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Review

Significance of flavonoids targeting PI3K/Akt/HIF-1α signaling pathway in therapy-resistant cancer cells – A potential contribution to the predictive, preventive, and personalized medicine

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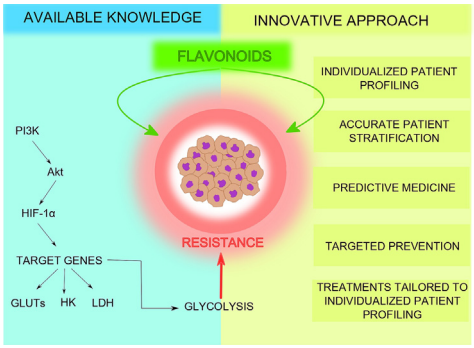
HIGHLIGHTS

- Paradigm shift from reactive to 3P medicine in essential in cancer management.
- Natural substances are characterized by potent anticancer effects in primary and secondary care.
- Working hypothesis proposes HIF-1α pathways to target by flavonoids against cancer resistance.
- Clinically relevant example: individuals with the Flammer (FS) syndrome phenotype.
- Economy relevant innovation is cost-effective prevention of the health-to-disease transition.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Cancer management faces multiple obstacles, including resistance to current therapeutic approaches. In the face of challenging microenvironments, cancer cells adapt metabolically to maintain their supply of energy and precursor molecules for biosynthesis and thus sustain rapid proliferation

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and tumor growth. Among the various metabolic adaptations observed in cancer cells, the altered glucose metabolism is the most widely studied. The aberrant glycolytic modification in cancer cells has been associated with rapid cell division, tumor growth, cancer progression, and drug resistance. The higher rates of glycolysis in cancer cells, as a hallmark of cancer progression, is modulated by the transcription factor hypoxia inducible factor 1 alpha (HIF-1α), a downstream target of the PI3K/Akt signaling, the most deregulated pathway in cancer.

Aim of Review: We provide a detailed overview of current, primarily experimental, evidence on the potential effectiveness of flavonoids to combat aberrant glycolysis-induced resistance of cancer cells to conventional and targeted therapies. The manuscript focuses primarily on flavonoids reducing cancer resistance *via* affecting PI3K/Akt, HIF-1α (as the transcription factor critical for glucose metabolism of cancer cells that is regulated by PI3K/Akt pathway), and key glycolytic mediators downstream of PI3K/Akt/HIF-1α signaling (glucose transporters and key glycolytic enzymes).

Key Scientific Concepts of Review: The working hypothesis of the manuscript proposes HIF-1α – the transcription factor critical for glucose metabolism of cancer cells regulated by PI3K/Akt pathway as an attractive target for application of flavonoids to mitigate cancer resistance. Phytochemicals represent a source of promising substances for cancer management applicable to primary, secondary, and tertiary care. However, accurate patient stratification and individualized patient profiling represent crucial steps in the paradigm shift from reactive to predictive, preventive, and personalized medicine (PPPM / 3PM). The article is focused on targeting molecular patterns by natural substances and provides evidence-based recommendations for the 3PM relevant implementation.

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Contents

Introduction . . . 104
Altered glucose metabolism of cancer cells . . . 105
HIF-1α downstream of PI3K/Akt . . . 105
Evidence on association between glucose metabolism, HIF-1α, and cancer resistance . . . 107
Targeting glycolysis-induced resistance: Current state of view . . . 107
Effects of flavonoids in cancer resistance related to glycolysis . . . 108
Flavonoids reversing cancer resistance by targeting PI3K/Akt signaling . . . 109
Flavonoids targeting HIF-1α to overcome the resistance of cancer cells . . . 109
Targeting HIF-1α signaling pathways in primary care: Clinically relevant examples of the paradigm shift from reactive to predictive, preventive, and personalized medicine . . . 112
Conclusions and future outlook . . . 113
Funding . . . 114
Declaration of Competing Interest . . . 114
References . . . 114

Introduction

Cancer comprises a heterogeneous group of diseases with a serious socio-economic burden on society [1–4]. Surgery, chemotherapy, and radiotherapy currently represent the conventional mainstays of cancer management [5]. In addition, targeted anti-cancer treatment options include endocrine therapy (e.g., tamoxifen as the first successful targeted therapy) [6], small molecules inhibitors (e.g., EGFR-tyrosine kinase inhibitors), or monoclonal antibodies. Moreover, stem cell therapies, gene therapies, or the utilization of naturally occurring phytochemicals represent advanced anticancer therapeutic approaches [5,7]. However, cancer management still faces a serious obstacle that is characterized as non-responsiveness to conventional anti-cancer therapeutic strategies [8]. Cancer resistance can be either primary (the resistance exists before the commencement of treatment) or acquired (the resistance that develops after the initial therapy and gradually reduces its effectiveness) [7]. Furthermore, multidrug resistance (MDR) is a phenomenon occurring in cancer cells after an exposure to a chemotherapeutic agent, leading to the acquisition of resistance to different unrelated drugs with differences in function, structure, or site of action [9].

The metabolic reprogramming is considered as the crucial hallmark of carcinogenesis [10]. The switch of cancer cells from normal respiratory chain to aerobic glycolysis is known as the Warburg effect [10–12]. Besides, rapid proliferation of cancer cells results in inadequate oxygen supply, also known as hypoxia, and the development of hypoxic or necrotic areas [13]. Although the hypoxic environment can be damaging to normal cells, hypoxia can paradoxically support invasive and metastatic potential of tumor cells and promote glycolysis. Cellular response to hypoxia is associated with processes crucial to maintain the energy supply of rapidly dividing cells, including elevated glucose transport and glycolytic metabolism, increased oxygen delivery, and a switch from oxidative phosphorylation to aerobic glycolysis [14]. The transcription factor Hypoxia-inducible factor 1 alpha (HIF-1α), as the name suggests, is induced in response to hypoxia/ischemia. HIF-1α regulates the expression of genes encoding key glycolytic mediators. Thus, aberrant glucose metabolism, as a crucial characteristic of carcinogenesis, is closely related to upregulated HIF-1α [13]. At the same time, HIF-1α is a downstream target of PI3K/Akt, one of the most deregulated signaling pathways in cancer [15]. Despite the initial assumption that HIF-1α expression is upregulated in a response to hypoxia, tumor cells can increase

HIF-1α also independently of oxygen supply [16]. Since aberrant glycolysis is closely related to drug resistance [17], the association between HIF-1α and resistance to anti-cancer therapeutics is widely discussed topic of current cancer research [14]. In particular, glycolysis-induced resistance of cancer cells comprises a fundamental obstacle in cancer management [17,18].

Therefore, the re-sensitization of cancer cells to conventional anticancer strategies could represents a key strategy improving the outcomes of cancer patients [8]. For this purpose we highlight the crucial potential of naturally occurring phytochemicals that could show a promising benefits as 1) effective sensitizers to anticancer therapy and 2) enhances the effectiveness of anticancer therapy (chemotherapy, radiotherapy, and targeted therapy) demonstrated in experimental and clinical trials [3,7,19]. Here, we discuss the potential effectiveness of flavonoids in reversing therapeutic resistance in cancer cells by targeting PI3K/Akt/HIF-1 α-associated aberrant glucose metabolism.

Altered glucose metabolism of cancer cells

Oxidative phosphorylation represents a primary mode of ATP generation in normal cells under normoxic conditions [20], while glycolysis is characterized as a physiological response to hypoxia [21]. Importantly, the metabolic reprogramming of cancer cells include enhanced fatty acid synthesis, glutamine and glucose metabolism, and other major metabolic pathways closely related to altered glycolysis [17]. Almost 100 years ago, Otto Warburg described the process, currently known as the Warburg effect, which has been characterized as the capability of tumor cells to take up glucose and produce lactate regardless of the availability of oxygen. Importantly, enhanced glycolysis provides the metabolic supply of rapidly dividing cancer cells [21] (mechanisms of the Warburg effect are in detail described in our previous paper by Samec et al. [20]). Notably, the metabolic reprogramming associated with cancer is described by several peculiarities. The switch from oxidative metabolism to glycolysis occurs rather in a section of tumor cells than in the whole tumor mass. Furthermore, tumor cells can switch from mitochondrial oxidative metabolism to aerobic glycolysis and *vice* versa [18]. Although lower efficiency in ATP generation, demonstrated via low ATP yield, when compared with oxidative phosphorylation [20], most cancer cells utilize aerobic glycolysis as a primary energy source [22] due to the faster ATP production [20]. Indeed, rapid ATP production per molecule of glucose obtained by aerobic glycolysis can be advantageous to meet high energy demands in specific conditions of carcinogenesis, for example during epithelial-mesenchymal-transition (EMT) [18]. As initially hypothesized, the dependence on aerobic glycolysis as a primary ATP source was suggested to be associated with inherent mitochondrial defects in cancer cells [20]. However, most cancers are characterized by functionally active mitochondria [23]. Furthermore, high ratios of ATP/ADP, NAD^+/NADH, and $NADP^+$/NADPH is required by rapidly proliferating cells; nevertheless, the balance of these ratios is underestimated under the conditions of oxidative phosphorylation [20]. Moreover, another reason of predominant use of aerobic glycolysis by cancer cells to support rapid proliferation is associated with promotion of the biomass precursors by fueling the glycolytic intermediates for nucleotide biosynthesis *via* the pentose phosphate (PPP) pathway for amino acid and lipid biosynthesis [18]. A shift from oxidative phosphorylation to glycolysis also contributes to a survival advantage for cancer cells under hypoxia, protection against oxidative damage, and apoptosis [24]. Specifically, glycolysis protects cancer cells against oxidative stress passively (*via* avoidance of oxidative phosphorylation, a main ROS source) as well as actively (fueling of glycolytic intermediates into PPP resulting in the production of NADPH and the synthesis of glutathione that is a well-known cellular antioxidant [18]. Notably, HIF-1α is recognized as a key protein in the regulation of aerobic glycolysis *via* induction of expression of genes encoding key glycolytic mediators, specifically GLUTs and glycolytic enzymes [25,26]. Importantly, altered glucose metabolism of cancer cells is considered to possess a significant role in disease progression and drug resistance [12,17].

