of Medicine, Iran University of Medical Sciences, Tehran, 1449614535, Iran
[i] School of Chemical Sciences, The University of Auckland, 23 Symonds Street, Auckland, 1010, New Zealand
[j] Department of Pharmacy, University of Naples "Federico II", Via D. Montesano 49, 80131, Naples, Italy
[k] International Research Center for Food Nutrition and Safety, Jiangsu University, Zhenjiang, 212013, China
[l] Department of Molecular Pharmacology, Albert Einstein College of Medicine, Bronx, NY, 10461, USA
[m] Department of Pharmacy, Faculty of Chemical and Life Sciences, Abdul Wali Khan University Mardan, Mardan, 23200, Pakistan
[n] Department of Pharmacy, Korea University, Sejong, 20019, South Korea

ARTICLE INFO

Keywords:
HGF/MET signaling pathway
Natural compounds
Cancer progression
Molecular targeting
Oncogenic signaling
Natural product-based therapy

ABSTRACT

The hepatocyte growth factor (HGF)/MET signaling pathway plays a pivotal role in cancer progression, metastasis, and therapeutic resistance, making it an attractive target for anticancer therapies. HGF, a multifunctional cytokine, binds to the MET receptor, triggering downstream pathways such as PI3K/AKT, MAPK/ERK, and STAT3, which regulate cell proliferation, survival, and epithelial-mesenchymal transition (EMT). Dysregulation of this pathway—through mutations, amplifications, or overexpression—contributes to tumorigenesis, drug resistance, and poor prognosis in various cancers, including lung, breast, gastric, and hepatocellular carcinomas. This review explores the molecular mechanisms of HGF/MET in cancer, highlights the therapeutic potential of natural compounds, and discusses ongoing clinical trials targeting this pathway. Despite advances in targeted therapies, resistance to MET inhibitors remains a clinical challenge, necessitating alternative strategies. Natural compounds, including flavonoids, curcumin, ginger derivatives, epigallocatechin-3-gallate (EGCG), honokiol, metformin, and resveratrol, exhibit potent inhibitory effects on the HGF/MET axis. These phytochemicals modulate MET expression, disrupt downstream signaling, and reverse chemoresistance by targeting key oncogenic mechanisms such as EMT, cancer stem cell (CSC) maintenance, and tumor microenvironment interactions. For instance, flavonoids like apigenin and quercetin suppress MET-mediated invasion, while curcumin inhibits PI3K/AKT/mTOR signaling. EGCG and honokiol demonstrate synergistic effects with conventional therapies, overcoming resistance in non-small cell lung cancer (NSCLC) and renal cell carcinoma. By synthesizing preclinical and clinical findings, this work highlights the therapeutic potential of phytochemicals as adjunctive or alternative agents, offering innovative approaches to enhance the efficacy and outcomes of cancer treatments.

* Corresponding author. USERN Office, Kermanshah University of Medical Sciences, Kermanshah, 6715847141, Iran.
** Corresponding author. Department of Pharmacy, Faculty of Chemical and Life Sciences, Abdul Wali Khan University Mardan, Mardan 23200, Pakistan.
E-mail addresses: medgenetic.1991@gmail.com (P. Goleij), Heidari.mo@iums.ac.ir (M.M. Heidari), hossein.motevalli1999@gmail.com (H. Motevalli), Dr.s.abolfazli75@gmail.com (S. Abolfazli), Aminkhazeeitabari@gmail.com (M.A. Khazeei Tabari), rezaee.aryan@gmail.com (A. Rezaee), d.larsen@auckland.ac.nz (D. S Larsen), maria.daglia@unina.it (M. Daglia), michael.aschner@einsteinmed.edu (M. Aschner), haroonkhan@awkum.edu.pk (H. Khan).

https://doi.org/10.1016/j.ejmech.2025.118027
Received 23 May 2025; Received in revised form 9 July 2025; Accepted 29 July 2025
Available online 30 July 2025

1. Introduction

Cancer remains one of the most significant global health challenges, imposing substantial psychological and financial burdens on affected individuals and their families. Its incidence has been rising in recent years, with epidemiological data indicating that approximately one in every four individuals may develop cancer during their lifetime, underscoring its high lifetime risk [1]. The development of effective cancer therapies remains one of the most extensively studied areas in biomedical research, owing to the high heterogeneity of tumor cells, which contributes to the complexity and challenges inherent in cancer treatment [2]. Cancer progression and normal physiologic processes are affected by HGF/MET signaling pathway, where HGF functions as a mitotic protein similar to some of the tumor cytotoxic fibroblast-derived cells [3,4]. Additionally, a cellular mechanism known as invasive growth, which facilitates cell proliferation, invasion, and survival, is mediated by the hepatocyte growth factor (HGF) signaling pathway. This pathway is activated when HGF binds to its receptor, a tyrosine kinase encoded by the *MET* proto-oncogene. Nevertheless, repetitive activation of MET can result in neoplasm development and metastasis [5]. Other receptor tyrosine kinase-associated signaling pathways such as MAPK, NF-κB, PI3K/AKT, RAC1, and STAT3, have been shown to share overlapping functions with the HGF/MET pathway. These pathways contribute to both physiological processes, including embryogenesis and postpartum tissue regeneration, as well as pathological processes such as cell migration, increased mitotic activity, and angiogenesis [6] (see Table 1).

Natural compounds, specifically plant-based extracts and phytochemicals, have gained greater attention in cancer management and prevention due to their anti-microorganism, anti-inflammatory, and antioxidant characteristics, especially as alternative therapeutic regimes [7]. Notable ingredients inherent to these natural compounds include Butein [8], kuwanon M [9], and genistein [10,11]. They have shown efficacy in ovarian cancer through activation of the IL-6/STAT3/FoxO3a pathway, lung cancer cells by modulating mitochondrial function, and colon and breast cancer cells, altering oxidative stress and inflammation, respectively.

Despite the development of anticancer drugs targeting various cancer-related mechanisms and molecular pathways, overall survival rates have not markedly improved. This may be attributed to several limitations, including the inability of current therapies to comprehensively inhibit complex signaling networks, the emergence of tumor resistance to therapeutic agents, and significant drug-associated toxicity. These challenges have spurred growing interest in adjunctive and alternative therapeutic strategies aimed at enhancing treatment efficacy while minimizing adverse effects [12].

This review aims to examine the mechanisms of natural compounds while targeting the HGF/MET pathway, and their effects on angiogenesis, invasion, migration, apoptosis, and EMT/stemness, to broaden the understanding of alternative therapeutic strategies.

2. Overview of the HGF/MET signaling pathway

Hepatocyte growth factor (HGF), also known as scatter factor (SF), was discovered in the early 1980s [13]; it functions as a c-MET receptor ligand (Fig. 1) [14]. The gene encoding pro-hepatocyte growth factor (pro-HGF) comprises 18 exons and 17 introns and is located on chromosome 7q21.11 [13]. Pro-HGF represents the inactive precursor form of the growth factor, characterized by a dimeric structure composed of a 57 kDa heavy α-chain and a 26 kDa light β-chain, linked via disulfide bonds [15]. Serine proteases consisting of hepsin, matripase, and HGF activator (HGFA) act through pro-HGF activation at the Arg494-Val495 bond [16–18]. Splicing leads to two truncated forms of HGF, including NK1 and NK2. NK1, comprising the N-terminal domains and a single kringle domain (K1), acts as a heparin-dependent partial agonist of the MET receptor, while exhibiting inhibitory effects in the absence of heparin. The NK2 fragment, consisting of the N-terminal, K1, and K2 domains, acts as a competitive inhibitor of pro-HGF. The production of HGF in both intrahepatic and extrahepatic tissues is regulated by inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), interleukin-1 (IL-1), and interleukin-6 (IL-6) [19].

Through transfection analysis of NIH/3T3 cells, MET, which is a receptor for HGF, found localized on chromosome 7q21-31 [20], has three distinct domains: extracellular, transmembrane, and intracellular [21]. There are two parts included in the extracellular domain, which has HGF binding and activation: α-subunit and partial portion of β-subunit. Several key regions are included here in this extracellular domain, which are SEMA domain, PSI domain, and four IPT domains (Immunioglobulin-like Plexin-Transcription Factor domains). Part of the portion of β-subunit also makes up this extracellular structure, which extends partially toward the region of intracellular domain. Three functional domains are included here in this intracellular segment: the JM domain, TK domain, and C-terminal docking region. After binding to MET, autophosphorylation occurs on tyrosine sites Y1234 and Y1235 in TK domain. It recruits adapter proteins through further phosphorylation on Y1349 and Y1356 in C-terminal docking region, which activates downstream pathways. These are PI3K/AKT, STAT3/5, MAPK/ERK, and focal adhesion kinase (FAK). Other than that, pathway action also occurs due to pro-inflammatory cytokines, which are IL-1, IL-6, TNF-α, and basic fibroblast growth factor (b-FGF). Other than that, other extracellular proteins besides GPCRs, proteoglycan CD44, integrins, and receptor tyrosine kinases (such as EGFR, IGF-1R, and ERBB3) also activate pathways after binding to monomeric MET [22].

Pro-inflammatory cytokines released by $CD8^+$ T cells and neutrophils can activate the MET signaling pathway. In turn, HGF contributes to the upregulation of several pro-inflammatory cytokines, including IL-1β, IL-4, MIP-1β, and GM-CSF. This upregulation enhances antigen presentation in immune cells such as monocytes, thereby amplifying the immune response [15]. Furthermore, although the pathway has been implicated in pro-inflammatory responses, accumulating evidence also highlights its anti-inflammatory roles, particularly through the modulation of dendritic cell (DC) function. This includes the suppression of DC activation via the induction of interleukin-10 (IL-10) secretion and

Table 1
Effects of HGF/MET signaling on the immune system and anti-tumor response.

Immune effect	Mediator/Mechanism	Cellular target	Functional outcome	Reference
Pro-inflammatory activation	↑ IL-1β, IL-4, MIP-1β, GM-CSF induced by HGF	Monocytes, $CD8^+$ T cells, Neutrophils	↑ Antigen presentation, immune stimulation	[15]
HGF secretion by cytokines	IL-1, IL-6, TNF-α, IFN-γ → ↑ HGF production	Stromal and immune cells	Amplifies inflammatory signaling via MET	[19]
Dendritic cell suppression	HGF → ↑ IL-10 secretion	Dendritic cells (DCs)	↓ DC activation, ↓ antigen presentation	[24]
Promotion of immune tolerance	↑ PD-L1 expression	Tumor cells, APCs	T cell suppression via immune checkpoint activation	[24]
Regulatory T cell expansion	↑ IL-27 secretion	Naive T cells	↑ Treg differentiation and expansion	[24]
Tolerogenic DC induction	↑ GILZ expression (via TGF-β, IL-10, glucocorticoids)	Dendritic cells	Promotes immune tolerance, suppresses adaptive immunity	[15,24]

the inhibition of antigen presentation, thereby promoting autocrine regulatory mechanisms [24]. Additionally, regulatory T cell expansion has been associated with increased expression of interleukin-27 (IL-27) and programmed death-ligand 1 (PD-L1). Moreover, the tolerogenic DC marker glucocorticoid-induced leucine zipper (GILZ) has been found to be upregulated in environments enriched with transforming growth factor-beta (TGF-β), glucocorticoids, and IL-10 [15]. Collectively, these mechanisms support the pathway's anti-inflammatory role, as demonstrated in multiple models of inflammatory disorders, including inflammatory bowel disease [25,26], arthritis [27], and chronic airway inflammation [28].

Moreover, research has demonstrated the modulatory roles of TGF-β in regulating the HGF/MET axis, showing the activation of the TGF-β receptor II-deleted fibroblast-related axis, which enhances HGF-mediated triggering of Ron and MET, subsequently resulting in the activation of STAT3 and MAPK signaling, thereby facilitating mammary tumor invasion [23]. Furthermore, in c-MET-positive models, TGF-β induces a reverse correlation with the axis in glioblastoma cell models through TGF-β receptor I (ALK-5)/SMAD-related signaling, in which the mechanism is also mediated by ERK and PI3K/AKT signaling pathways

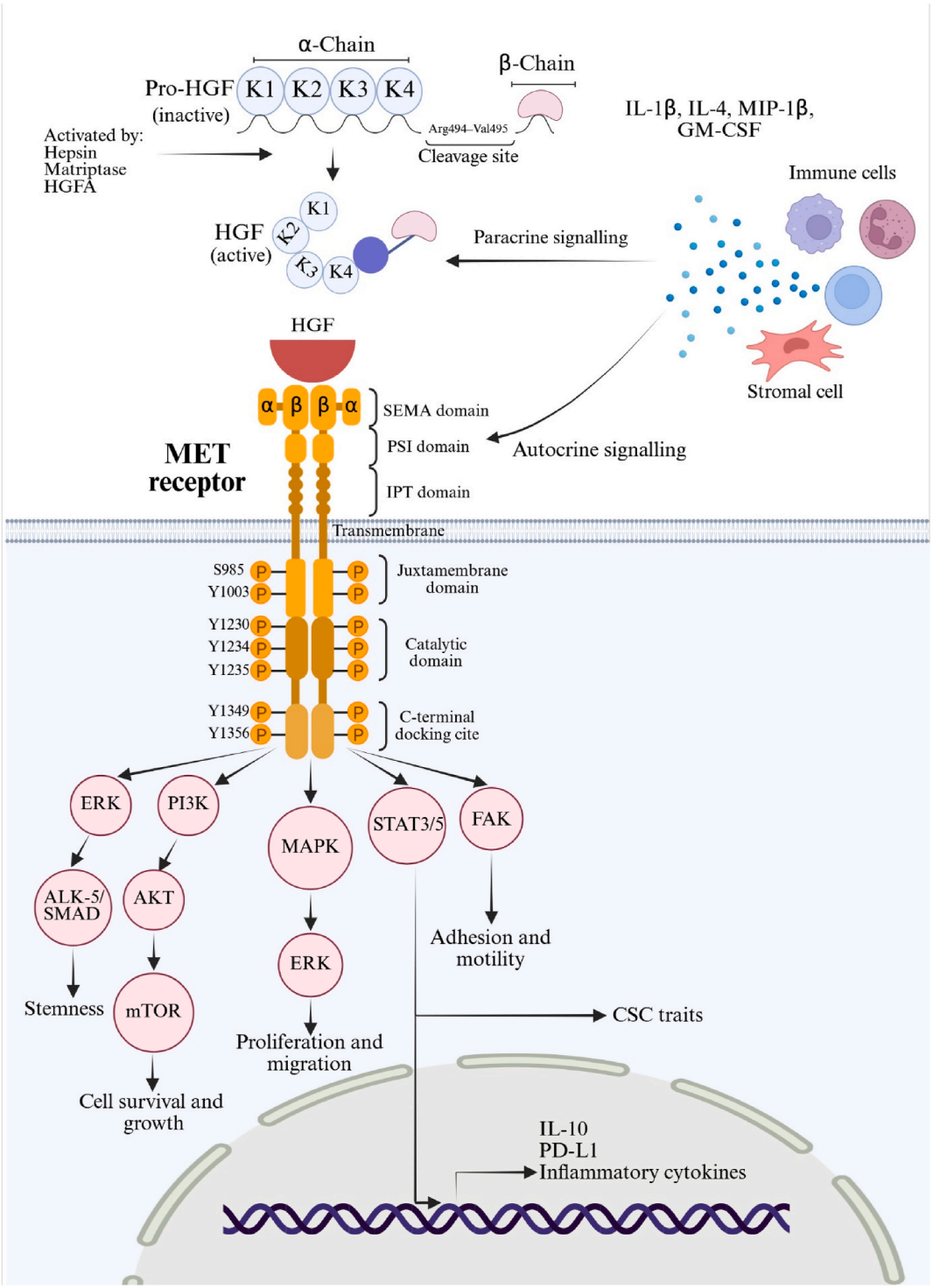

Fig. 1. Schematic illustration of the HGF/MET signaling pathway and its downstream effects. Created with BioRender.com.

in restraining the HGF/MET cascade. Nevertheless, the inhibitory function of which relies on the activity of MET, as TGF-β-related response failed to be distinguished in c-MET-negative models, emphasizing on the intertwined correlation of MET modulation and TGF-β [24].

3. Role of HGF and MET in tumorigenesis

3.1. Effect of cancer biology

The MET proto-oncogene encodes a receptor tyrosine kinase that is widely expressed across various cell types, including hematopoietic cells [30], melanocytes [31], neurons [32], hepatocytes [17], and endothelial cells [33]. Initially identified in N-methyl-N′-nitrosoguanidine-induced osteosarcoma cells [34], MET has been implicated in the development and progression of numerous malignancies, including epithelial tumors, renal carcinoma, mesothelioma, small cell lung cancer, breast and ovarian cancer, central nervous system neoplasms, and gastrointestinal cancers (gastric, colon, and rectal) [35]. Its overexpression and dysregulation are frequent in these cancers and are associated with poor prognosis.

Various genetic alterations, such as point mutations, gene amplification, insertional mutations, chromosomal translocations, and retroviral transduction, can lead to aberrant MET activation, resulting in enhanced cell proliferation, resistance to apoptosis, and sustained oncogenic signaling [36,37]. Dysregulation of MET contributes to cancer hallmarks including invasion, angiogenesis, epithelial-to-mesenchymal transition (EMT), metastasis, and chemoresistance [38–41]. Overexpression of MET can arise from increased transcription driven by Ets and Sp1 transcription factors or hypoxia-inducible factor-1α (HIF-1α). In addition, loss of regulatory microRNAs (e.g., miR-1, miR-34, miR-449a) also contributes to elevated MET expression [42,43]. Oncogenic stimuli such as K-RAS activation and chronic inflammation may further enhance MET expression and ligand-independent activation, amplifying oncogenic pathways and correlating with reduced survival in several cancers, including glioblastoma, hepatocellular carcinoma, and colorectal cancer [35,44].

Gene amplification is a major mechanism of MET overexpression. Increased MET copy number (CNG) has been documented in non-small cell lung cancer (NSCLC), particularly in EGFR inhibitor-resistant tumors, as well as in metastatic colorectal cancer where liver metastases exhibit higher CNG compared to primary tumors [45]. In hereditary papillary renal carcinoma, MET amplification due to exon 16 mutations and trisomy of chromosome 7 has also been reported [46]. MET amplification is commonly assessed using methods such as quantitative PCR and fluorescence in situ hybridization (FISH), though variability in detection criteria has led to inconsistent reporting across studies [47].

Mutations affecting key functional domains of the MET protein—namely the juxtamembrane (JM), kinase, and SEMA domains—also contribute to oncogenesis. These mutations can activate downstream pathways such as Ras-Raf-MEK-ERK and PI3K-AKT, promoting unchecked proliferation and apoptosis resistance [48]. Specific mutations in the kinase domain (e.g., Thr1191Ile, Tyr1248Cys, Asp1228Val) have been identified in cancers such as hepatocellular carcinoma, papillary renal carcinoma, NSCLC, and head and neck cancers [49–51]. JM domain mutations (e.g., Tyr1010Ile, Pro1009Ser, Arg988Cys) are found in several cancer types, including lung and gastrointestinal malignancies [49]. Although SEMA domain mutations (e.g., Asn375Ser, Leu299Phe) have not been as extensively studied, they are hypothesized to alter MET structure and function [52–54].

Exon 14 skipping mutations in MET, which disrupt the CBL-binding site at Tyr1003 in the JM domain, impair MET ubiquitination and degradation, leading to prolonged MET signaling and oncogenic activity [55–58]. These mutations occur in 3–5 % of NSCLC cases, particularly in pulmonary sarcomatoid carcinoma, and are also present at lower frequencies in other malignancies [59–62]. Their identification has therapeutic relevance, as MET inhibitors may be particularly effective in tumors harboring these alterations (Fig. 2). Research investigating the topic has led to the design of several MET tyrosine kinase inhibitors, such as sevolitinib, capmatinib, and tepotinib. NSCLC patients with MET exon 14 skipping mutations. Also, in patients with MET gene amplification, while capamatinib exhibited a poor response with lower-than-10 gene copy numbers and a moderate success rate of 40 % in high-level amplification rates, tepotinib has demonstrated to manifest with the best response in the treatment-naïve subgroup of patients with MET amplification with an objective response rate of 71.4 % [25,26].

Cytoskeleton remodeling and cellular migration is noted to be one of the key mechanisms driving cancer invasion through HGF/MET signaling, as Gab1 recruits Dock7 to c-MET, triggering isolated RAC1, leading to cell migration while leaving the proliferation rate unchanged [27]. Furthermore, MET-AXL complex gets arranged through HGF stimulation, leading to the Tyr-779 level-transphosphorylation of AXL by c-MET, subsequently resulting in GAS6-independent plasma membrane-level RAC1 activation through ELMO2-DOCK180 complex [28]. RAC1 activation has also been demonstrated to be correlated with the RhoA-ROCK1 pathway, enhancing the stress fiber setup and contractility of the cytoskeleton, accelerating the tumor invasion, a cascade that was shown to be negatively affected through a known natural compound named paeoniflorin, which acts by halting the phosphorylation of c-MET and its downstream RhoA-ROCK1 pathway [29]. Studies investigating the HGF/MET-related cancer invasion and cell migration, have also identified the CDCP1-SRC-ARHGEF7-RAC1 signaling pathway as a main modulator of which SRC stimulates the PI3K-MET pathway through a transmembrane protein, named CDCP1, resulting in the accumulation of PIP3, which subsequently triggers RAC1 by recruiting ARHGEF7, leading to remodeling of actin cytoskeleton and increased cellular motility [30].

3.2. Mechanisms of HGF/MET-mediated chemoresistance

Chemoresistance has emerged as a major obstacle in cancer therapy, prompting extensive investigations into the genetic and microenvironmental determinants that underlie tumor insensitivity to conventional treatments [63]. In hepatocellular carcinoma (HCC), the tumor microenvironment—particularly the infiltration of hepatic stellate cells such as LX-2—has been shown to enhance MET receptor activity, thereby promoting epithelial-to-mesenchymal transition (EMT). This process is characterized by reduced nuclear translocation of β-catenin, downregulation of E-cadherin, and increased expression of vimentin and N-cadherin. Simultaneously, MET activation contributes to the induction of cancer stem cell (CSC)-like traits via upregulation of Klf4, Bmi1, and CD133, ultimately diminishing cisplatin sensitivity. Notably, suppression of HGF signaling can reverse these EMT-related changes, highlighting the central role of the HGF/MET axis in therapy resistance and CSC enrichment [63].

Further evidence demonstrates that cancer-associated fibroblast (CAF)-derived CD73 mediates resistance to sorafenib and cisplatin through HGF-dependent activation of the MET and MEK-ERK1/2 pathways [64]. A functional crosstalk between the HGF/MET and Wnt/β-catenin pathways has also been implicated in chemoresistance via MET overexpression and nuclear accumulation of β-catenin, which promotes EMT through activation of the transcription factor Snail [65].

In breast cancer, MET is overexpressed in tumor tissues compared to normal breast tissue. This overexpression correlates with increased Ki-67 levels and reduced expression of topoisomerase II (TOPO II), suggesting that HGF/MET signaling may suppress TOPO II as part of a broader mechanism driving drug resistance [66].