HIF-1α downstream of PI3K/Akt

Rapid proliferation and tumor growth is closely associated with hypoxia, the lack of oxygen supply [27]. Paradoxically, tumors expand even under hypoxic conditions due to hypoxia-induced genomic changes enabling to survive and continue in rapid cell division. Moreover, prolonged hypoxia is also associated with a selective pressure, which eventually results in the propagation of cancer cells that are most aggressive and stress resistant. Notably, Codony and Tavassoli [28] recently highlighted the benefits of reversing or diminishing hypoxia in sensitization head and neck cancers to radiotherapy, chemotherapy, or immunotherapies [28].

The transcription factor HIF-1α is a key regulator of response to hypoxia [29] and is widely increased and stabilized under hypoxia [27]. HIF-1 complex includes α and β subunits and when stabilized, HIF-1α together with HIF-1β bind to hypoxia-responsive elements (HREs) that are localized in promoter region of HIF-1 target genes [25,26], which regulate cell survival, proliferation, angiogenesis, and metabolism, including genes encoding glucose transporters (GLUTs) and glycolytic enzymes, namely hexokinase (HK), pyruvate dehydrogenase (PDH), and lactate dehydrogenase (LDH) allowing the increase in glycolysis [25]. Overall, hypoxia promotes glycolytic flux into cancer cells while the glycolytic efficiency is pointed out by the rate of glucose uptake and lactate production [30]. Therefore, lactate level and end products of glycolysis tend to be elevated in aggressive drug-resistant tumors [26].

Phosphoinositide 3-kinase (PI3K)/Akt pathway is under physiologic conditions activated in response to insulin, growth factors, or cytokines [31]. However, aberrantly activated PI3K/Akt represents one of the most deregulated pathways in cancer that controls multiple processes of carcinogenesis, including survival, metastasis, and metabolism [32]. PI3K/Akt functions at the interface of oncogenic signaling and cancer metabolism. Indeed, the downstream targets of PI3K/Akt affect cellular metabolism *via* either the direct regulation of nutrient transporters and metabolic enzymes or the control of transcription factors regulating the expression of key metabolic mediators. Therefore, the downstream effects of PI3K/Akt on the proliferation and metabolic reprogramming of cancer cells comprise the critical process of carcinogenesis [31]. Overall, aberrant PI3K/Akt activation promotes tumor progression and treatment resistance [33,34]. For example, Kilic-Eren et al. [35] demonstrated that PI3K/Akt activation contributes to HIF-1α activation under hypoxia and HIF-1α-mediated resistance to apoptosis in childhood tumors (rhabdomyosarcoma and Ewing's sarcoma) [35]. Fig. 1 shows the regulation of glucose metabolism in cancer *via* PI3K/Akt signaling pathway, specifically the activation of Akt by PI3K and further control of glucose metabolism *via* transcriptional control of HIF-1α, downstream of Akt [31]. The Fig. 1 also depicts the oxygen-dependent behavior of HIF-1α in both normoxic and hypoxic conditions (translocation into nucleus and affecting expression of HIF-1α-target genes critical for multiple cellular processes including cancer metabolism of glycolysis).

Despite the initial assumption of HIF-1α responding to hypoxia, recent evidence suggests the role of hypoxia-independent mechanisms of HIF-1α activation [16]. Indeed, HIF-1α stabilization independently of hypoxia may explain the acceleration of glycolysis under normoxic conditions [13,39]. Notably, oxygen-independent

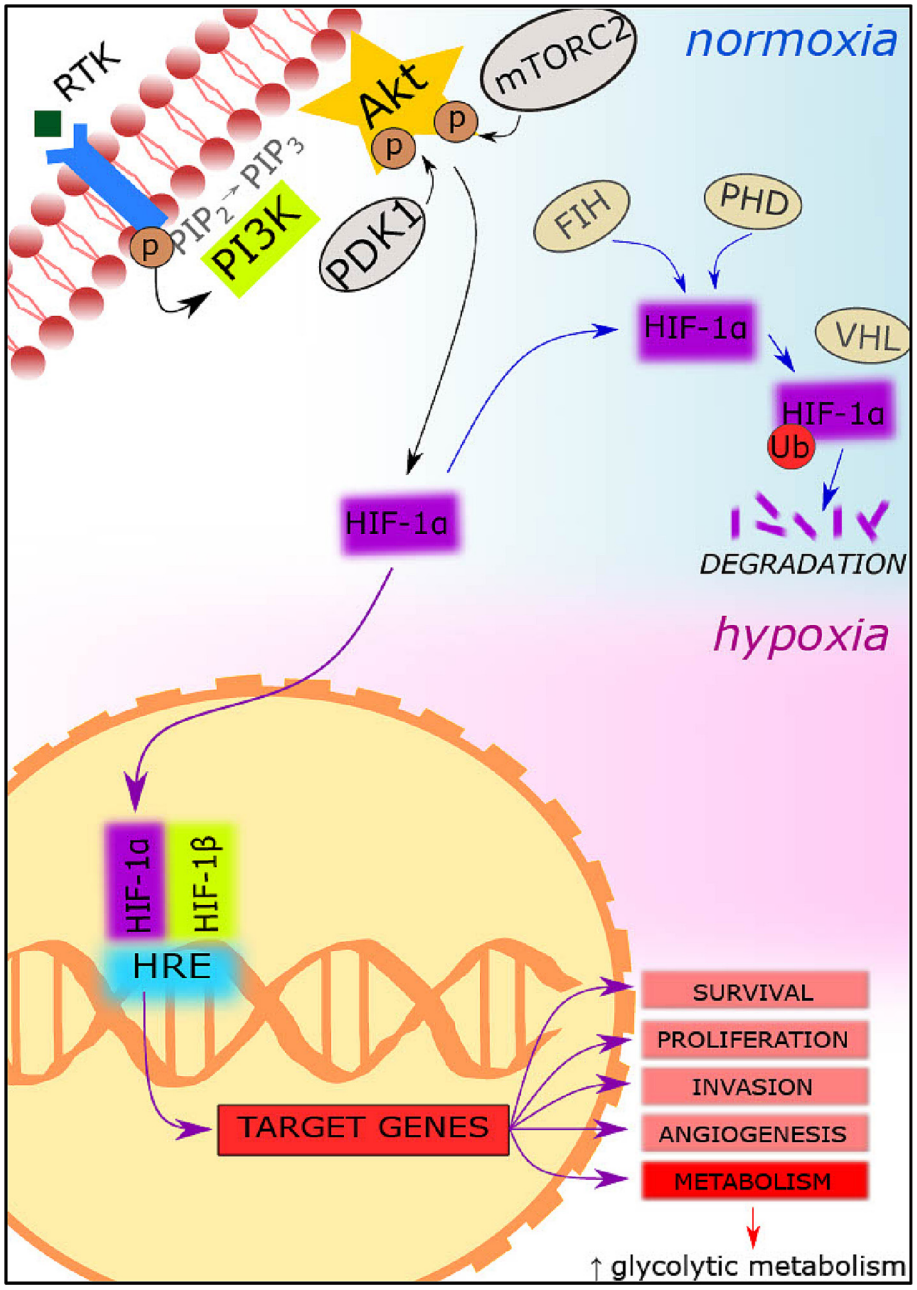

Fig. 1. HIF-1α as downstream targets of PI3K/Akt signaling and HIF-1α oxygen-dependent behavior under normoxia (blue background) and hypoxia (purple background). *Explanatory notes*: Blue arrows – normoxia; purple arrows – hypoxia. *Figure description*: RTKs, a transmembrane protein family, represent the main upstream activators of PI3K/Akt. RTKs involve epidermal growth factor receptors (EGFRs), vascular endothelial growth factor receptors (VEGFRs), and fibroblast growth factor receptors (FGFRs), [32]. RTKs activation leads to the formation of binding sites to recruit PI3K to the plasma membrane. PI3K phosphorylates PIP_2 to produce PIP_3 (PIP_3 can be dephosphorylated by PTEN back to PIP_2) [36]. PIP_3 mediates cellular functions *via* interactions with pleckstrin homology (PH) domain-containing proteins, such as Akt (the central mediator of PI3K signaling) [36]. PIP_3 recruits Akt to the plasma membrane where is Akt fully activated *via* phosphorylation by phosphoinositide-dependent protein kinase 1 (PDK1) and mTOR complex 2 (mTORC2) [37]. Akt is activated also by hypoxia in various tumors [38]. Akt transcriptionally controls various metabolic processes including glucose metabolism – *via* regulation of critical cellular proteins, such as HIF-1 [31]. Under normoxia, HIF-1α stability is regulated by oxygen-dependent degradation domain through hydroxylation of proline residues 402 and 564 by prolyl hydroxylase domain proteins (PHD). These modifications support the interaction with von Hippel-Lindau tumor suppressor (VHL) protein (PHD-VHL axis) and subsequent proteasomal degradation. Ubiquitously expressing HIF-1α subunit inhibitor HIF1AN (FIH1) can also attenuate HIF-1α under normoxia by hydroxylation of Asp site 803 of HIF-1α protein. These critical enzymes require oxygen for catalytic reactions, thus hypoxia could inhibit these reaction resulting in HIF-1α stabilization [16]. Under hypoxia, HIF-1α is translocated into nucleus and binds together with HIF-1β to hypoxia-responsive elements (HREs) in the promoter region of HIF-1 target genes [25,26], including genes encoding glucose transporters (GLUTs) and glycolytic enzymes, namely hexokinase (HK), pyruvate dehydrogenase, or lactate dehydrogenase (LDH) allowing cancer cells to upregulate glycolysis [25]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

activation of HIF-1α can result from pseudo-hypoxic condition [16]. For example, the upregulation of HIF-1α can be performed through von Hippel-Lindau gene (VHL) genetic loss leading to tumors in cerebellum, renal, or retina tissues [39]. Moreover, mutations in p53 can inhibit oxygen-independent degradation of HIF-1α performed *via* Mouse double minute 2 homolog (MDM2) (disruption of p53/MDM2 axis in normoxia). HIF-1α can also be regulated by Heat shock protein 90 (HSP90) while the disruption of HSP90/HIF-1α interactions allow the binding of Receptor for activated C kinase 1 (RACK1) leading to HIF-1α degradation. In addition, de-

ubiquitination of HIF-1α (by for example Ubiquitin specific peptidase 20, USP20) also results in HIF-1α stabilization [16].

In short, HIF-1α, a downstream target of PI3K/Akt signaling, represents a transcriptional factor closely associated with regulation of the expression of genes encoding essential proteins of glucose metabolism [31]. Indeed, glycolysis-induced resistance of cancer cells to current anticancer therapeutics represents a severe obstacle in cancer management [17,18].

Evidence on association between glucose metabolism, HIF-1α, and cancer resistance

HIF-1α is a transcriptional regulator of genes controlling glycolysis [31], while an increase in glycolysis is a characteristic feature of cancer progression [20] and MDR [14]. Notably, HIF-1α is increased in response to hypoxia. Hypoxic cancer cells are more resistant to standard cytotoxic drugs such as cisplatin or doxorubicin. Also, hypoxia promotes resistance to radiotherapy because oxygen is essential for optimal DNA damage induced by ionizing radiation [40]. However, as stated above, cancer cells can also utilize alternative ways to upregulate HIF-1α, independently of oxygen supply [16]. On the whole, aberrant glycolysis is a common characteristic of resistant cancer cells [17] while upregulated HIF-1α promotes the expression of key mediators of glucose metabolism [20,25].

Aberrant activation of PI3K/Akt is a hallmark of cancer aggressiveness and drug resistance. HIF-1α, which controls the expression of genes encoding critical mediators of glucose metabolism, including GLUTs and glycolytic enzymes, represents a downstream target of PI3K/Akt [31]. Indeed, aberrant glycolysis is closely associated with resistance to cancer therapies [17]. For example, GLUT-1 is associated with the up-regulation of genes involved in drug resistance, including multidrug resistance-1 (MDR-1) and p-glycoprotein (P-gp) [41]. Interestingly, Jiang et al. [42] observed that the inhibition of GLUT-1 and PI3K/Akt enhanced the chemosensitivity of laryngeal cancer cells; however, the authors concluded the observed effects of increased chemo-sensitivity to be related rather to HIF-1α than GLUT-1 or PI3K/Akt [42]. Notably, HIF-1α could affect MDR-1 activation and thus contribute to the drug resistance of cancer cells. Indeed, MDR-1, as an energy-dependent drug-efflux pump, decreases the drug's concentration inside cancer cells [43].

To sum up, glycolysis-induced drug resistance occurs in a response to various stimuli including onco-proteins or factors of the tumor microenvironment such as mechanical cues, hypoxia, or pseudohypoxia. The mechanisms of glycolytic metabolism-associated drug resistance include inhibition of apoptosis, EMT or autophagy induction, drug influx inhibition, or drug efflux increase [18]. Importantly, Woo et al. [26] demonstrated that inhibition of aerobic glycolysis repressed Akt/mTOR/HIF-1α axis and restored tamoxifen sensitivity in anti-estrogen-resistant breast cancer cells [26]. Moreover, Table 1 exemplifies the association between enzymes critical for aerobic glycolysis regulated by HIF-1α. The precise mechanisms of the associations between glycolytic mediators and cancer resistance are described in a recent review by Peng et al. [17].

Targeting glycolysis-induced resistance: Current state of view

Glycolysis-induced resistance is described in multiple anticancer strategies, such as chemotherapeutics, radiotherapy, hormone antagonists, immune checkpoint inhibitors, monoclonal antibodies, or small molecule therapeutics (e.g., tyrosine kinase inhibitors) [18].

Elements of glycolytic metabolism that play a role in drug resistance involve GLUTs and glycolytic enzymes including HK, PK, LDH, phosphoglycerate kinase (PGK), fructose biphosphate aldolase (ALDO), enolase (ENO), 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase (PFKFB), or glyceraldehyde 3-phosphate dehydrogenase (GAPDH). Besides, glycolysis-induced drug resistance in cancer can be induced either *via* deregulation of an individual element of glycolytic metabolism or by the overall enhancement of glycolysis [18]. More specifically, Marcucci et al. (2021) described mechanisms of glycolysis-induced drug resistance as anti-apoptotic, EMT-inducing, drug efflux-promoting, or drug influx-inhibiting [18].

The progress in cancer management requires effective targeting therapeutic resistance. Current research provides several approaches to overcome cancer resistance or to re-sensitize resistant cancer cells to therapeutics *via* targeting glycolysis. For example, inhibiting key glycolytic enzymes (HK2, PKM2) resulted in overcoming resistance to taxol and cisplatin in ovarian cancer cells and osteosarcoma stem cells [17,64,65]. Moreover, Zhou et al. [66] recently published a study evaluating the potential of overcoming resistance to chemotherapy *via* nano-shells targeting hypoxic tumor microenvironment, demonstrated through decreased HIF-1α [66].

Due to the promising potential of targeting glycolysis to overcome the resistance of cancer cells to current treatments, we highlight the anti-cancer effects of flavonoids, naturally occurring

Table 1
The association between therapy resistance and key mediators of aerobic glycolysis regulated by HIF-1α.

Enzyme	Effect on glucose metabolism	Association with therapy resistance	Ref.
GLUTs	GLUT-1 → regulation of the flux of glucose into cells	GLUT-1 → correlation with resistance to chemotherapy, radiotherapy, EGFR inhibitors GLUT-1 → upregulation of MDR-1 and P-gp	[25,41,44–47]
HK2	HK2 → catalysis of the first step of glucose metabolism	HK2 → contribution to chemo-resistance *via* blockage of apoptosis HK2 → resistance to 4-hydroxytamoxifen (breast cancer cells) ROS derived from gemcitabine → HK2 dimerization and binding to VDAC → apoptosis inhibition → gemcitabine resistance (pancreatic cancer)	[17,48–51]
PK (PKM2)	PKM2 → regulation of rate-limiting step of glycolysis	PKM2 inhibition → enhanced sensitivity to therapeutics PKM2 → predictive value of response to epirubicin, 5-FU (breast cancer); PKM2 increase → enhancing resistance to adriamycin by promoting glycolysis (breast cancer cells) PKM2 PKM2 upregulation → mTOR resistance (castration-resistant prostate cancer)	[10,17,25,52–56]
PDK and PDH	Phosphorylation of PDH complex by PDK → blockage of OXPHOS and promotion of aerobic glycolysis	Targeting PDH → enhancement of cancer treatment High PDK1-3 → therapy resistance (paclitaxel, 5-FU, cisplatin, among others) PDK1 → driver of radio-resistance PDK1 → cisplatin resistance (ovarian cancer)	[17,23–25,57–59]
LDH (LDHA)	Rapid ATP production, conversion of pyruvate to lactate; Key checkpoint of aerobic glycolysis	LDHA → resistance to 5-FU, docetaxel, cetuximab, paclitaxel, doxorubicin (breast, pancreatic, colon, and oral cancer cells)	[17,60–63]

Abbreviations: HK2, hexokinase2; LDH, lactate dehydrogenase; LDHA, lactate dehydrogenase A isoform; OXPHOS, oxidative phosphorylation; PDH, pyruvate dehydrogenase; PDK, pyruvate dehydrogenase kinase; PK, pyruvate kinase; PKM2, pyruvate kinase M2; VDAC, voltage-dependent anion channel.

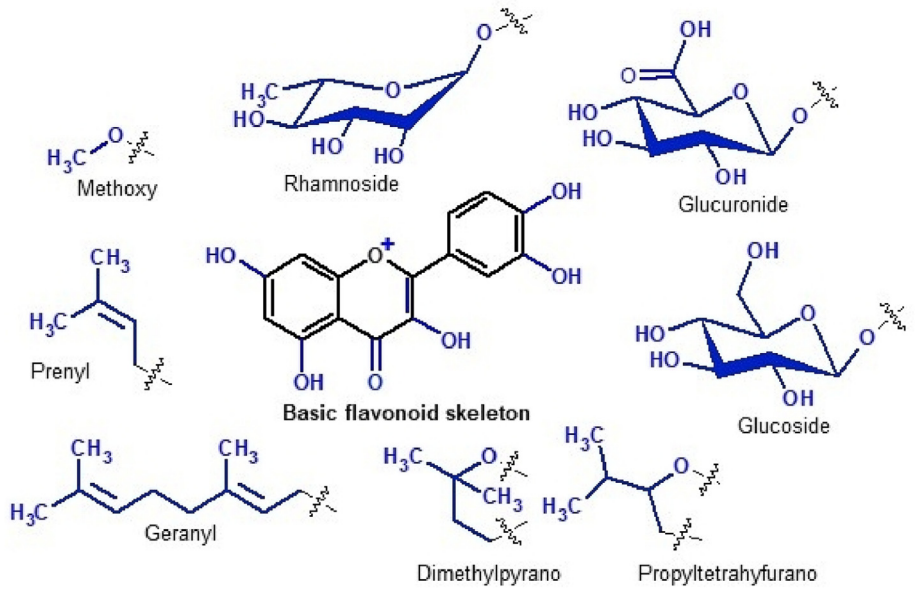

Fig. 2. Basic flavonoid skeleton and examples of substitution and modification (in blue color). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

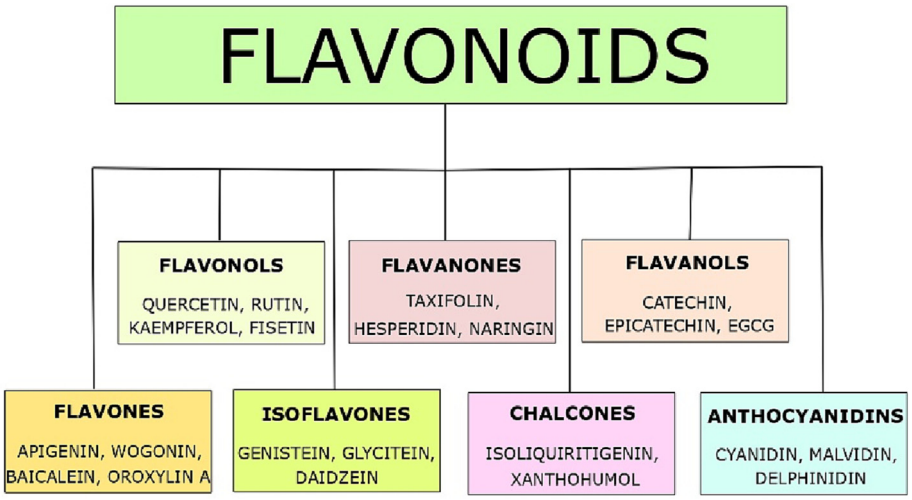

Fig. 3. Classification and selected representatives of flavonoids.

phytochemicals. Here, we provide a detailed discussion on the effects of flavonoids to combat cancer drug resistance *via* targeting aberrant glycolysis.