In non-small cell lung cancer (NSCLC), CAF-secreted HGF induces overexpression of glucose-regulated protein 78 (GRP78), which activates the MET and PI3K/AKT pathways, subsequently reducing apoptosis in A549 cells and enhancing resistance to chemotherapy [67]. Similarly, in small cell lung cancer (SCLC), the HGF/MET axis has been

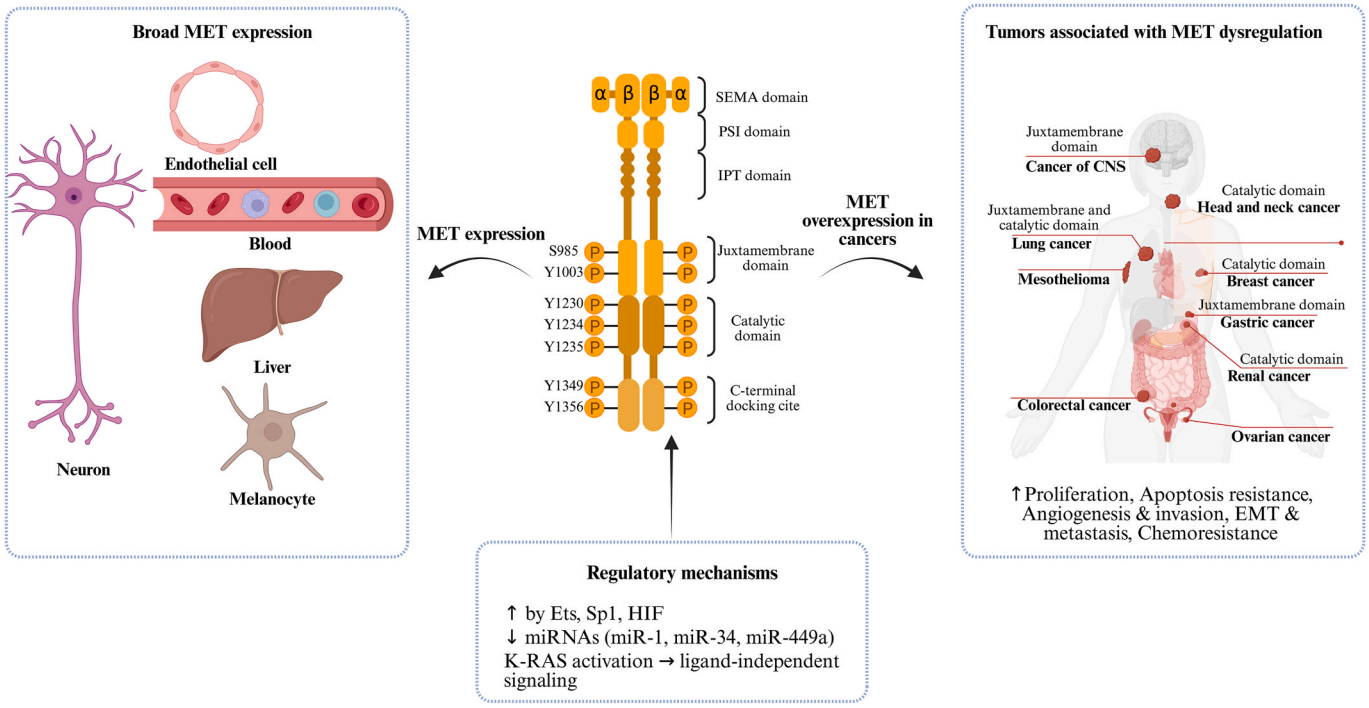

Fig. 2. Overview of MET dysregulation in cancer; MET is broadly expressed in various normal tissues (e.g., neurons, liver, blood, melanocytes, endothelial cells). Its overexpression or mutation is associated with multiple cancers, promoting proliferation, survival, angiogenesis, invasion, EMT, metastasis, and chemoresistance. MET activity is regulated by transcription factors, miRNAs, and oncogenic signaling. Created with BioRender.com.

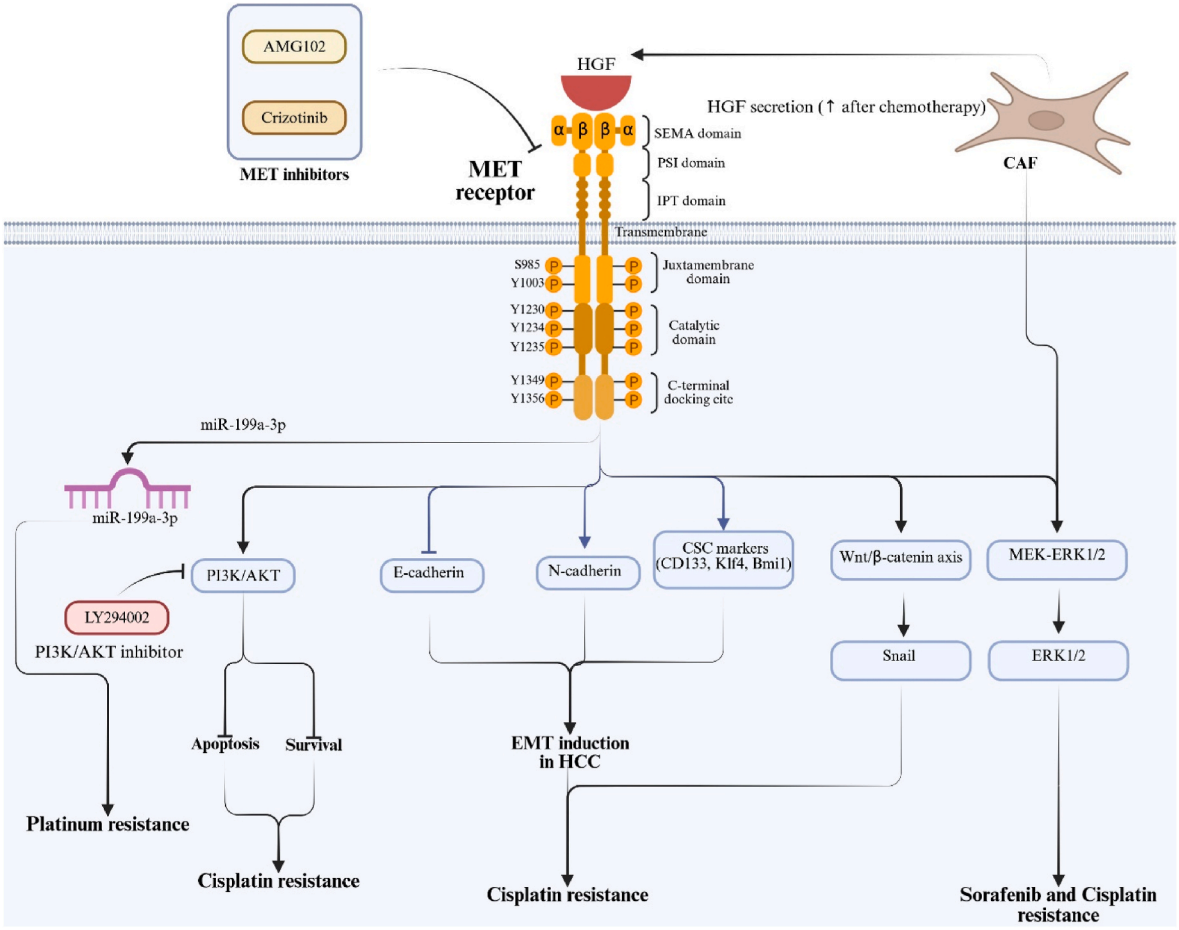

Fig. 3. Schematic represents how the HGF/MET signaling pathway enhances chemoresistance in cancer. Created with BioRender.com.

implicated in EMT-mediated resistance, with MET inhibition restoring therapeutic response [68].

In ovarian cancer, stromal-derived factors including HGF, uPAR, IL-6, and adipocyte-conditioned medium contribute to platinum resistance via the HGF/MET pathway. Notably, the dual MET/ALK inhibitor crizotinib has been shown to reverse this resistance, underscoring the therapeutic potential of targeting this pathway [69]. Additionally, HGF-driven activation of the MET/PI3K/AKT pathway suppresses miR-199a-3p expression, which in turn enhances stemness and chemoresistance—highlighting miR-199a-3p as a potential therapeutic target [70].

In pancreatic cancer, pancreatic stellate cells (PSCs) secrete HGF, activating MET signaling and promoting EMT in pancreatic cancer cells (PCCs), thereby conferring resistance to gemcitabine. Inhibition of MET (via AMG102 or PHA665752) or downstream PI3K/AKT signaling (via LY294002) can reverse EMT features and restore drug sensitivity [71]. Moreover, inflammatory cytokines such as IL-1α induce HGF expression in PSCs, linking inflammatory signaling, desmoplasia, and chemoresistance [72].

In gastric cancer, interferon-induced transmembrane protein 3 (IFITM3)—a marker associated with poor prognosis—interacts with MET and its downstream effector AKT. This interaction suppresses FOXO3 expression and increases c-MYC levels, thereby promoting CSC properties and resistance to chemotherapy, further implicating the HGF/MET axis in gastric cancer pathogenesis [73].

Finally, in head and neck squamous cell carcinoma (HNSCC), resistance to EGFR-targeted therapies (e.g., erlotinib, cetuximab, gefitinib) is often attributed not to EGFR mutations, but to compensatory activation of alternative pathways, particularly HGF/MET signaling [74]. Inhibiting MET in EGFR-overexpressing HNSCC subtypes has been shown to sensitize tumors to EGFR inhibitors, reinforcing MET's role as a critical modulator of therapeutic resistance [20,31] (Fig. 3).

4. Mechanisms of action of natural compounds on HGF/MET pathway in cancer

HGF/MET signaling pathways play a critical role in promoting cell proliferation, survival, migration, invasion, angiogenesis, and metastasis [32]. Cancers often exhibit aberrant activation of this pathway. HGF/MET axis modulation has been shown to be impacted by several natural compounds. Several natural compounds have been shown to modulate the HGF/MET axis in cancer by inhibiting its signaling through various molecular mechanisms.

4.1. Compounds with direct inhibitory impacts on HGF/MET

4.1.1. Ginger

Plants in the Zingiberaceae family include ginger (Zingiber officinale Roscoe) [33]. Ginger is the most commonly used herbal drug in many countries [34]. Ginger has antioxidant and anti-inflammatory properties, but a less-studied bioactivity may relate to its neuroprotective properties [35]. *Zingiber officinale* is one of the medicinal plants that have beneficial health effects and are widely used in pharmaceuticals and food products [36]. In traditional medicine, ginger rhizomes have been used as a spice or dietary supplement for centuries [37]. Integrating computational docking, molecular dynamics simulation, and pull-down assay revealed that ginger extract directly acts on overexpressed c-MET in osteosarcoma (OS) tissues. Two of the chief components of ginger extract, 6-gingerol and 6-shogaol exerted high binding affinity to c-MET as supported by stable docking and simulation results. Pull-down assays also confirmed physical interaction between ginger extract and c-MET in OS cells. Functionally, the treatment with ginger extract inhibited c-MET activation and thwarted downstream signaling cascades such as PI3K/AKT, ERK, and STAT3. The same was replicated after knockdown of c-MET that downregulated OS cell growth, decreased colony formation, and promoted apoptosis. All these results suggest that ginger extract displays anti-osteosarcoma activity by direct inhibition of c-MET and its signal cascade [38] (Fig. 4).

4.1.2. Resveratrol

Resveratrol (3,4′,5-trihydroxy-transstilbene) is a nutraceutical "miracle" in the fight against cancer. Phytoalexins like resveratrol protect plants from stress and pathogens [39]. Resveratrol has been shown to suppress the HGF/c-Met signaling pathway in human hepatocellular carcinoma (HCC) cells, contributing to its antitumor effects. Short-term treatment with resveratrol significantly attenuates HGF-induced activation of the c-Met pathway, while prolonged exposure results in a marked reduction in c-Met phosphorylation. Additionally, resveratrol impairs HGF-driven cellular invasion, an effect that is diminished upon c-Met knockdown, indicating that resveratrol's anticancer efficacy is at least partly mediated through c-Met inhibition. *In vivo* xenograft studies further confirmed the compound's antitumor potential, substantially reducing tumor growth [93]. In epithelial prostate cancer (CaP) cells, resveratrol disrupts HGF-dependent stromal–epithelial interactions required for cellular migration by inhibiting c-Met receptor engagement, thereby attenuating EMT-related processes [40] (Fig. 4).

4.1.3. Honokiol (HNK)

In addition to possessing antitumor activity against a number of human cancer cell lines, honokiol ((3′,5-di-(2-propenyl)-1,1′-biphenyl-2,2′-diol) is a promising lignan. *In vitro* and *in vivo* studies have shown that honokiol inhibited cancer cell proliferation, invasion, and survival. Its antineoplastic effects are induced by interfering with signaling pathways [41]. Using a model of calcineurin inhibitor (CNI)-induced renal tumor progression, Balan and colleagues investigated how the c-Met signaling pathway affected the anticancer activity of honokiol (HNK). Their findings showed that CNI increased both Ras activation and c-Met expression. Furthermore, HNK treatment led to decreased c-Met phosphorylation and Ras activity in renal carcinoma cells. Additionally, HNK suppressed the upregulation of HO-1 driven by both CNI and c-Met, while promoting apoptosis in tumor cells. Overall, HNK significantly curtailed CNI-induced renal tumor growth, reduced levels of phosphorylated c-Met and HO-1, and lowered tumor vascularization [42]. Sabarwal and colleagues demonstrated that combining rapamycin with honokiol effectively suppressed Ras activation and cell proliferation while inducing G1 phase cell cycle arrest in renal carcinoma cells. This combination also led to a marked increase in ROS production and apoptotic cell death, even in the presence of active c-Met signaling. Notably, honokiol downregulated c-Met-driven expression of PD-L1, a key immune checkpoint molecule that facilitates immune evasion in renal cancer. Furthermore, the rapamycin–honokiol combination enhanced immune-cell-mediated cytotoxicity against mouse renal cancer cells and Balb/c splenocytes, potentially through PD-L1 suppression [43] (Fig. 4).

4.1.4. Quercetin

Quercetin, a flavonoid classified within the flavone subclass, possesses a characteristic C6–C3–C6 three-ring structure comprising rings A, B, and C. Quercetin plays a multifaceted role in plants by promoting seed germination, pollen tube elongation, and enhancing photosynthetic performance and antioxidant capacity. Its potent antioxidative properties are particularly vital in conferring resilience against various biotic and abiotic stresses, thereby contributing to improved plant growth, development, and stress tolerance [44]. HGF-stimulated melanoma cell invasion and migration were suppressed by quercetin dose-dependently. C-Met expression was reduced by quercetin's effect on fatty acid synthase. Moreover, quercetin inhibited signaling molecules downstream c-Met, such as GRB2-associated-binding protein 1 (Gab1), focal adhesion kinases (FAK), and p21-activated kinases (PAK). The inhibitory effect of quercetin on melanoma cell migration was significantly diminished by overexpression of FAK or PAK [45]. Inhibition of the HGF signaling pathway represents a promising strategy for preventing and

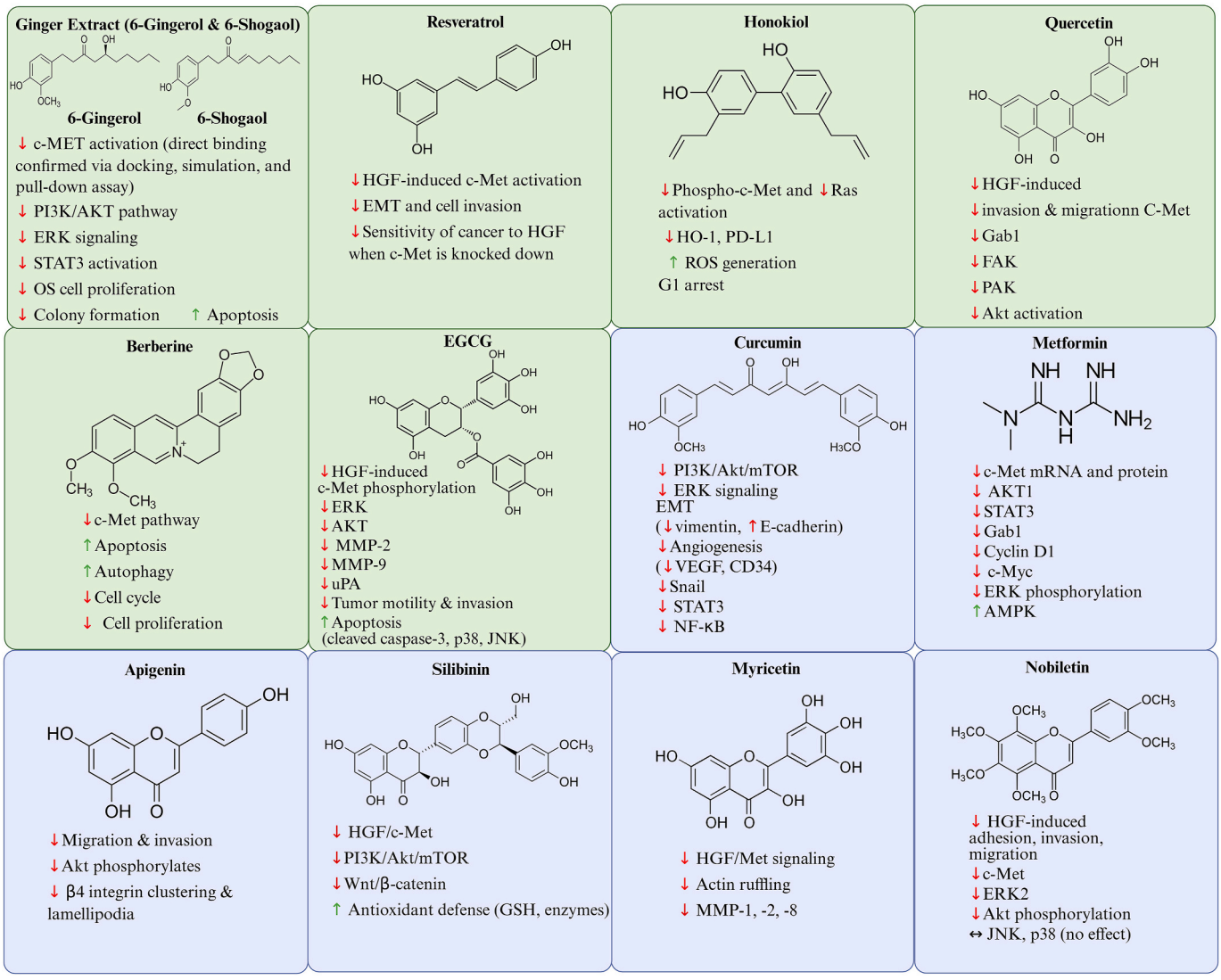

Fig. 4. Natural compounds moderating the HGF/MET signaling pathway in cancer. The figure illustrates the chemical structures and molecular impacts of selected phytochemicals, including Ginger Extract (6-Gingerol & 6-Shogaol), Resveratrol, Honokiol, Quercetin, Berberine, EGCG, Curcumin, Metformin, Apigenin, Silibinin, Myricetin, and Nobiletin. Compounds are classified based on their mechanisms of action: green denotes compounds that directly inhibit MET, while blue denotes those that indirectly modulation of the HGF/MET signaling axis. Created with BioRender.com. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

treating human medulloblastoma, given the critical role of HGF and its receptor, MET, in promoting tumor growth and metastasis. In medulloblastoma cell lines, the flavonoids quercetin, kaempferol, and myricetin were shown to suppress MET-induced cellular migration and inhibit the formation of actin-rich membrane ruffles. Moreover, both quercetin and kaempferol significantly attenuated HGF-mediated activation of the AKT signaling pathway, further supporting their potential as therapeutic agents targeting the HGF/MET axis [46] (Fig. 4).

4.1.5. *Berberine*

A potential bioactive agent, berberine (BBR), has remarkable health benefits. Several studies have examined BBR's anticancer potential, noting that apoptosis, cell cycle control, and autophagy were all inhibited by BBR. Downregulation of metastasis-related proteins by BBR also inhibited tumor cell invasion and metastasis [47]. In a 2022 study by Chen et al., the combination of berberine (BBR) and osimertinib was shown to induce apoptosis in multiple MET-amplified, EGFR-mutant NSCLC cell lines, likely by upregulating the pro-apoptotic protein Bim and downregulating the anti-apoptotic protein Mcl-1. MET kinase assays confirmed that BBR directly inhibited MET activity. Notably, this therapeutic combination significantly suppressed the growth of osimertinib-resistant, MET-amplified xenograft tumors in nude mice [48] (Fig. 4).

4.1.6. *Epigallocatechin-3-gallate (EGCG)*

EGCG, a major polyphenolic compound derived from green tea extract, exhibits both anticancer and anti-inflammatory properties through modulation of multiple cellular signaling pathways. EGCG has been shown to inhibit the HGF/c-Met axis in various cancer models, including immortalized MCF10A and MDA-MB-231 breast epithelial cells, where it suppressed HGF-induced activation of MET, ERK, and AKT, thereby blocking cell motility and invasion at concentrations as low as 0.3–5.0 μM [96]. Furthermore, in hypopharyngeal carcinoma cells, EGCG inhibited HGF-mediated increases in MMP-9 and urokinase-type plasminogen activator (uPA) activity, both of which are crucial for tumor cell invasiveness [97]. EGCG also markedly attenuated c-Met phosphorylation and downstream signaling via AKT and ERK, while concurrently activating the pro-apoptotic p38 and JNK pathways and increasing the cleavage of caspase-3 and poly (ADP-ribose) polymerase (PARP), indicating enhanced apoptotic induction. *In vivo* studies

confirmed EGCG's therapeutic efficacy, demonstrating significant tumor growth suppression and increased apoptosis, thereby supporting its potential as an HGF/c-Met-targeting chemopreventive agent [95–98] (Fig. 4).

4.2. Compounds with indirect influences on HGF/MET

4.2.1. Curcumin

The turmeric plant, *Curcuma longa*, contains curcumin, which has anti-inflammatory and antineoplastic properties. Curcumin exhibits potent antineoplastic effects by modulating multiple oncogenic and inflammatory pathways. It exerts its anticancer activity through the inhibition of pro-inflammatory mediators such as cytokines, cyclooxygenase-2 (COX-2), and reactive oxygen species (ROS), and by suppressing key signaling cascades including NF-κB, JNK, and STAT3 [77]. In lung cancer cell lines A549 and PC-9, curcumin attenuated HGF-induced epithelial–mesenchymal transition (EMT), preventing associated morphological changes and migratory behavior by blocking c-Met phosphorylation and downstream signaling through AKT, mTOR, and S6 [78]. It also restored epithelial markers such as E-cadherin while downregulating mesenchymal and angiogenic markers including vimentin, CD34, and VEGF *in vivo*. In DU145 prostate cancer cells, curcumin significantly reduced HGF-induced scattering, invasion, and vimentin expression by suppressing phosphorylated c-Met, ERK, and Snail, indicating a regulatory role in EMT via the HGF/PI3K/AKT axis [79]. Similarly, in A549 and PC-9 cells, curcumin downregulated PI3K/AKT/mTOR signaling, thereby inhibiting angiogenesis and EMT [80]. In human malignant meningioma models, curcumin disrupted HGF-mediated proliferation, migration, invasion, and EMT via suppression of the same pathway [81]. In oral squamous cell carcinoma (OSCC) cell lines HSC4 and Ca922, curcumin counteracted HGF-induced EMT potentially driven by ERK activation [82]. Collectively, these findings highlight curcumin as a promising candidate for targeting HGF/MET-driven oncogenic processes, particularly EMT, across various tumor types including OSCC (Fig. 4).

4.2.2. Metformin

Originally known as metformin (1,1-dimethylbiguanide), this biguanide-based pharmaceutical is derived from *Galega officinalis* [49]. In clinical trials, metformin has been shown to be safe and well-tolerated oral drug for treating type 2 diabetes through LKB1/AMPK-dependent activity [49]. Both c-Met mRNA and protein levels were decreased in MDA-MB-468 cells treated with metformin. Compared to 468/C cells, metformin abrogated inhibition of ALDH1+ cells. Activation of STAT3 and AKT1 and upregulation of Gab1 were found to be downstream effects of c-Met [50]. A conserved kinase complex called AMP-activated protein kinase (AMPK) facilitates the maintenance of energy homeostasis in cells. In addition, activated AMPK inhibits cell proliferation under energy-restricted conditions, suggesting that it acts as a tumor suppressor [51]. Metformin is reducing the risk of HCC in diabetic patients with chronic liver disease, and it is having protective effects against the development of HCC as well as chemically induced transgenic or diet models of hepatocarcinogenesis [52–54]. Genetic approaches *in vitro* confirmed AMPK's role in alleviating AKT/c-Met-induced hepatocarcinogenesis induced by metformin. Metformin also repressed FASN and HK-2 expression *in vitro* by targeting c-Myc through AMPK. *In vivo*, metformin reduced Cyclin D1 and c-Myc expression, as well as phospho-ERK (Thr202/Tyr204). In AKT/c-Met mice, metformin inhibited malignant transformation of hepatocytes. Furthermore, metformin inhibits PKM2 expression with anti-AMPK compound C, suggesting that it acts independently of AMPK [55] (Fig. 4).