Effects of flavonoids in cancer resistance related to glycolysis

Flavonoids are naturally present in various plant foods such as fruit, vegetable, herbs, olive oil, cacao, or nuts among others. More than 10,000 different flavonoid compounds have been isolated and identified. The basic chemical carbon backbone of flavonoids comprises C6-C3-C6 arranged as two aromatic rings linked by a three-carbon bridge [67,68]. The classification of flavonoids depends on the oxidation level, methoxylation, prenylation, glycosylation, and substitution pattern of heterocyclic pyrane ring (C ring) [1,13,69,70] (Fig. 2).

The individual compounds within flavonoids are determined by the substitution of benzene rings (ring A and B) [1,13,69,70]. Flavonoids are divided into 7 sub-families: flavones, flavanones, flavonols, flavan-3-ols, isoflavones, anthocyanidins, and chalcones [67,68]. Flavan-3-ols can form oligomers. Fig. 3 shows the classification and selected representatives of flavonoids.

Flavonoids show pleiotropic effects and possess many pharmacological and biochemical positive efficacy maintained through their antimicrobial, antioxidant, anti-inflammatory, hepatoprotective, cardio-protective, and anticancer properties [71,72].

The main advantage of natural substances is the capability to affect various processes and signaling pathways associated with each of the multistep process of carcinogenesis. In our previous review articles, we discussed the anticancer potential of flavonoids or natural substances, either isolated or mixture of phytochemicals present in whole plants, mediated *via* affecting apoptosis, proliferation, metastasis, inflammation, the activity of carcinogens, or cancer metabolism. Despite anticancer effects of isolated phytochemicals, the additive or synergic effects of multiple phytochemicals within a whole plant significantly contribute to the potent anticancer efficacy of whole-plant foods [1,7,12,20,70,73–75]. Due to the capacity of phytochemicals to affect multiple sig-

naling pathways deregulated in carcinogenesis, here we focus on the potential of flavonoids to combat the resistance of cancer cells to therapeutics mediated, firstly, *via* affecting PI3K/Akt and secondly *via* modulating HIF-1α and or/ HIF-1α-mediated resistance related to aberrant glucose metabolism.

Therapeutic resistance of cancer cells represents a severe obstacle hindering proper cancer treatment [7]. Therefore, search for novel options for improving anticancer therapy, potentially *via* naturally occurring phytochemicals, would improve overall cancer management and survival of cancer patients. Despite the excellent properties of these substances, their isolation and potential implementation in cancer management call for further research.

Flavonoids reversing cancer resistance by targeting PI3K/Akt signaling

Current research provides valid evidence on the effects of flavonoids in enhancing the sensitivity of cancer cells to standard therapeutics *via* the modulation of PI3K/Akt signaling pathway.

Quercetin is a flavonol aglycon widely found in fruits and vegetable such as capers, dill, onions, apples, or berries [76]. Interestingly, quercetin reversed resistance to docetaxel *via* affecting androgen receptor and PI3K/Akt signaling in docetaxel-resistant prostate cancer cells *in vitro* and xenograft model *in vivo* [77]. Moreover, quercetin increased chemo-sensitivity to gemcitabine and cell death through impairing RAGE/PI3K/Akt/mTOR in human pancreatic cancer cells [78]. Furthermore, quercetin enhanced the effects of docetaxel *via* modulation of several signaling pathways including PI3K/Akt in breast cancer cells *in vitro* [79]. In another *in vitro* investigation, quercetin induced apoptosis against Epstein–Barr virus-infected Burkitt's lymphoma cells through diminishing PI3K/Akt/mTOR signaling pathway and repressing the expression of c-Myc, a cellular myelocytomatosis oncogene. The study suggests that quercetin may act synergistically with conventional anticancer drugs to overcome drug resistance [80]. A chalcone flavokawain B, derived from the root of the kava-kava plant (*Piper methysticum* G. Forst) traditionally used in South Pacific islands [81], exerted anticancer effects mediated through affecting various processes associated with carcinogenesis, including PI3K/Akt blockage in gemcitabine-resistant lung cancer *in vitro* [82]. In addition, recent research proved also potent anti-cancer effects of apigenin, a flavone in onion, parsley, oranges, and chamomile among others [83]. Chen et al. (2019) focused on the evaluation of anticancer effects of apigenin in cisplatin-resistant colon cancer model and its effect on mTOR/PI3K/Akt among other cancer-associated signaling. Overall, the provided results highlighted the potent efficacy of apigenin to inhibit the growth of cisplatin-resistant colon cancer cells *in vitro* and *in vivo* and to suppress mTOR/PI3K/Akt signaling [84]. Similarly, nobiletin, a flavone isolated from citrus peel, promoted the sensitivity of colorectal cancer cells to oxaliplatin *via* PI3K/Akt/mTOR downregulation *in vitro* [85]. Furthermore, wogonin (a flavone isolated from *Scutellaria baicalensis* Georgi, also known as the Chinese skullcap) enhanced the sensitivity to cisplatin in ovarian cancer cells mediated through the inhibition of PI3K/Akt [86]. In addition, a flavone C-glycoside vicenin-2 showed radio-sensitizing effects in non-small cell lung cancer demonstrated *via* affecting phosphorylation of Akt [87]. Last but not least, kaempferol, which is a flavonol in nature widely present in tea, cabbage, kale, or broccoli [1,88], synergistically reversed resistance in human 5-fluorouracil (5-FU)-resistant colon cancer cells *in vitro* accompanied by its positive effects on various cellular signaling molecules, including PI3K/Akt [89].

In conclusion, aberrantly activated PI3K/Akt is closely associated with cancer resistance [31] while the above discussed study results support the potent capacity of flavonoids to target cancer resistance *via* PI3K/Akt as demonstrated in cancer models *in vitro* and *in vivo*. In addition to the effectiveness of flavonoids to target cancer resistance *via* PI3K/Akt, flavonoids also show a potential to target its downstream target HIF-1α, a transcription factor regulating critical mediators of glucose metabolism, including GLUTs and glycolytic enzymes [31].

Flavonoids targeting HIF-1α to overcome the resistance of cancer cells

Although cancer cells can upregulate HIF-1α independently of oxygen supply [16], HIF-1α is still considered a key regulator of response to hypoxia [29]. Flavonoids exert potent capacity to inhibit HIF-1α, the transcription factor directly affecting the expression of key glycolytic mediators [13,14,31], and thus show promising potential to re-sensitize or enhance the sensitiveness of resistant cancer cells to therapeutics. In this regard, Wang et al. (2013) evaluated the effects of wogonin on hypoxia resistance. Hypoxia decreases the sensitivity of human colon cancer cells to the drug. Also, high HIF-1α has been observed in analyzed colon cancer cells under hypoxia. However, wogonin attenuated hypoxia resistance through the downregulation of HIF-1α and glycolysis *via* PI3K/Akt inhibition in human colon cancer cells *in vitro* and inhibition of tumor growth and HIF-1α also *via* PI3K/Akt suppression *in vivo* [14].

Baicalein is another flavone derived from the root of the traditional Chinese herb *Scutellaria baicalensis* [90]. Hypoxic conditions promote the resistance of gastric cancer cells to 5-FU; however, baicalein reversed resistance to 5-FU induced by hypoxia through the suppression of glycolysis and PTEN/Akt/HIF-1α signaling, specifically *via* suppression of Akt phosphorylation and promotion of PTEN, an upstream negative regulator of Akt, under hypoxia in gastric cancer cells *in vitro* [30]. In addition, Chen et al. [8] recently demonstrated the capacity of baicalein to re-sensitize tamoxifen-resistant breast cancer cells *in vitro* and *in vivo* through the attenuation of aerobic glycolysis and reversion of mitochondrial dysfunction *via* reduced HIF-1α expression and transcriptional activity [8]. Similarly, baicalein enhanced radio-sensitivity and inhibited the progression of esophageal squamous cell carcinoma by affecting HIF-1α and PKM2. The inhibition of HIF-1α and PKM2 by baicalein resulted in the glycolysis suppression. The mechanisms beyond the capacity of baicalein to suppress the radio-resistance of esophageal cancer cells involve targeting HIF-1α, which is associated with glucose metabolism and regulation of Cyclin D1/CDK4 axis and cell cycle. Baicalein decreased G1 phase-related genes and proteins. Notably, cells are observed to be most radio-sensitive in G2-M phase and less radio-sensitive in G1 phase. The authors concluded the potential effectiveness of baicalein to enhance radiotherapy efficacy in esophageal cancer [91].

Temozolomide is an alkylating agent used as a first-line therapy in glioma functioning *via* its DNA-damaging effects. However, some glioma cells are capable to repair this DNA damage that results in resistance to temozolomide. Moreover, increased HIF-1α is associated with the activation of Hedgehog pathway (promoting autocrine secretion of sonic Hedgehog protein Shh and upregulating transfer of Gli into the nucleus) resulting in temozolomide resistance. Nevertheless, oroxylin A (a flavone derived from *S. baicalensis*) increased the sensitivity to temozolomide in a hypoxic model of glioma mediated by HIF-1α/Hedgehog pathway under hypoxia [92].

Recently, Hassan et al. [43] demonstrated the effects of combined treatment of quercetin, gemcitabine, and doxorubicin in enhancing chemotherapeutic effectiveness *via* HIF-1α and MDR-1 inhibition in pancreatic and hepatic cancer models. As stated

Table 2
Flavonoids targeting cancer resistance *via* HIF-1α as the key regulator of glucose metabolism.