4.2.3. Apigenin

4′,5,7-trihydroxyflavone, also known as apigenin, is a natural flavonoid compound found in various fruits, vegetables, and functional foods. Studies have shown that apigenin has cytostatic and cytotoxic effects on cancer cells [56]. Lee et al. examined the effects of several flavonoids, apigenin, naringenin, genistein, and kaempferol, on MDA-MB-231 human breast cancer cells induced by HGF. Apigenin exhibits the strongest anti-migration and anti-invasion properties in the Boyden chamber assay. In addition to inhibiting HGF-induced cell migration and invasion, apigenin suppresses cellular motility and scattering in a dose-dependent manner. It selectively inhibits AKT phosphorylation, while having no significant effect on the phosphorylation of MET, ERK, or JNK. This suppression of AKT activation by apigenin is observed in both MDA-MB-231 breast cancer cells and SK-Hep1 hepatoma cells. HGF-induced lamellipodia and clustering of β 4 integrins at actin-rich adhesive sites are inhibited by apigenin in a PI3K-dependent manner [57] (Fig. 4).

4.2.4. Silibinin

Known for its antioxidant, antineoplastic, and hepatoprotective properties, silibinin is derived from milk thistle (*Silybum marianum*) [58, 59]. A study was conducted to evaluate the antitumor potential of *Silybum marianum* total extract (STE), silymarin (Sm), and silibinin (Sb) in a rat model of chemically induced HCC. Cancerous lesions in rats were inhibited by STE, Sm, and Sb treatment. HGF/c-Met, and PI3K/AKT/mTOR and Wnt β/-catenin pathways were also inhibited along with Ki-67 expression. It was also noted that the treatment reduced hepatic lipid peroxide production, increased glutathione content, and increased antioxidant enzyme activities in rats [60] (Fig. 4).

4.2.5. Myricetin

The flavonoid myricetin (MYR) occurs in a wide variety of natural plants, for instance, bayberry. MYR was reported to have various biological activities, for instance, anti-inflammatory and anti-microbial activities. MYR was reported to be useful for therapy of thrombosis, diabetes, cerebral ischemia, Alzheimer's disease and atherosclerosis [61]. A malignant brain tumour commonly found in children, medulloblastoma, was shown to be sensitive to MYR. In medulloblastoma DAOY cells, MYR inhibited HGF/MET signaling and prevented membrane ruffling induced by actin [62]. MYR's antineoplastic effects on HGF signaling were evaluated under lipopolysaccharide (LPS)-induced inflammatory conditions. Additionally, the anti-osteoclastogenic effects of MYR were assessed in receptor activator of nuclear factor kappa-B ligand (RANKL)-stimulated RAW264.7 macrophage cells. MYR did not affect cell viability, but MMP-1, -2, and -8 mRNA expression and enzyme activity were [63] (Fig. 4).

4.2.6. Nobiletin

The polymethoxylated flavonoid nobiletin is found in citrus fruit peels and exerts anti-tumor, anti-inflammatory, anti-oxidative, anti-apoptotic and cardiovascular effects [64]. Nobiletin has been shown to inhibit HGF-induced adhesion, invasion, and migration in cell-matrix adhesion assays. Additionally, nobiletin inhibited the formation of filopodia and lamellipodia induced by HGF. Nobiletin inhibited phosphorylation of c-Met, ERK2, and AKT caused by HGF, but not JNK1/2 or p38 [65] (Fig. 4).

4.3. Compounds with uncertain or less-defined mechanisms on HGF/MET

4.3.1. Ginsenosides

The main constituents of ginseng are ginsenosides, which have unique biological properties, including antitumor, anti-apoptotic, antioxidant, and anti-inflammatory [66]. A-Panaxadiol group (for example, Rb1, Rb2, Rb3, Rc, Rd, Rg3, and Rh2), B-Panaxatriol group (for example, Re, Rg1, Rg2, and Rh1), and C-Oleanolic acid group (for example, Ro) are ginsenosides classified by their sugar moiety position and quantity [67,68]. In a study by Kwok et al., ginsenoside-Rg1 reverse-regulated MET-tyrosine kinase receptor expression through miR-23a to induce angiogenesis [69].

5. Effects of phytochemicals on HGF/MET for modulation of chemoresistance

Understanding the molecular pathways that afford resistance to targeted therapies is crucial for developing effective alternative treatments. Investigating the molecular mechanisms underlying drug resistance is essential for improving the efficacy of MET-targeted therapies. Resistance to MET TKIs may involve alterations, not only in the MET gene itself, but also in other genes that promote cell survival [4]. The MET receptor and downstream proliferation pathways are prolongedly activated in MET dysregulation due to a heterogeneous array of alterations [70]. MET mutations occur in 3–5 % of NSCLC patients, mainly adenocarcinomas, with an overrepresentation in sarcomatoid cases [71,72]. It is estimated that 1 %–5 % of patients with NSCLC will develop de novo MET amplifications, as well as most patients with adenocarcinoma [73]. About 4 % of patients with NSCLC who are TKI naive have MET amplifications that may drive oncogenesis [74]. Resistance mechanisms to EGFR TKI therapy have also been identified in MET exon 14 alterations [75]. MET amplifications were detected in approximately 12 % of patients with NSCLC with ALK rearrangements who developed resistance to second-generation inhibitors and 22 % of those who progressed on lorlatinib [70]. Luteolin acts on the HGF-MET-AKT signaling pathway to counteract resistance to osimertinib. In NSCLC, the T790 M mutation confered resistance to first- and second-generation EGFR TKIs [76]. Although osimertinib remained effective initially, acquired resistance often develops. This resistance is frequently driven by MET amplification and increased AKT activation. However, combining luteolin with osimertinib has been shown to overcome this resistance, suggesting that NSCLC patients may potentially benefit from this combination therapy [77]. Radiosensitization and chemotherapy associated side effects can be reduced by luteolin treatment secondary to the inhibition of Nrf2 and HGF-MET-AKT signaling pathways. Due to its inhibitory effects on NF-κB and p38 MAPK signaling pathways, luteolin can also alleviate cancer related complications. Consequently, luteolin holds potential therapeutic value in the management of cancer-associated cachexia and malignant bone pain. Additionally, it has been shown to inhibit the PD-1/PD-L1 immune checkpoint interaction and to induce autophagy during the early stages of tumor development [78]. Gab1, a key signal transduction pathway effector in HGF/MET, mediates alectinib resistance. MET was shown to overcome alectinib resistance induced by HGF/MET signaling by disrupting the MET–Gab1 complex and modulating downstream signaling pathways [79].

6. Targeted treatments focusing on the HGF/MET pathway in cancer

Preclinical studies have identified the dominant roles of HGF/c-MET signaling in selected cancers that have galvanized efforts to treat selected patient populations who ideally can have clinical effects by targeted therapy aimed at the HGF/c-MET pathway. Agents that target this pathway can, in a very broad sense, be roughly categorized into several categories: anti-*c*-MET monoclonal antibodies, anti-HGF antibodies, non-selective c-MET tyrosine kinase inhibitors (TKIs), and selective c-MET TKIs [80]. We discuss the latest clinical trials that focused on HGF/MET signaling in cancers, either alone or in conjunction with other drugs.

Early clinical data indicate that administering MET chimeric antigen receptor (CAR) T-cells directly into breast cancer tumors induced tumor necrosis, hemorrhage, and infiltration of inflammatory cells, all while maintaining a favorable safety profile [81]. In a phase I clinical trial (NCT03060356) assessing for the safety of c-MET-targeted CAR T cells via intravenous RNA electroporation in melanoma or metastatic breast cancer, six patients had grades 1 or grades 2 toxicities only. It should, however, be recalled that there were no cases of severe toxicities (grade 3 and above) or neurotoxicities, and drug discontinuations, which therefore mean that the therapeutic strategy remained tolerable and relatively safe [82]. Cabozantinib, a multi-target MET inhibitor, has demonstrated notable efficacy in treating ovarian cancer. In contrast, cabozantinib showed little effect when used as a second or third line treatment for primary peritoneal, fallopian tube, or clear cell carcinoma [83,84]. There were no responders to phase I study of sole-agent regimen of YYB-101, HGF blockade, in ovarian cancer, when YYB-101 had already been given to patients who had failed more than four preceding regimens [85–87].

Two large phase III clinical trials concluded that overall survival failed to improve compared to placebo for tivantinib. Twice-daily administration of 120 mg of tivantinib failed to show convincing survival advantage compared to placebo administration in advanced MET-high hepatocellular carcinoma (HCC) patients in METIV-HCC study. Progression-free survival (PFS) also proved to be the same for both arms. Subgroups analysis also failed to affirm superiority of tivantinib in all patient subgroups. Analogously, JET-HCC study, conducted in Japan, concluded that once-daily administration of oral tivantinib failed to enhance statistically overall survival or PFS in MET-high HCC patients, who were relapsed or intolerable to sorafenib, affirming results of METIV-HCC study [88,89]. Nonetheless, cabozantinib therapy proved to demonstrate unprecedented survival and PFS improvement in advanced HCC cases, which proved to have been confirmed in the randomized, placebo-controlled, phase III study, CELESTIAL [90].

In a clinical investigation conducted in 2017, a phase I run-in study evaluated the combination of tivantinib with FOLFOX chemotherapy in solid tumors, followed by a phase II trial assessing its efficacy as a first-line treatment for esophagogastric cancer. Tivantinib did not confer any significant therapeutic advantage, with overall response rates comparable to historical data for FOLFOX monotherapy. Furthermore, no significant correlation was identified between MET protein expression levels and immunohistochemical (IHC) analysis [91]. In another study, nine gastric cancer patients were treated with capmatinib; stable disease was observed in only two patients. Additionally, no clear correlation was found between treatment response and the different diagnostic techniques used to evaluate MET overexpression [92]. Following clinical success in several cases of MET-amplified esophagogastric cancer, a phase II trial was initiated to evaluate crizotinib. Among participants, tumor responses were observed in 67 % (2 out of 3) of patients with low-level MET amplification and in 50 % (3 out of 6) of those with intermediate amplification. However, the study was prematurely discontinued due to insufficient patient enrollment [93]. A subsequent phase II trial was conducted in patients with previously treated advanced esophagogastric cancer and other solid tumors to assess the efficacy of AMG337, a highly selective small-molecule inhibitor targeting c-Met signaling. Despite initial promise, the study was terminated early due to the inability of AMG337 to replicate the previously observed objective response rate (ORR) of up to 62 % in a small group of 13 patients. Biomarker analysis revealed a mean MET/CEP7 ratio of 7.7 in the 8 responders and 7.1 in the 39 non-responders, indicating no significant correlation between MET gene amplification levels and treatment response. The single-arm design and premature discontinuation of the trial may have limited a comprehensive evaluation of AMG337's therapeutic potential [94]. A phase II non-randomized, single-arm trial evaluated emibetuzumab in patients with advanced gastric cancer who had completed second-line chemotherapy. Eligibility was based on MET protein expression assessed by IHC, with inclusion requiring 2+ or 3+ staining in over 60 % of tumor cells. Despite this selection, no patients achieved a partial response. One patient exhibited a 22 % reduction in the target lesion; however, the development of ascites led to classification as progressive disease [95].

In a retrospective cohort analysis of 112 non-clear-cell renal cell cancer patients treated with cabozantinib, next-generation sequencing results were available in 54 cases. Most common mutated somatic genes were MET (patients 11, 20 %) and CDKN2A (12, 22 %). There were observed therapeutic effects regardless of their presence or absence of

such clear genetic mutations [96]. No treatment-related fatalities were reported. A phase III, open-label, randomized multicenter trial involving 60 patients with MET-driven papillary renal cell carcinoma (PRCC) compared the efficacy of savolitinib monotherapy to sunitinib monotherapy. Although progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) were numerically higher in the savolitinib group, the difference in median PFS between the two treatment arms did not reach statistical significance [97]. Another study demonstrated a notable improvement in both progression-free survival (PFS) and response rate with the use of cabozantinib, a dual inhibitor targeting both vascular endothelial growth factor (VEGF) and MET pathways, when compared to sunitinib. Interestingly, sunitinib showed superior clinical efficacy compared to more selective MET inhibitors such as crizotinib and savolitinib [98]. Furthermore, sunitinib exhibited better clinical activity than the more selective MET inhibitors crizotinib and savolitinib [19]. Additionally, findings from a single-arm phase II clinical trial indicated that the combination of durvalumab and savolitinib was well tolerated in patients with metastatic papillary renal cancer (PRC). Among those with MET-driven disease, the confirmed response rate (cRR) reached a promising 59 %. Although the combination did not achieve its primary response endpoint in the overall study population, favorable trends were observed across key efficacy outcomes, including PFS, OS, and duration of response [99].

Compared to patients with intermediate (MET/CEP7 ratio >2.2 to <4) or low (MET/CEP7 ratio >1.8 to <2.2) levels of MET amplification, those with high-level MET gene amplification (MET/CEP7 ratio ≥4) as determined by fluorescence in situ hybridization (FISH) demonstrated a markedly improved median progression-free survival (PFS) when treated with crizotinib. Specifically, patients with high-level amplification exhibited a median PFS of 6.7 months, in contrast to 1.9 months and 1.8 months for the intermediate and low amplification groups, respectively [100], while a phase II clinical trial demonstrated limited clinical benefit, with an ORR of 27 % and a median PFS of 4.4 months [101]. A separate phase II clinical trial reported comparable outcomes. Among patients with ≥6 copies of the c-Met gene, the objective response rate (ORR) reached 16 % and progression-free survival (PFS) was 3.2 months. In comparison, patients across all c-Met mutation cohorts demonstrated an ORR of 10.7 % and a median PFS of 2.2 months [102]. According to an independent review, tepotinib in patients with advanced NSCLC who had MET alterations, such as MET exon 14 skipping mutations and MET amplification, was associated with a median ORR of 46 % and a median PFS of 8.5 months in the phase II VISION trial. Additionally, there were no discernible differences in the responses of naïve and previously treated patients. Furthermore, tepotinib's safety and effectiveness in a subgroup of elderly patients (over 75) with NSCLC were comparable to those of the other enrolled patients (ORR 39.7 %, median PFS 8.6 months) [103]. Furthermore, there was no difference in the intention-to-treat population's clinical outcomes between a phase 2 study of erlotinib with or without emibetuzumab in patients with advanced epidermal growth factor receptor (EGFR)-mutated NSCLC. Nevertheless, a post hoc exploratory assessment showed that the combination regimen had a superior median PFS (20.7 months) versus erlotinib monotherapy (5.4 months) [104].

7. Bioavailability challenges of natural compounds

A compound's health benefits cannot be realized before it undergoes metabolism in the intestines [105]. Bioactive compounds must be bioavailable to be effective [106]. Investigating dietary bioactive compounds' health effects may be redundant without knowing their bioavailability. A key step is determining the bioavailability of food components and associated health claims, followed by knowing circulating metabolites, which facilitates understanding the mechanism of action [107].

Compared to pharmaceutical drugs, unraveling the bioavailability of food constituents is more challenging due to their complexity, several factors that influence their transition during digestion, and the different mechanisms of absorption of water-soluble and lipid-soluble molecules [107]. To take synthetic/semi-synthetic drugs at the right time and in the correct dose is essential. Phytochemicals are consumed at irregular intervals at low and variable levels as part of a regular diet [108]. Phytochemicals are, therefore, difficult to assess for their specific health benefits. Additionally, due to physicochemical changes, phytochemicals' oral bioavailability and bioactivity may differ after processing, long-term storage, and oral intake [108,109].

Bioavailability and bioactivity of phytochemicals are highly dependent on their structure, quantity, and foods they are consumed with [110,111]. Moreover, phytochemicals possess an enormous range of molecular weights, charge, functional groups, and polarity, which result in diverse solubility, partitioning, stability under various environmental circumstances, and physical states [112]. After oral route administration, phytochemicals have to dissolve in gastrointestinal fluids (GIFs), but one of the largest barriers to efficient oral delivery are their low solubility rates in GIFs. GIFs contains pH ranging 1.2 in stomach to 6.8 in small intestine, and action of gut enzymes propel their metabolism. Accordingly, most of phytochemicals are decomposed by gastric acidity of gut and are subject to metabolism by various enzymes, which result in low oral bioavailability [113]. In addition, high lipophilicity of phytochemicals results in low absorbability in intestines, which consequently decrease their bioavailability. Main factors, which affect phytochemical bioavailability, are lipophilicity, intestinal absorbability, and gastrointestinal fluids stability [114,115]. Polyphenols, e.g., curcumin and tea, are absorbed efficiently via lymphatics compared to circulatory systems. Phenolic molecular structure, glycone or aglycone, can affect their absorbability, which result in variability in their bioavailability [116]. Polyphenol absorbability rates range 0.3 %–43 % and their metabolites frequently have low plasma levels [106]. Hydrophilic drugs or polyphenols are always absorbed better than lipophilic drugs or polyphenols are. Polyphenols found in foods are most of the time existed in esters, glycosides, or polymers, which are not absorbed in their undigested conformers [117]. Enzymes found in small intestine hydrolyze most of polyphenols at brush border of epithelial cells [118,119]. Flavonoid aglycones are also conjugated by Phase II enterocyte enzymes, which results in methylated or glucuronidated derivatives. These are exported to the intestinal lumen by ABC transporters [117,118,120]. Apart from that, unconjugated flavonoids and their metabolism are also conjugated by hepatocytes, which are secreted to the bloodstream or bile by the hepatic portal vein. From systemic circulation, polyphenol metabolism are subsequently excreted in urine [118,119,121]. Finally, polyphenols are also broken down by the large intestine's microbiota and other bigger molecules that are not absorbed in the small intestine.

8. Conclusion and future perspective

The HGF/MET signaling pathway plays a crucial role in driving oncogenesis, metastasis, and therapeutic resistance in a wide array of cancers. Its activation contributes to tumor progression by promoting unchecked cellular proliferation, resistance to apoptosis, angiogenesis, and the EMT—a key step in metastasis. Because of its central involvement in cancer biology, this pathway has become a major target for therapeutic intervention. Despite the development of MET inhibitors, including monoclonal antibodies, small-molecule TKIs, and combination therapies, clinical outcomes have often fallen short of expectations. One major hurdle is the emergence of intrinsic and acquired resistance, which has prompted a search for alternative or complementary therapeutic strategies. Among these, natural compounds are gaining attention due to their multi-targeted actions and generally favorable safety profiles compared to synthetic drugs. Phytochemicals such as flavonoids, curcumin, EGCG, honokiol, and resveratrol have shown substantial promise in modulating the HGF/MET axis. These compounds interfere with the pathway through various mechanisms. For example, apigenin

and quercetin can directly inhibit MET phosphorylation, thereby dampening downstream signaling. Curcumin blocks key downstream effectors such as the PI3K/AKT/mTOR pathway, while resveratrol reversed EMT and inhibited HGF-induced invasion, thereby reducing metastatic potential. Some compounds, like luteolin, enhance the effects of conventional therapies; in non-small cell lung cancer (NSCLC), luteolin helped overcome resistance to the EGFR inhibitor osimertinib.

Preclinical studies have consistently demonstrated that natural compounds not only inhibit tumor growth and metastasis but also sensitize tumors to chemotherapy and targeted agents. EGCG and honokiol, for example, help re-sensitize resistant cancer cells by disrupting MET-mediated survival signals. Even metformin, a commonly used antidiabetic drug, has been shown to suppress MET expression and downstream pathways, underscoring the anticancer potential of repurposed natural agents. These findings support the idea of using natural compounds as adjuncts in precision oncology. However, several challenges must be addressed before these promising compounds can be widely adopted in clinical practice. One of the foremost issues is optimizing their bioavailability and delivery. Many natural compounds are hindered by poor solubility, rapid metabolism, and limited systemic availability. To overcome these limitations, innovative drug delivery systems, such as nanoparticles, liposomes, and polymer-based carriers, are being developed. For instance, nano-curcumin has shown improved pharmacokinetic properties in early-phase trials, suggesting a practical path toward clinical use. A deeper understanding of the mechanisms by which these compounds modulate the HGF/MET pathway is also essential. Although numerous studies confirm their anticancer activity, many questions remain about their specific molecular targets and the context in which they are most effective. Advanced research tools such as CRISPR-based functional screens, proteomics, and single-cell RNA sequencing can help identify critical nodes in the pathway and uncover resistance mechanisms. Additionally, identifying predictive biomarkers—such as MET amplification or exon 14 skipping mutations—will be key to selecting patients who are most likely to benefit from these therapies. Combination strategies represent another promising avenue. Given the biological complexity and heterogeneity of MET-driven cancers, natural compounds are unlikely to be effective as monotherapies in most settings. Rational combinations—such as pairing flavonoids with immune checkpoint inhibitors, or combining curcumin with MET TKIs—should be explored in both preclinical and early-phase clinical trials. These combinations have the potential to overcome resistance mechanisms while reducing toxicity through dose sparing. To facilitate the translation of preclinical findings into clinical practice, rigorously designed clinical trials are urgently required. Much of the current evidence supporting the use of natural compounds is derived from *in vitro* studies or animal models. Human trials, particularly Phase I and II studies focused on safety, dosing, and early efficacy, are critical next steps. Examples include the testing of EGCG in MET-amplified gastric cancer and resveratrol in hepatocellular carcinoma. Randomized controlled trials comparing natural compounds as adjuncts versus standard therapy will be essential for establishing clinical relevance. Emerging research also suggests that the HGF/MET pathway can modulate the tumor immune microenvironment. Natural compounds such as honokiol and quercetin have shown the ability to downregulate PD-L1 and enhance T-cell responses. This paves the way for exploting whether these agents can potentiate the effects of immunotherapies in MET-altered cancers, a possibility that merits further experimentation. In conclusion, the HGF/MET signaling pathway remains a critical target in cancer treatment, and natural compounds offer a compelling, low-toxicity avenue for modulating this pathway. While significant strides have been made in understanding their mechanisms and potential applications, bridging the gap between preclinical promise and clinical implementation will require robust translational research, interdisciplinary collaboration, and well-structured clinical trials. By addressing the current limitations—such as bioavailability challenges, mechanistic uncertainties, and a lack of clinical validation—natural agents could emerge as vital components of next-generation oncology, used alone or in synergistic combination with existing therapies. Continued investment in this area holds the promise of improving outcomes for patients with MET-driven malignancies.

CRediT authorship contribution statement

Pouya Goleij: Writing – review & editing, Writing – original draft, Conceptualization, Supervision. **Mohammad Mahdi Heidari:** Writing – original draft, Data curation. **Hossein Motevalli:** Writing – original draft, Resources, Data curation. **Sajad Abolfazli:** Writing – original draft, Resources. **Mohammad Amin Khazeei Tabari:** Writing – review & editing. **Aryan Rezaee:** Visualization, Resources. **Danaé S Larsen:** Writing – review & editing. **Maria Daglia:** Writing – review & editing, Supervision. **Michael Aschner:** Writing – review & editing. **Haroon Khan:** Writing – review & editing, Supervision.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used Al-assisted technologies to rephrase to reduce plagiarism and improve language and grammar. After using this tool/service, the authors reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We thank our colleagues for providing valuable comments on the manuscript.

Data availability

No data was used for the research described in the article.