Flavonoid	Cancer type (resistance)	Study details	Effects	Year	Ref.
Wogonin	CC (cisplatin resistance)	HCT116 cells *in vitro*	↑ sensitivity to cisplatin; ↓ HIF-1α; ↓ glycolysis-related proteins (HK2, PDHK1, LDHA); ↓ glucose uptake and lactate generation; ↓ PI3K/Akt;	2014	[14]
		Male BALB/c mice (tumor xenograft model – HCT116 transplanted)	↓ growth; ↓ HIF-1α *via* ↓ PI3K/Akt		
Baicalein	GC (5-FU resistance)	AGS cells *in vitro*	↓ proliferation under hypoxia; ↕ hypoxia-induced 5-FU resistance; ↓ glucose uptake and lactate under hypoxia; ↓ glycolytic-related enzymes under hypoxia (HK2, LDHA, PDK1); ↓ HIF-1α *via* PTEN/Akt (↓ Akt phosphorylation, ↑ PTEN protein expression) under hypoxia	2015	[30]
Baicalein	BC (TAM resistance)	TAM-resistant BC cell lines (MCF-7TR, T-47DTR, BT-474TR, ZR-75-1TR)	↓ cell growth (OHT + baicalein vs OHT alone); ↓ cell viability, IC_{50} (OHT + baicalein); ↓ clonal numbers (baicalein) and further ↓ when OHT + baicalein; ↑ apoptotic effect of OHT; ↓ HIF-1α (↓OHT-induced HIF-1α activation); ↓ aerobic glycolysis; ↕ mitochondrial dysfunction (↑ mitochondrial biogenesis); ↑ OHT-induced mitochondria-mediated ROS (↑ apoptosis)	2021	[8]
		Female NOD/SCID mice (MCF-7TR cells inoculated)	↑ inhibitory effects of TAM; ↓ tumor proliferation, ↑ apoptosis (TAM + baicalein vs TAM or baicalein alone); ↓ HIF-1α (baicalein or TAM + baicalein); ↑ sensitivity to TAM (↓ aerobic glycolysis and ↑ mitochondrial biosynthesis); ↓ LDHA and ↑ PGC-1α (baicalein or TAM + baicalein)		
Baicalein	EC (radiotherapy resistance)	EC cell line KYSE150 cells irradiated with 6 Gy	↓ radiotherapy resistance (↓ proliferation and not forming clones in baicalein + radiation vs radiation alone group); ↓ glycolysis (↓HIF-1α and HIF-1α PKM2); ↓ G1-related genes and proteins (regulation of CyclinD1/CDK4)	2022	[91]
Oroxylin A	Glioma	Hypoxic model of glioma cells (human U251, rat C6, mouse GL261) *in vitro*	↑ sensitivity of TMZ; ↓ HIF-1α/Hedgehog (↑ HIF-1α degradation, ↓ Shh, ↓ Gli1);	2019	[92]
		Female BALB/c mice – inoculated GL261 and U251 cells	↑ antitumor effect TMZ;		
Apigenin (combined with paclitaxel)	HCC	HepG2 cells	↓ HIF-1α; ↓ Akt/p-Akt, HSP90 (↑ anticancer activity of paclitaxel); ↕ hypoxia-induced resistance;	2020	[93]
Quercetin (combined with gemcitabine or doxorubicin)	PC and HCC (chemotherapy efficiency)	Pancreatic adenocarcinoma cells (AsPC-1) and HCC cells (HepG2)	↓ MDR1 efflux (3D cultures); ↓ HIF-1α (3D cultures); ↑ apoptosis	2020	[43]
Hispidulin	GaC	GBC-SD cells	↑ sensitivity to gemcitabine and 5-FU	2015	[94]
Silibinin	NPC	Primary NPC biopsies (n = 20)	↓ cancer cells viability (*via* affecting glycolytic activity); ↓ glycolysis (loss of LDHA-mediated lactate release); ↑ activation of TCA cycle; ↓ HIF-1α (LDHA, PD-L1)		[95]
Green tea catechins	HCC	HCC cell line BEL-7404 and BEL-7404/DOX *in vitro*	↑ sensitivity to DOX; ↓ cell survival and proliferation; ↑ intracellular DOX accumulation (in BEL-7404/DOX); ↓ P-gp, MDR1, HIF-1α	2010	[9]
		Male and female BALB/c nu/nu mice (BEL-7404/DOX cells transplanted)			

Explanatory notes: ↑, increase/upregulates; ↓ decrease/downregulated; ↕, reversed; +, plus.
Abbreviations: 5-FU, 5-fluorouracil; BC, breast cancer; CC, colon cancer; DOX, doxorubicin; EC, esophageal cancer; GaC, gallbladder cancer; GC, gastric cancer; GLUT-1 AS-ODNs, antisense oligonucleotides against GLUT-1; HCC, hepatocellular cancer; HK2, hexokinase 2; LaC, laryngeal carcinoma; LC, lung cancer; LDHA, lactate dehydrogenase. NPC, nasopharyngeal carcinoma; OHT, 4-hydroxytamoxifen; PC, pancreatic cancer; PDK1, pyruvate dehydrogenase kinase (PDHK1); TAM, tamoxifen; TCA, tricarboxylic acid cycle; TMZ, temozolomide.

above, HIF-1α can activate MDR-1 and thus contributes to the drug resistance of cancer cells [43]. As another example, apigenin suppressed HIF-1α in hypoxic tumors *via* the inhibition of Akt/p-Akt and HSP90 while these effects are applicable for the enhancement of anticancer effects of paclitaxel [93]. In addition, hispidulin sensitized gallbladder cancer cells to gemcitabine and 5-FU *via* repression of HIF-1α/P-gp *in vitro* [94].

Sellam et al. [95] recently discussed the association between checkpoint inhibitor PD-L1, the induction of which is linked to promoted aerobic glycolysis associated with HIF-1α and LDHA activity in cancer. The authors demonstrated the capacity of silibinin, a flavonoid-type compound (flavonolignan) extracted from *Silybum marianum* L., to decrease PD-L1 in nasopharyngeal carcinoma affecting cell metabolism mediated by HIF-1α/LDHA. These results

support the potential of silibinin to overcome PD-L1-mediated resistance of nasopharyngeal carcinoma [95].

In addition to isolated flavonoids, several authors highlight the promising anticancer potential of a mixture of phytochemicals based on the additive or synergistic effects of multiple phytochemicals present in the whole plant [70,75,96–99]. Green tea is an essential source of multiple phenolics, derived from flavann-3-ol, mainly represented by epicatechin gallate (ECG) and epigallocatechin gallate (EGCG), the phytochemicals also known as the green tea catechins [9,100]. Green tea catechins could potentially promote cell killing induced by doxorubicin and sensitize chemoresistant hepatocellular carcinoma cells to doxorubicin. The authors also evaluated the effects of green tea catechins on the expression of genes associated with MDR. They observed reduced HIF-1α after combining EGCG and doxorubicin compared with doxorubicin alone or control [9].

In conclusion, Table 2 summarizes the above-discussed effects of flavonoids on the sensitization of cancer cells to therapeutics *via* targeting HIF-1α, a transcription factor regulating multiple processes of carcinogenesis, including glucose metabolism.

Flavonoids targeting glycolytic enzymes to overcome resistance

Flavonoids also show a potent capacity to overcome resistance in cancer cells via affecting GLUTs and key glycolytic enzymes [101,102], the downstream targets of HIF-1α [103].

In laryngeal carcinoma cells *in vitro,* apigenin combined with cisplatin decreased p-Akt and GLUT-1 and thus supported the sensitivity of cancer cells to cisplatin; however, the authors observed no significant effects of either individual administration of apigenin or cisplatin [41]. Moreover, apigenin suppressed GLUT-1 and PI3K/Akt signaling and improved radio-sensitivity of laryngeal carcinoma *in vivo* [44]. Also, Chen et al. (2019) recently concluded the potential of apigenin in combination with gefitinib as an effective alternative strategy for acquired resistance to EGFR-TKIs in non-small cell lung cancer. Specifically, apigenin combined with gefitinib suppressed oncogenic drivers, including HIF-1α, c-Myc, and EGFR, reduced GLUTs and MCT1, and inactivated AMPK signaling that is associated with the uptake of glucose and energy metabolism leading to the energy utilization decline in EGFR L858R-T790M-mutated H1975 lung cancer cells [104]. Moreover, Han et al. [101] described the ability of a flavan-3-ol catechin to suppress the resistance of gastric cancer cells to 5-FU. The authors initially observed higher lactate production and expression of glycolytic enzymes (LDHA) in 5-FU resistant gastric cancer cells when compared to parent cells. Catechin restricted glycolysis (specifically *via* inhibiting LDHA) that resulted in the sensitization of gastric cancer cells to 5-FU. Eventually, catechin combined with 5-FU promoted apoptosis and increased mitochondrial ROS in gastric cancer cells [101]. Moreover, kaempferol showed the potential to overcome resistance to 5-FU in human colorectal cancer cells *in vitro via* suppressing glycolysis mediated by inhibition of PKM2, a rate-limiting enzyme of glycolysis that plays a crucial role in the drug resistance of cancer cells [102]. As shown in Table 3, flavonoids exert efficiency in sensitizing cancer cells to therapeutics *via* targeting GLUTs and/or key glycolytic enzymes (such as PDK, LDHA), all of which are downstream targets of HIF-1α.

In conclusion, as is shown in Fig. 4, mechanisms of glycolysis-induced drug resistance involve anti-apoptotic effects, EMT induction, activation of autophagy, increased drug efflux, or inhibited drug influx [18]. The expression of genes encoding critical mediators of glucose metabolism is regulated by HIF-1α, a downstream target of PI3K/Akt signaling [31]. The multistep process of carcinogenesis is associated with deregulation of PI3K/Akt and HIF-1α resulting in increased glycolysis rate [31]. Besides, glycolysis-induced drug resistance comprises a severe obstacle in cancer management [17]. To contribute to solve this problem, here we provided a detailed overview of the mostly current scientific evidence on the potential of flavonoids to combat the resistance of cancer cells to therapeutics, targeted specifically at glycolytic

Table 3
Flavonoids targeting key glycolytic enzymes in resistant cancer cells.

Flavonoid	Cancer type (resistance)	Study details	Effects	Year	Ref.
Apigenin + cisplatin	LaC	Hep-2 cells *in vitro*	↑ sensitivity to cisplatin; ↓ GLUT-1; ↓ p-Akt;	2014	[41]
Apigenin or apigenin + GLUT-1 AS-ODNs	LaC (radiotherapy efficiency)	Male BALB/c mice (Hep-2 cells inoculated)	↑ radio-sensitivity; ↓ GLUT-1, Akt, and PI3K mRNA after X-ray radiation	2015	[44]
Apigenin (combined with gefitinib)	LC	EGFR-TKIs resistant NSCLC cells (NCI-H1975); human epithelial cell line (BEAS-2B); human lung squamous cell carcinoma and immortalized human liver cell line (95-D and HL7702)	↓ inhibition of EGFR L858R-T790M mutant H1975 cells; ↓ proliferation, metastasis; ↑ cell cycle arrest at G_0/G_1 and apoptosis; ↓ glucose uptake, lactate production; ↓ GLUT-1, GLUT-3, GLUT-4, PDK1; ↓ HIF-1α, c-Myc	2019	[104]
Catechin	GC	GC 5-FU resistant (SNU620/5FU) and parent (SNU620) cells *in vitro*	↓ LDHA activity in 5-FU resistant cells; ↕ 5-FU resistance; ↑ mitochondrial ROS-dependent apoptosis (catechin + 5-FU)	2021	[101]
Kaempferol	CC	CC 5-FU resistant (HCT8-R) cells *in vitro*	↕ 5-FU resistance; ↑ 5-FU sensitivity (by ↓ glycolysis and ↓ PKM2);	2022	[102]

Explanatory notes: ↑, increase/upregulates; ↓ decrease/downregulated; ↕, reversed; +, plus.
Abbreviations: 5-FU, 5-fluorouracil; CC, colorectal cancer; GC, gastric cancer.

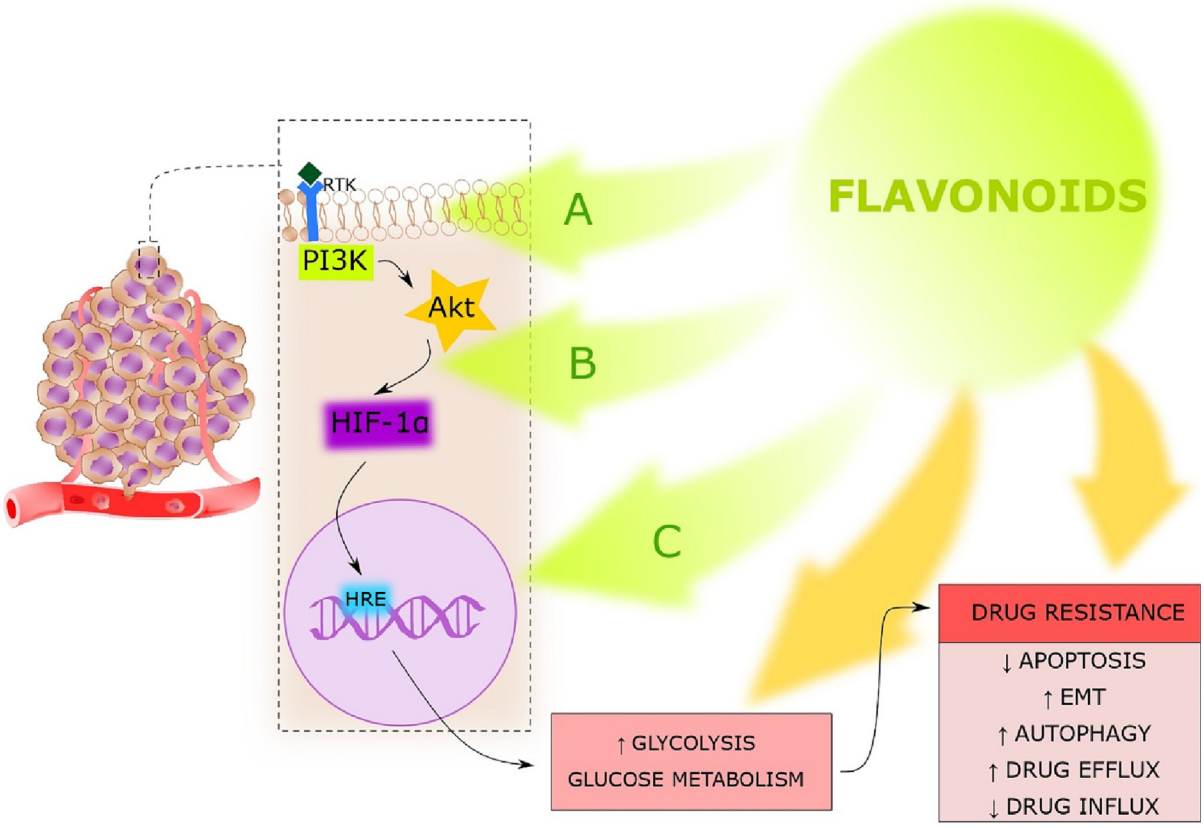

Fig. 4. The potential of flavonoids to combat glycolysis-induced drug resistance in cancer *via* affecting key signaling upstream of glucose metabolism. *Explanatory notes:* HIF-1α is a downstream target of PI3K/Akt signaling that regulates the expression of genes encoding key mediators of glucose metabolism *via* the binding of HIF-1α and HIF-1β to hypoxia-responsive element (HRE) in the nucleus [31]. Carcinogenesis is associated with deregulation at the level of PI3K/Akt and HIF-1α resulting in an increased rate of glycolysis [31] while drug-resistant cancer cells are characterized by aberrant glycolysis [17]. Mechanisms of glycolysis-induced drug resistance involve anti-apoptotic effects, EMT induction, autophagy induction, increased drug efflux, or inhibited drug influx [18]. Flavonoids exert potential to target key signaling of drug resistance in cancer and thus re-sensitizing cancer cells to therapeutics: A) PI3K/Akt (as the most often deregulated signaling pathway in cancer and upstream regulator of HIF-1α), B) HIF-1α, and/or C) HIF-1α-regulated mediators of aberrant glycolysis in cancer cells (GLUTs and glycolytic enzymes).

mediators (GLUTs and enzymes involved in glucose metabolism) and/or upstream effectors (HIF-1α and PI3K/Akt signaling pathways) of glucose metabolism. Fig. 5 displays the chemical structures of all reviewed flavonoids presented in this paper.

Targeting HIF-1α signaling pathways in primary care: Clinically relevant examples of the paradigm shift from reactive to predictive, preventive, and personalized medicine

Inappropriate regulation at the level of mitochondrial metabolism is considered a pre-condition of drug resistance in cancer. Moreover, impaired mitochondrial health has been attributed to sub-optimal health conditions with a reversible health impairment. At the primary care level, the stage of health-to-disease transition is indicative for a disease prediction and targeted prevention that is associated with numerous advantages including the overall course of the disease and cost-effectiveness in the disease management. Nevertheless, from a perspective of cost-effectiveness, the effective practical implementation can only be performed if affected individuals can be easily identified and stratified, which can be accomplished for example *via* clearly described phenotype. A prominent example of the Flammer syndrome phenotype (FSP) may therefore be clinically useful for primary (sub-optimal health) and secondary (cancer management) care.

FSP is characterized as a sub-optimal condition of health that is detectable early in life (pubertal maturation) [106,107]. FSP is also closely associated with subtle hypoxic-ischemic lesions [105]. FSP risk factors include primary vascular dysregulation of peripheral vessels, low BMI, high endothelin-1 blood level, and stress-relevant psychosocial behavioral patterns, which altogether synergistically leading to an imbalance of stress overload and predisposition to aggressive cancer sub-types as well as frequently silent (lacunar) brain infarction, and other neurological disorders that may be clinically manifested at young age [4,108–111]. Limited energy supply and ischemic-reperfusion events have been suggested as characteristic for FSP and FSP-associated disorders. Indeed, FSP-associated disorders involve the crucial contribution of strongly compromised mitochondrial health, which is proposed as a promising target for improved strategies of health management. Such strategies are fundamental not only for the stratification of patients but also for diagnostics predictive in nature and cost-effective primary prevention and treatments tailored to the person [112–114]. Since HIF-1 activation is „at the crossroads“ of hypoxia, mitochondrial impairments, non-physiologic inflammation, and cancer initiation [115–117], signaling pathways linked to HIF-1 represent an attractive target for an application of natural substances, in particular in reversible damage to health at the stage of health-to-disease transition [3,70,118]. Thus, an accurate phenotyping (similarly as in case of FSP) is essential for implementation of 3PM approach. The possibility of applicability of specialized surveys, non-invasive diagnostics (utilizing liquid biopsy), the control of mitochondrial health quality, and targeted therapeutic strategies at the stage of health-to-disease transition are instrumental for cost-effective primary care. Besides, effective primary care is closely associated with a potential to alter current trends, for