References

[1] P.S. Roy, B.J. Saikia, Cancer and cure: a critical analysis, Indian J. Cancer 53 (3) (2016) 441–442.
[2] M. Cordani, et al., Signaling, cancer cell plasticity, and intratumor heterogeneity, Cell Commun. Signal. 22 (1) (2024) 255.
[3] A. Addante, et al., A signaling crosstalk between BMP9 and HGF/c-Met regulates mouse adult liver progenitor cell survival, Cells 9 (3) (2020).
[4] X. Huang, et al., The HGF-MET axis coordinates liver cancer metabolism and autophagy for chemotherapeutic resistance, Autophagy 15 (7) (2019) 1258–1279.
[5] J. Qian, et al., Upregulation of PDGF mediates robust liver regeneration after nanosecond pulsed electric field ablation by promoting the HGF/c-Met pathway, BioMed Res. Int. 2020 (2020) 3635787.
[6] G. Gupta, et al., The role of HGF/MET in liver cancer, Future Med. Chem. 13 (21) (2021) 1829–1832.
[7] D.G. Pons, Roles of phytochemicals in cancer prevention and therapeutics, Int. J. Mol. Sci. 25 (10) (2024).
[8] S.A. Park, et al., Butein inhibits cell growth by blocking the IL-6/IL-6Rα interaction in human ovarian cancer and by regulation of the IL-6/STAT3/FoxO3a pathway, Int. J. Mol. Sci. 24 (7) (2023).
[9] M. Ma, et al., A mulberry diels-alder-type adduct, Kuwanon M, triggers apoptosis and paraptosis of lung cancer cells through inducing endoplasmic reticulum stress, Int. J. Mol. Sci. 24 (2) (2023).
[10] M. Alorda-Clara, et al., High concentrations of genistein decrease cell viability depending on oxidative stress and inflammation in Colon cancer cell lines, Int. J. Mol. Sci. 23 (14) (2022).
[11] D.G. Pons, et al., The phytoestrogen genistein affects breast cancer cells treatment depending on the ERα/ERβ ratio, J. Cell. Biochem. 117 (1) (2016) 218–229.
[12] M. Ahmed, et al., Phytochemicals as chemo-preventive agents and signaling molecule modulators: current role in cancer therapeutics and inflammation, Int. J. Mol. Sci. 23 (2022) 15765.

[13] T. Nakamura, S. Mizuno, The discovery of hepatocyte growth factor (HGF) and its significance for cell biology, life sciences and clinical medicine, Proc. Jpn. Acad. Ser. B Phys. Biol. Sci. 86 (6) (2010) 588–610.
[14] H.K. Byeon, M. Ku, J. Yang, Beyond EGFR inhibition: multilateral combat strategies to stop the progression of head and neck cancer, Exp. Mol. Med. 51 (1) (2019) 1–14.
[15] Z. Sagi, T. Hieronymus, The impact of the epithelial-mesenchymal transition regulator hepatocyte growth factor receptor/met on skin immunity by modulating langerhans cell migration, Front. Immunol. 9 (2018) 517.
[16] E. Gherardi, et al., Targeting MET in cancer: rationale and progress, Nat. Rev. Cancer 12 (2) (2012) 89–103.
[17] T. Nakamura, et al., Hepatocyte growth factor twenty years on: much more than a growth factor, J. Gastroenterol. Hepatol. 26 (s1) (2011) 188–202.
[18] Kate A. Owen, et al., Pericellular activation of hepatocyte growth factor by the transmembrane serine proteases matriptase and hepsin, but not by the membrane-associated protease uPA, Biochem. J. 426 (2) (2010) 219–228.
[19] R. Tanaka, et al., The role of HGF/MET signaling in metastatic uveal melanoma, Cancers (Basel) 13 (21) (2021).
[20] S. Raj, et al., Molecular mechanism(s) of regulation(s) of c-MET/HGF signaling in head and neck cancer, Mol. Cancer 21 (1) (2022) 31.
[21] S. Yao, et al., Unveiling the role of HGF/c-Met signaling in non-small cell lung cancer tumor microenvironment, Int. J. Mol. Sci. 25 (16) (2024).
[22] A.Z. Lai, J.V. Abella, M. Park, Crosstalk in met receptor oncogenesis, Trends Cell Biol. 19 (10) (2009) 542–551.
[23] N. Cheng, et al., Transforming growth factor-beta signaling-deficient fibroblasts enhance hepatocyte growth factor signaling in mammary carcinoma cells to promote scattering and invasion, Mol. Cancer Res. 6 (10) (2008) 1521–1533.
[24] E. Papa, et al., Negative control of the HGF/c-MET pathway by TGF-β: a new look at the regulation of stemness in glioblastoma, Cell Death Dis. 8 (12) (2017) 3210.
[25] Y. Han, et al., Targeting MET in NSCLC: an ever-expanding territory, JTO Clinical and Research Reports 5 (2) (2024).
[26] G. Spitaleri, et al., MET in non-small-cell lung cancer (NSCLC): cross 'a Long and Winding Road' looking for a target, Cancers (Basel) 15 (19) (2023).
[27] D.W. Murray, et al., Guanine nucleotide exchange factor Dock7 mediates HGF-induced glioblastoma cell invasion via Rac activation, Br. J. Cancer 110 (5) (2014) 1307–1315.
[28] W. Li, et al., HGF-induced formation of the MET-AXL-ELMO2-DOCK180 complex promotes RAC1 activation, receptor clustering, and cancer cell migration and invasion, J. Biol. Chem. 293 (40) (2018) 15397–15418.
[29] G. Yu, et al., Paeoniflorin inhibits Hepatocyte growth Factor- (HGF-) induced migration and invasion and actin rearrangement via suppression of c-Met-Mediated RhoA/ROCK signaling in glioblastoma, BioMed Res. Int. 2019 (2019) 9053295.
[30] N. Kawase, et al., SRC kinase activator CDCP1 promotes hepatocyte growth factor-induced cell migration/invasion of a subset of breast cancer cells, J. Biol. Chem. 298 (3) (2022) 101630.
[31] L.P. Stabile, et al., c-Src activation mediates erlotinib resistance in head and neck cancer by stimulating c-Met, Clin. Cancer Res. 19 (2) (2013) 380–392.
[32] F. Moosavi, et al., HGF/MET pathway aberrations as diagnostic, prognostic, and predictive biomarkers in human cancers, Crit. Rev. Clin. Lab Sci. 56 (8) (2019) 533–566.
[33] K. Singletary, Ginger: an overview of health benefits, Nutr. Today 45 (4) (2010) 171–183.
[34] I.R. Kubra, L.J.M. Rao, An impression on current developments in the technology, chemistry, and biological activities of ginger (Zingiber officinale roscoe), Crit. Rev. Food Sci. Nutr. 52 (8) (2012) 651–688.
[35] R. Arcusa, et al., Potential role of ginger (Zingiber officinale roscoe) in the prevention of neurodegenerative diseases, Front. Nutr. 9 (2022) 809621.
[36] S. Fakhri, et al., Ginger and heart health: from mechanisms to therapeutics, Curr. Mol. Pharmacol. 14 (6) (2021) 943–959.
[37] Y.A. Mohd Yusof, Gingerol and its role in chronic diseases, Drug discovery from mother nature (2016) 177–207.
[38] R. Yanzhang, et al., Ginger extract inhibits c-MET activation and suppresses osteosarcoma in vitro and in vivo, Cancer Cell Int. 25 (1) (2025) 130.
[39] P. Langcake, R. Pryce, The production of resveratrol by Vitis vinifera and other members of the vitaceae as a response to infection or injury, Physiol. Plant Pathol. 9 (1) (1976) 77–86.
[40] T.C. Hsieh, J.M. Wu, Resveratrol suppresses prostate cancer epithelial cell scatter/invasion by targeting inhibition of hepatocyte growth factor (HGF) secretion by prostate stromal cells and upregulation of E-cadherin by prostate cancer epithelial cells, Int. J. Mol. Sci. 21 (5) (2020).
[41] A. Rauf, et al., Honokiol: an anticancer lignan, Biomed. Pharmacother. 107 (2018) 555–562.
[42] M. Balan, et al., Honokiol inhibits c-Met-HO-1 tumor-promoting pathway and its cross-talk with calcineurin inhibitor-mediated renal cancer growth, Sci. Rep. 7 (1) (2017) 5900.
[43] A. Sabarwal, et al., A novel combination treatment with honokiol and rapamycin effectively restricts c-Met-induced growth of renal cancer cells, and also inhibits the expression of tumor cell PD-L1 involved in immune escape, Cancers 12 (7) (2020) 1782.
[44] P. Singh, et al., The role of quercetin in plants, Plant Physiol. Biochem. 166 (2021) 10–19.
[45] H.-H. Cao, et al., Quercetin inhibits HGF/c-Met signaling and HGF-stimulated melanoma cell migration and invasion, Mol. Cancer 14 (1) (2015) 103.
[46] D. Labbé, et al., The flavonols quercetin, kaempferol, and myricetin inhibit hepatocyte growth factor-induced medulloblastoma cell Migration123, J. Nutr. 139 (4) (2009) 646–652.
[47] A. Rauf, et al., Berberine as a potential anticancer agent: a comprehensive review, Molecules 26 (23) (2021) 7368.
[48] Z. Chen, et al., The natural product berberine synergizes with osimertinib preferentially against MET-amplified osimertinib-resistant lung cancer via direct MET inhibition, Pharmacol. Res. 175 (2022) 105998.
[49] C.J. Bailey, Metformin: historical overview, Diabetologia 60 (9) (2017) 1566–1576.
[50] D.M.A. Gant, A.B. Parris, X. Yang, Metformin-induced downregulation of c-Met is a determinant of sensitivity in MDA-MB-468 breast cancer cells, Biochem. Biophys. Res. Commun. 613 (2022) 100–106.
[51] D. Carling, et al., AMP-activated protein kinase: new regulation, new roles? Biochem. J. 445 (1) (2012) 11–27.
[52] V. Donadon, et al., Metformin and reduced risk of hepatocellular carcinoma in diabetic patients with chronic liver disease, Liver Int. 30 (5) (2010) 750–758.
[53] L. Zheng, et al., Prognostic significance of AMPK activation and therapeutic effects of metformin in hepatocellular carcinoma, Clin. Cancer Res. 19 (19) (2013) 5372–5380.
[54] J. Li, et al., Anti-tumor effects of metformin in animal models of hepatocellular carcinoma: a systematic review and meta-analysis, PLoS One 10 (6) (2015) e0127967.
[55] C. Zhang, et al., Metformin delays AKT/c-Met-driven hepatocarcinogenesis by regulating signaling pathways for de novo lipogenesis and ATP generation, Toxicol. Appl. Pharmacol. 365 (2019) 51–60.
[56] X. Zhou, et al., Apigenin: a current review on its beneficial biological activities, J. Food Biochem. 41 (4) (2017) e12376.
[57] W.-J. Lee, et al., Apigenin inhibits HGF-promoted invasive growth and metastasis involving blocking PI3K/Akt pathway and β4 integrin function in MDA-MB-231 breast cancer cells, Toxicol. Appl. Pharmacol. 226 (2) (2008) 178–191.
[58] J.M. Kaipa, et al., Transcriptome profiling reveals silibinin dose-dependent response network in non-small lung cancer cells, PeerJ 8 (2020) e10373.
[59] S. Verdura, et al., Lung cancer management with silibinin: a historical and translational perspective, Pharmaceuticals 14 (6) (2021) 559.
[60] N.Y.S. Yassin, et al., Silybum marianum total extract, silymarin and silibinin abate hepatocarcinogenesis and hepatocellular carcinoma growth via modulation of the HGF/c-Met, Wnt/β-catenin, and PI3K/Akt/mTOR signaling pathways, Biomed. Pharmacother. 145 (2022) 112409.
[61] X. Song, et al., Myricetin: a review of the most recent research, Biomed. Pharmacother. 134 (2021) 111017.
[62] D. Labbé, et al., The flavonols quercetin, kaempferol, and myricetin inhibit hepatocyte growth factor-induced medulloblastoma cell migration, The Journal of nutrition 139 (4) (2009) 646–652.
[63] S.-Y. Ko, Myricetin suppresses LPS-induced MMP expression in human gingival fibroblasts and inhibits osteoclastogenesis by downregulating NFATc1 in RANKL-induced RAW 264.7 cells, Arch. Oral Biol. 57 (12) (2012) 1623–1632.
[64] Y. Qin, et al., Recent advances in the therapeutic potential of nobiletin against respiratory diseases, Phytomedicine (2024) 155506.
[65] M.-D. Shi, et al., Nobiletin attenuates metastasis via both ERK and PI3K/Akt pathways in HGF-treated liver cancer HepG2 cells, Phytomedicine 20 (8) (2013) 743–752.
[66] M. Zheng, et al., Ginsenosides: a potential neuroprotective agent, BioMed Res. Int. 2018 (1) (2018) 8174345.
[67] K.-C. Shin, D.-K. Oh, Characterization of a novel recombinant β-glucosidase from Sphingopyxis alaskensis that specifically hydrolyzes the outer glucose at the C-3 position in protopanaxadiol-type ginsenosides, J. Biotechnol. 172 (2014) 30–37.
[68] L. Wang, et al., Identification of the protopanaxatriol synthase gene CYP6H for ginsenoside biosynthesis in Panax quinquefolius, Funct. Integr. Genom. 14 (2014) 559–570.
[69] H.-H. Kwok, et al., Ginsenoside-Rg1 induces angiogenesis by the inverse regulation of MET tyrosine kinase receptor expression through miR-23a, Toxicol. Appl. Pharmacol. 287 (3) (2015) 276–283.
[70] A. Friedlaender, et al., The METeoric rise of MET in lung cancer, Cancer 126 (22) (2020) 4826–4837.
[71] E. Aguilar, et al., Outcomes to first-line pembrolizumab in patients with non-small-cell lung cancer and very high PD-L1 expression, Ann. Oncol. 30 (10) (2019) 1653–1659.
[72] X. Liu, et al., Detection of Frequent MET Exon 14 Skipping Events in Pulmonary Sarcomatoid Carcinoma and Response to Targeted Inhibition, American Society of Clinical Oncology, 2015.
[73] A. Drilon, et al., Targeting MET in lung cancer: will expectations finally be MET? J. Thorac. Oncol. 12 (1) (2017) 15–26.
[74] H. Go, et al., High MET gene copy number leads to shorter survival in patients with non-small cell lung cancer, J. Thorac. Oncol. 5 (3) (2010) 305–313.
[75] K. Suzawa, et al., Acquired MET Exon 14 Alteration Drives Secondary Resistance to Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor in EGFR-mutated Lung Cancer, vol. 3, JCO precision oncology, 2019, pp. 1–8.
[76] J. Wu, Z. Lin, Non-small cell lung cancer targeted therapy: drugs and mechanisms of drug resistance, Int. J. Mol. Sci. 23 (23) (2022) 15056.
[77] G. Huang, et al., Luteolin overcomes acquired resistance to osimertinib in non-small cell lung cancer cells by targeting the HGF-MET-Akt pathway, Am. J. Cancer Res. 13 (9) (2023) 4145.
[78] J. Zhang, Y. Ma, Luteolin as a potential therapeutic candidate for lung cancer: emerging preclinical evidence, Biomed. Pharmacother. 176 (2024) 116909.