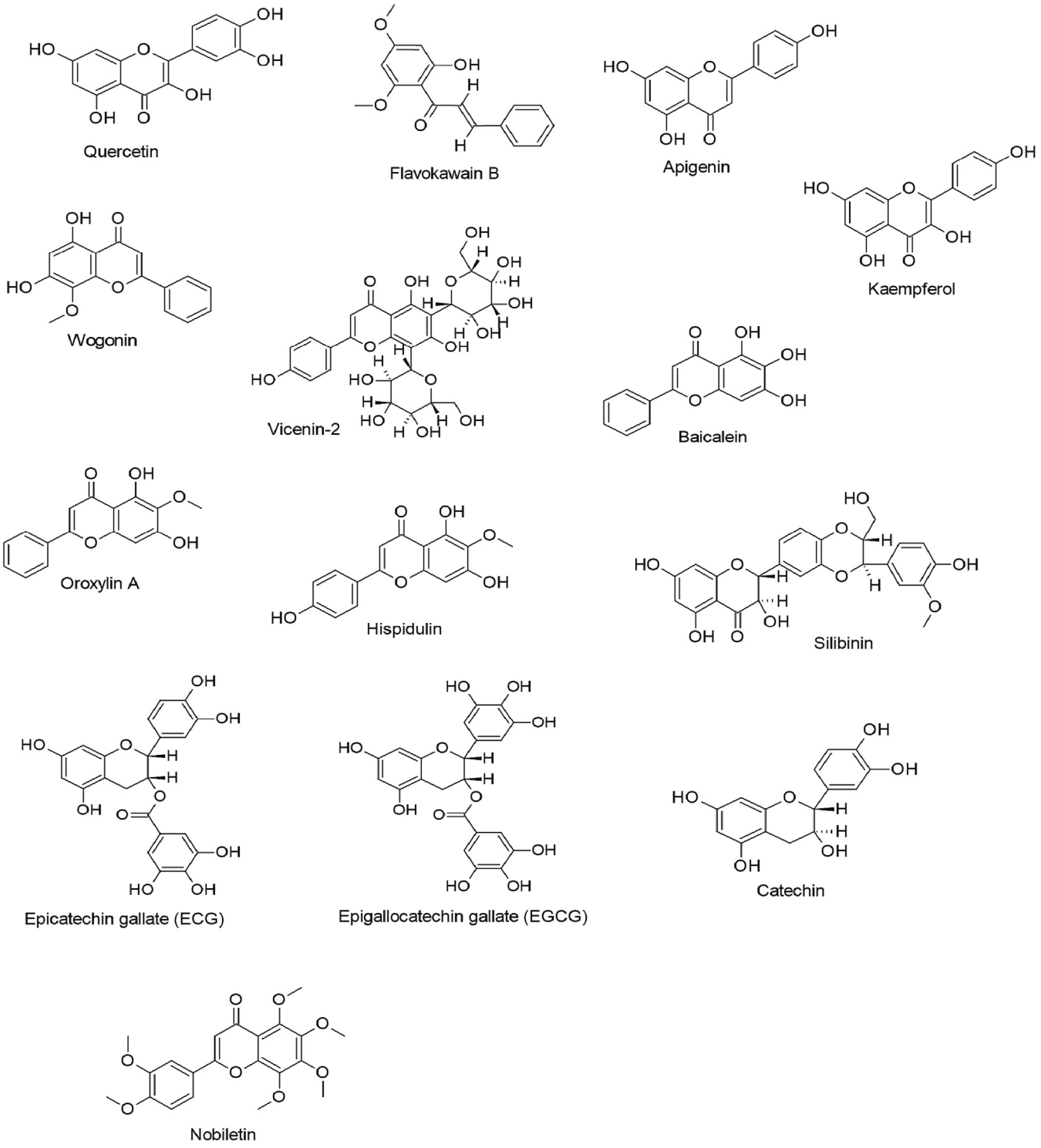

Fig. 5. Chemical structures of the reviewed flavonoids.

example in overall management of breast and prostate cancers [3,118–120]. Innovation by the 3PM approach specifically in the area of sub-optimal health management is well recognized by the World Health Organization [121].

Conclusions and future outlook

Naturally occurring phytochemicals are capable to modulate multiple signaling mechanisms dysregulated in cancer. Here we demonstrate the evident capacity of flavonoids to affect PI3K/Akt/HIF-1α signaling pathway, which is crucial for the therapy resistance in cancer. Thus, we propose the potential of implementation of flavonoids, as one of the most widely occurring phytochemicals, to target glycolysis-induced resistance mechanisms related to aberrant PI3K/Akt/HIF-1α signaling. Clinical utility of naturally occurring compounds to mitigate therapeutic anticancer resistance is a highly innovative approach which has to be further explored in the framework of 3PM on a case-by-case basis. Further, targeting HIF-1α signaling pathway is clinically relevant to cost-

effectively protect affected individuals against health-to-disease transition in primary care at the level of sub-optimal health.

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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.

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Alena Mazurakova, Dr. rer. nat., PhD. is a researcher at Jessenius Faculty of Medicine in Martin. Dr. Alena Mazurakova holds a PhD. degree from Jessenius Faculty of Medicine in Martin, Dr. rer. nat. degree from Pavol Jozef Safarik University in Kosice, master's (Mgr.) degree from Constantine the Philosopher University in Nitra, and bachelor's (Bc.) degree from Catholic University in Ruzomberok. Her research interest focus on the analysis of anticancer effects of phytochemicals present in whole plants in experimental mammary carcinogenesis, specifically animal chemopreventive and therapeutical models as well as the analysis of mechanisms beyond the chemopreventive effects of phytosubstances, including the effects of phytochemicals on the parameters of apoptosis, proliferation, angiogenesis, oxidative stress, and cancer stem cells. Dr. Alena Mazurakova is the first author of 11 articles and co-author of other 57 articles published in journals registered in the WOS and Scopus databases (Google scholar H-index 29, Scopus H-index 26). Dr. Alena Mazurakova was responsible for the conception of the review article. Alena Mazurakova provided the outline of the manuscript, participated in the writing of the manuscript, and redistributed the work in the writing of the manuscript. Alena Mazurakova designed and prepared the figures.

Lenka Koklesová, Dr. rer. nat. is a PhD student at the department of gynecology and obstetrics at Jessenius Faculty of Medicine in Martin. Lenka Koklesová received a Dr. rer. nat. degree of biology from Pavol Jozef Šafárik University in Košice, master's (Mgr.) degree of genetics and bachelor's (Bc.) degree of biology obtained from Faculty of Natural Sciences of Comenius University in Bratislava. She is a part of professor Kubatka's work team that focuses on chemopreventive and therapeutic efficacy of plant natural substances in experimental models of breast carcinoma. Her research interest specifically focuses on the influence of whole plant food on epigenetic alterations, including DNA methylation, histone modifications, and miRNA expressions, using rat model of mammary carcinogenesis. According to the WOS and Scopus databases, Lenka Koklesová is the first author of 7 articles and co-author of other 34 articles (Scopus H-index 17, Google scholar H-index 19). Dr. Lenka Koklesova participated in the literature search and writing of the manuscript.

MVDr. Sandra Hurta Csizmár after earning her doctors degree in veterinary medicine (DVM) started her doctorate studies at Jessenius Faculty of Medicine in Martin in the field of Anatomy, Histology and Embryology. Dr. Sandra Hurta Csizmár is engaged in teaching Histology to medical students and working on her doctoral research. Her research focuses on identification of new diagnostic, prognostic or differentiation biomarkers as well as epithelial mesenchymal transition mainly in the lesions of the uterine cervix. In 2022 Dr. Sandra Hurta Csizmár won 2nd place in classical research talk at the First European Student Symposium on Anatomical Research. She is awaiting the publication of her first author article and is a co-author in an article published in journal reistered in Scopus. Dr. Sandra Hurta Csizmár participated in the literature search and writing of the manuscript.

Marek Samec, Dr. rer. nat., Ph.D.., is a researcher at the Department of Pathological Physiology JFM CU in Martin. He obtained titles Bc. and Master. in 2014 and 2016 at the Faculty of Natural Sciences, CU in Bratislava. In 2021, he defended his Ph.D. degree at JFM CU in Martin, at the Department of Gynecology and Obstetrics. The methods he was trained in include: Real-Time PCR, fragment analysis (MLPA), sequencing, and analyzing the methylation profile of gene promoters (PyroMark Q96). Also, Dr. Marek Samec participates in the project focused on preparing molecular tools to monitor the Spatio-temporal dynamics of SARS-CoV-2 entry into the cell. Dr. Marek Samec is the author of the 10 first-author articles published in journals registered in the WOS and Scopus databases and co-author of other 45 articles (Google scholar H-index 24, Scopus H-index 21). Most of his publication activity is focused on the role of secondary metabolites of plants (including flavonoids) on epigenetic mechanisms that participate in cancer development. Moreover, his field of interest includes the impact of flavonoids on cancer metabolism via the modulation of various metabolic pathways (glycolysis, lipid metabolism, and redox metabolism). Dr. Marek Samec performed the literature search and contributed to sections discussing PI3K/Akt/HIF-1α from the view of molecular genetics.

Aranka Brockmueller is member of Professor Shakibaei's research group at Faculty of Medicine at Ludwig-Maximilians-University in Munich/Germany. She works in the fields of tumor biology and tissue engineering, with a focus on combating cancer-associated inflammation using phytopharmaceuticals. Her current publication list includes 22 peer-reviewed papers with almost 400 citations and a H-index of 11 (Google Scholar). Aranka Brockmüller participated in the literature search and writing of the manuscript.

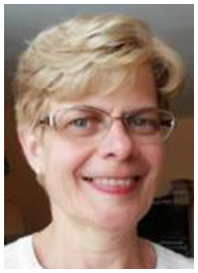
Dr. Miroslava Šudomová's research interests are focused on natural products and their biological activities, especially infectious diseases and cancers associated with tumor viruses. Aside from being an active scientific writer for various popular science magazines and medical journals, Dr. Šudomová has reviewed more than 80 scientific papers for different journals published by Elsevier, Wiley, MDPI, Springer Nature, and Taylor and Francis. The scientometric profile (list of publications, total citations, and H-index) can be found in the ORCID profile: https://orcid.org/my-orcid?orcid=0000-0001-9744-4270. Dr. Miroslava Šudomová participated in the writing of the manuscript and performed literature search.

Kamil Biringer, M.D., Ph.D., is an associate professor and a researcher at Jessenius Faculty of Medicine, Martin, Comenius University Bratislava, Slovak Republic. He is an expert in gynecology and obstetrics, and in ultrasound in gynecology and obstetrics. He holds a Ph.D. degree in gynecology and obstetrics from Jessenius Faculty of Medicine Martin, Slovakia. He focuses his research on perinatology, gynecology oncology, and mammology. Kamil Biringer is the first author of 8 articles and co-author of other 56 articles published in journals registered in the WOS and Scopus databases (Google scholar H-index: 18, Scopus H-index: 15), number of citations: 499. Dr. Kamil Biringer critically revised the manuscript.

Erik Kudela, M.D., PhD. I finished the medical studies at Jessenius Faculty of Medicine in Martin (Comenius University in Bratislava, Slovakia) in 2010. My PhD degree was successfully claimed in 2014 with the PhD thesis focused on molecular markers of cervical carcinogenesis. Since 2019 I have been working as an associate professor at the Clinic of Obstetrics and Gynecology (Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava). My specializations include molecular carcinogenesis, mammology (clinical management and surgical treatment of benign and malignant breast diseases) and HPV induced cervical carcinogenesis (clinical management together with expert colposcopy and HPV research related to malignant potential of precancerous lesions). From 2021 I am listed (Ministry of Justice) as a forensic expert for Gynecology and Obstetrics. Dr. Erik Kudela participated in the literature search and writing of the manuscript.