[79] H. Chen, et al., Metformin reduces HGF-induced resistance to alectinib via the inhibition of Gab1, Cell Death Dis. 11 (2) (2020) 111.
[80] J. Fu, et al., HGF/c-MET pathway in cancer: from molecular characterization to clinical evidence, Oncogene 40 (28) (2021) 4625–4651.
[81] J. Tchou, et al., Safety and efficacy of intratumoral injections of chimeric antigen receptor (CAR) T cells in metastatic breast cancer, Cancer Immunol. Res. 5 (12) (2017) 1152–1161.
[82] P.D. Shah, et al., Phase I trial of autologous RNA-electroporated cMET-directed CAR T cells administered intravenously in patients with melanoma and breast carcinoma, Cancer Res. Commun. 3 (5) (2023) 821–829.
[83] K. Moran-Jones, The therapeutic potential of targeting the HGF/cMET axis in ovarian cancer, Mol. Diagn. Ther. 20 (3) (2016) 199–212.
[84] H.J. Kim, Therapeutic strategies for ovarian cancer in point of HGF/c-MET targeting, Medicina 58 (5) (2022) 649.
[85] H.J. Kim, et al., Humanized anti-hepatocyte growth factor monoclonal antibody (YYB-101) inhibits ovarian cancer progression, Front. Oncol. 9 (2019) 571.
[86] H.J. Kim, K. Heo, YYB-101, a humanized antihepatocyte growth factor monoclonal antibody, inhibits ovarian cancer cell motility and proliferation, Anticancer Res. 41 (2) (2021) 671–678.
[87] S.T. Kim, et al., First-in-human phase I trial of anti-hepatocyte growth factor antibody (YYB101) in refractory solid tumor patients, Ther. Adv. Med. Oncol. 12 (2020) 1758835920926796.
[88] L. Rimassa, et al., Tivantinib for second-line treatment of MET-high, advanced hepatocellular carcinoma (METIV-HCC): a final analysis of a phase 3, randomised, placebo-controlled study, Lancet Oncol. 19 (5) (2018) 682–693.
[89] M. Kudo, et al., A randomized, double-blind, placebo-controlled, phase 3 study of tivantinib in Japanese patients with MET-high hepatocellular carcinoma, Cancer Sci. 111 (10) (2020) 3759–3769.
[90] G.K. Abou-Alfa, et al., Cabozantinib in patients with advanced and progressing hepatocellular carcinoma, N. Engl. J. Med. 379 (1) (2018) 54–63.
[91] S. Pant, et al., A phase II study of the c-met inhibitor Tivantinib in combination with FOLFOX for the treatment of patients with previously untreated metastatic adenocarcinoma of the distal esophagus, gastroesophageal junction, or stomach, Cancer Invest. 35 (7) (2017) 463–472.
[92] Y.J. Bang, et al., Phase 1 study of capmatinib in MET-positive solid tumor patients: dose escalation and expansion of selected cohorts, Cancer Sci. 111 (2) (2020) 536–547.
[93] T. Aparicio, et al., The activity of crizotinib in chemo-refractory MET-amplified esophageal and gastric adenocarcinomas: results from the AcSé-crizotinib program, Targeted Oncol. 16 (2021) 381–388.
[94] E. Van Cutsem, et al., A multicenter phase II study of AMG 337 in patients with MET-amplified gastric/gastroesophageal junction/esophageal adenocarcinoma and other MET-amplified solid tumors, Clin. Cancer Res. 25 (8) (2019) 2414–2423.
[95] D. Sakai, et al., A non-randomized, open-label, single-arm, phase 2 study of emibetuzumab in Asian patients with MET diagnostic positive, advanced gastric cancer, Cancer Chemother. Pharmacol. 80 (2017) 1197–1207.
[96] N.M. Chanzá, et al., Cabozantinib in advanced non-clear-cell renal cell carcinoma: a multicentre, retrospective, cohort study, The lancet oncology 20 (4) (2019) 581–590.
[97] T.K. Choueiri, et al., Efficacy of savolitinib vs sunitinib in patients with MET-driven papillary renal cell carcinoma: the SAVOIR phase 3 randomized clinical trial, JAMA Oncol. 6 (8) (2020) 1247–1255.
[98] S.K. Pal, et al., A comparison of sunitinib with cabozantinib, crizotinib, and savolitinib for treatment of advanced papillary renal cell carcinoma: a randomised, open-label, phase 2 trial, Lancet 397 (10275) (2021) 695–703.
[99] C. Suárez, et al., Phase II study investigating the safety and efficacy of savolitinib and durvalumab in metastatic papillary renal cancer (CALYPSO), J. Clin. Oncol. 41 (14) (2023) 2493–2502.
[100] D.R. Camidge, et al., Crizotinib in patients with MET-amplified NSCLC, J. Thorac. Oncol. 16 (6) (2021) 1017–1029.
[101] L. Landi, et al., Crizotinib in MET-deregulated or ROS1-rearranged pretreated non–small cell lung cancer (METROS): a phase II, prospective, multicenter, two-arms trial, Clin. Cancer Res. 25 (24) (2019) 7312–7319.
[102] D. Moro-Sibilot, et al., Crizotinib in c-MET-or ROS1-positive NSCLC: results of the AcSé phase II trial, Ann. Oncol. 30 (12) (2019) 1985–1991.
[103] P.K. Paik, et al., Tepotinib in non–small-cell lung cancer with MET exon 14 skipping mutations, N. Engl. J. Med. 383 (10) (2020) 931–943.
[104] G. Scagliotti, et al., A randomized-controlled phase 2 study of the MET antibody emibetuzumab in combination with erlotinib as first-line treatment for EGFR mutation–positive NSCLC patients, J. Thorac. Oncol. 15 (1) (2020) 80–90.
[105] J.C. Espín, M.T. García-Conesa, F.A. Tomás-Barberán, Nutraceuticals: facts and fiction, Phytochemistry 68 (22–24) (2007) 2986–3008.
[106] C. Manach, et al., Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies, The American journal of clinical nutrition 81 (1) (2005) 230S–242S.
[107] M.J. Rein, et al., Bioavailability of bioactive food compounds: a challenging journey to bioefficacy, Br. J. Clin. Pharmacol. 75 (3) (2013) 588–602.
[108] D.J. McClements, H. Xiao, Excipient foods: designing food matrices that improve the oral bioavailability of pharmaceuticals and nutraceuticals, Food Funct. 5 (7) (2014) 1320–1333.
[109] G. Davidov-Pardo, D.J. McClements, Nutraceutical delivery systems: resveratrol encapsulation in grape seed oil nanoemulsions formed by spontaneous emulsification, Food Chem. 167 (2015) 205–212.
[110] J. Gleeson, Diet, food components and the intestinal barrier, Nutr. Bull. 42 (2) (2017) 123–131.
[111] D.J. McClements, H. Xiao, Designing food structure and composition to enhance nutraceutical bioactivity to support cancer inhibition, in: Seminars in Cancer Biology, Elsevier, 2017.
[112] D.J. McClements, Advances in nanoparticle and microparticle delivery systems for increasing the dispersibility, stability, and bioactivity of phytochemicals, Biotechnol. Adv. 38 (2020) 107287.
[113] S.S. Imam, et al., Recent advancement in chitosan-based nanoparticles for improved oral bioavailability and bioactivity of phytochemicals: challenges and perspectives, Polymers 13 (22) (2021) 4036.
[114] K. Oehlke, et al., Potential bioavailability enhancement of bioactive compounds using food-grade engineered nanomaterials: a review of the existing evidence, Food Funct. 5 (7) (2014) 1341–1359.
[115] X. Nie, et al., Oral nano drug delivery systems for the treatment of type 2 diabetes mellitus: an available administration strategy for antidiabetic phytocompounds, International journal of nanomedicine (2020) 10215–10240.
[116] V.P. Chavda, et al., Nano-drug delivery systems entrapping natural bioactive compounds for cancer: recent progress and future challenges, Frontiers in oncology 12 (2022) 867655.
[117] C. Manach, et al., Polyphenols: food sources and bioavailability, The American journal of clinical nutrition 79 (5) (2004) 727–747.
[118] C. Manach, J.L. Donovan, Pharmacokinetics and metabolism of dietary flavonoids in humans, Free Radic. Res. 38 (8) (2004) 771–786.
[119] D. Del Rio, G. Borges, A. Crozier, Berry flavonoids and phenolics: bioavailability and evidence of protective effects, British journal of nutrition 104 (S3) (2010) S67–S90.
[120] J. Viskupičová, M. Ondrejovič, E. Šturdík, Bioavailability and metabolism of flavonoids, J. Food Nutr. Res. 47 (4) (2008).
[121] G. Williamson, The use of flavonoid aglycones in in vitro systems to test biological activities: based on bioavailability data, is this a valid approach? Phytochem. Rev. 1 (2002) 215–222.