Prof. Martin Péč (Jessenius Faculty of Medicine, Comenius University in Bratislava, Slovakia) studies the biological aspects of mastocytosis and other dermatological diseases, primarily oncological ones, as well as the experimental model of breast cancer. Prof. Péč is the author of more than 200 scientific articles published in peer-reviewed journals (H-index 23 Google Scholar). He serves as the primary coordinator of numerous research projects and is a reviewer for numerous international scientific journals. Prof. Martin Pec critically revised the manuscript.

Dr. Samuel hails from Kerala, India and is currently the Research Associate in Physiology and Biophysics at Weill Cornell Medicine-Qatar. After completing his B.Sc (1998), M.Sc (2003) and M.Phil (2005) in Biochemistry (University of Kerala, Kerala, India), he enrolled for his Ph.D program at the University of Kerala and performed his Ph.D work as an exchange student, with Prof. Dr. Nilanjana Maulik at the Molecular Cardiology and Angiogenesis Laboratory, University of Connecticut Health Center, Farmington, CT, USA (Sep 2006 - Jan 2010) after which he successfully defended his thesis and was awarded his Ph.D degree (Dec 2010) from the University of Kerala. Dr. Samuel has more than 6 years of post-doctoral experience with Prof. Dr. Chris R. Triggle and Dr. Hong Ding at the WCM-Q (May 2011-June 2017). During his post-doctoral fellowship, Dr. Samuel was also a recipient of the successfully completed Junior Scientist Research Experience Program (JSREP) grant (Feb 2013-Nov 2016) awarded by QNRF. He had been in Prof. Dr. Dietrich Büsselberg's team as a visiting scientist from Dec 2017 – Dec 2018 after which he has continued as a Research Associate from July 2019 onwards. He has sound research experience in diabetes, endothelial dysfunction, myocardial angiogenesis, and tumor angiogenesis and has over 50 peer-reviewed original and review articles (Google scholar H-index 34, Scopus H-index 30). He has publications in high-impact journals such as Circulation, Trends in Microbiology, Diabetes, Cancer Treatment Reviews, and Cancers. ORCID ID: https://orcid.org/0000-0002-5541-6623. Dr. Samson Mathews Samuel critically revised and contributed to the writing of the manuscript.



Monika Kassayová studied General Biology (1985-1990) at the Faculty of Science of the Pavol Jozef Šafárik University in Košice, Slovakia. Her doctoral thesis (1996) focused on the effects of ionising radiation on melatonin synthesis in the pineal gland of laboratory rats. She joined the aforementioned faculty in 1990 as a researcher and Assistant Professor at the Department of Animal Physiology, Institute of Biology and Ecology, where she currently works as an Associate Professor. Her research focuses on the effects of natural and synthetic substances (melatonin, coxibs, statins, resveratrol, probiotic bacteria) in experimental mammary and colon carcinogenesis. She has been collaborating with Prof. Peter Kubatka for a long time on testing anti-tumour activity of phytochemicals in breast cancer. Dr Kassayová is the author of 50 publications registered in WOS and Scopus databases, with more than 400 citations. Dr. Monika Kassayova participated in the literature search, writing of the manuscript and critical revision of the manuscript.

Dr. Sherif T.S. Hassan's research interests are focused on infectious diseases (from disease onset to therapy) and natural products and their therapeutic effects on human health. Dr. Hassan is currently an editorial board member of various international journals indexed in Web of Science (Clarivate Analytics) and Scopus, such as PLOS ONE, BMC Microbiology, Current Issues in Molecular Biology, Molecular Medicine Reports, Frontiers in Pharmacology, Frontiers in Microbiology, Frontiers in Nutrition, Current Reviews in Clinical and Experimental Pharmacology, Data in Brief, BMC Research Notes, Frontiers in Bioscience-Elite, and among others. For more information, please refer to https://orcid.org/0000-0003-3922-2738. The list of publications, total citations, and H-index can be found in databases of Scopus, Web of Science, and Google Scholar, which are listed with their links in the ORCID profile: https://orcid.org/0000-0003-3922-2738. Dr. Sherif T.S. Hassan critically revised the manuscript.

Faculty of Pharmacy, Masaryk University, Brno, Dr. Šmejkal is working on the isolation and identification of different plant phenolics from natural (plant material). Furthermore, he is coordinator of bioactivity testing – anti-inflammatory activity based both on enzymatic and cellular assays, antioxidant activity using biochemical and cellular methods, and antibacterial activity focusing especially on resistant bacterial species. As visible from above presented and other publications, he is a head of team which is responsible for isolation of cca 30 newly identified compounds with important bioactivity. Last 5 years he was author and co-author of 45 papers or highly cited reviews in the field of phytochemistry and pharmacognosy in journals with IF. Research Interests: (1) Phytochemistry – especially separation and identification of natural substances. Target substances – especially prenylated phenols from Moraceae plants, Amaryllidaceae alkaloids, lignans of Schisandra chinensis. Chromatographic methods, identification of metabolites (IR, CD, MS, NMR) (2) Bioactivity of natural compounds. This is carried out in cooperation with field specialists – anticancer (effect on cell cycle), anti-inflammatory (COX inhibitors, NF-κB), antibacterial activity (anti MRSA) 97 publications according to WoS, total number of citations 2100, H-index 27. URL for web site: https://www.researchgate.net/profile/Smejkal_Karel; https://orcid.org/0000-0002-4336-7924; https://www.mendeley.com/authors/36904440400/, Dr. Karel Smejkal participated in the literature search, writing of the manuscript, and critical revision of the manuscript.

Prof. Dr. Mehdi Shakibaei is Professor at Ludwig-Maximilians-University in Munich/Germany, Faculty of Medicine, Institute of Anatomy. He has been teaching human anatomy for 30 years and conducts research on musculoskeletal tissue engineering and tumor biology with emphasis on modulation of inflammation by phytopharmaceuticals. With about 330 scientific publications, over 20,500 citations and a h-index of 85 (Google Scholar). (https://scholar.google.de/citations?user=Xt5vwSoAAAAJ&hl=de&oi=ao). He edited more than 15 monographs. The AD Scientific Index places him 2022 in the top 2% of the most cited scientists in the world. Prof. Mehdi Shakibaei critically revised the manuscript.

Dr. Dietrich Büsselberg (Professor of Physiology and Biophysics, Associate Dean for Admissions) joined Weill Cornell Medicine - Qatar (WCM-Q) in January 2010. Before joining WCM-Q, he served as a Professor of Physiology and Neuroscience at Texas Tech University, Health Science Center, Paul L. Foster School of Medicine. Dr. Büsselberg holds a State Exam for Teaching from the University of Hannover, Germany (1981), a B.S and M.S. from the University of Hohenheim, Stuttgart, Germany (1987), and a Ph.D. from the University of Hohenheim (Germany), Institute of Zoology in collaboration with the University of Albany (U.S.), School of Public Health (1989). In 1995, he received a habilitation and venia legendi for Physiology from the Heinrich-Heine University of Düsseldorf Medical School. Following his formal education, he served as a substitute for the Chair of Physiology at the University of Essen, Institute of Physiology; as Assistant Professor (Priv.-Doz.) at the University of Göttingen, Institute of Physiology; and as Associate Professor (Apl. Professor) at the University of Duisburg-Essen, Institute of Physiology. Prof. Dietrich Büsselberg critically revised the manuscript and provided skilled assistance over the conceptualization of the manuscript.

Prof. Luciano Saso (Faculty of Pharmacy and Medicine, Sapienza University of Rome, Italy) is author of more than 350 scientific articles published in peer reviewed international journals (H-index Google Scholar 59, Scopus 49). He coordinated several research projects and has been referee for many national and international funding agencies and international scientific journals in the last 30 years. Prof. Luciano Saso is an highly cited researcher https://clarivate.com/highly-cited-researchers/ , Prof. Luciano Saso participated in the conceptualization of the manuscript and provided skilled assistance over the conceptualization of the manuscript.

Prof. Peter Kubatka, Dr. rer. nat., PhD. as a scientific investigator deals with the topic of anticancer therapy for 25 years. Within his research area, he published more than 190 papers in extenso (Scopus, Web of Science core coll.) with the Hirsch index = 37 (excluding self-citations). He is the first author of 47 scientific articles (Scopus). As a researcher, he evaluated/s the chemopreventive/anti-cancer effectiveness of retinoids, non-steroidal anti-inflammatory drugs, selective estrogen receptor modulators, aromatase inhibitors, antidiabetics, statins, melatonin, and phytochemicals/plant foods. He cooperates with several renowned laboratories around the world. Prof. Kubatka has the main merit of the methodical development of evaluated breast carcinoma models, he leads the team that is focused on the analysis of the mechanism of action (apoptosis, proliferation, angiogenesis, antioxidation) of various pharmaceuticals and their impact on cancer stem cells or epigenome. Prof. Peter Kubatka participated in the conceptualization of the manuscript, provided skilled assistance and supervised the overall preparation of the manuscript.

Prof. Dr. Golubnitschaja is the head of the world first **Predictive, Preventive Personalised (3P) Medicine** unit at the University Hospital Bonn, Rheinische Friedrich-Wilhelms-Universität Bonn, Germany. OG is educated in journalism, biotechnology and medicine. Dr. Golubnitschaja is **the author of more than 400 international publications** in the innovative field of predictive, preventive and personalised medicine (3PM). Google Scholar ***h*-index is 60**. **Awards:** National & International Fellowship of the Alexander von Humboldt-Foundation; Highest Prize in Medicine and Eiselsberg-Prize in Austria; Springer-Nature Award; EMA Award. Dr. Golubnitschaja **is the President of the "European Association for Predictive, Preventive & Personalised Medicine"** (EPMA, Brussels) networking over 50 countries worldwide; **Editor-in-Chief** of the EPMA J; **Editor-in-Chief** of the Book Series "Advances in Predictive, Preventive & Personalised Medicine"; **European Representative** in the EDR-Network at the National Institutes of Health USA. Dr. Golubnitschaja is an evaluation expert at the European Commission, and was involved in creating the PPPM related contents of the European Programme "**Horizon 2020**". Dr. Golubnitschaja is **Vice-Chair** of the Habilitation Committee (responsible for **all medical specialisations**) at the Medical Faculty, University of Bonn, Germany. Dr. Golubnitschaja is **Vice-Chair of the Evaluation Panel for Marie Curie Mobility Actions at the European Commission in Brussels.**