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Harnessing Phytochemical Synergy in Functional Foods to Target Hypoxia Inducible Factor (HIF) for Effective Cancer Therapy

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ABSTRACT

The origin, growth and spread of various cancers follow some common regulatory paths. Although hundreds of genes are involved in this process, most of these paths are initiated and controlled by one dominant and a central factor, the Hypoxia Inducible Factor 1α (HIF-1α). Therefore, instead of targeting individually several hallmark characters of cancer, scientists now attempt to seek a multifaceted approach by targeting this dominant factor, HIF-1α. Cancer cells have developed multiple paths in order to escape when a particular path is targeted as a survival mechanism. This is true while targeting HIF-1α also as it involves multiple paths. This necessitates finding some multiple inhibitors from various sources to plug its multiple molecular paths. As most of the conventional therapies targeting this factor failed to yield desirable results, seeking solutions from non-conventional therapies has become imperative. In this connection, it is reported that many functional foods having good amount of anti-cancer compounds are recommended and consumed for combating against cancer. Among them some are said to be very effective in controlling HIF-1α by acting on different molecular pathways. By this means, a possible synergistic mechanism is proposed in inhibiting the various molecular pathways of HIF-1α more effectively through varied molecular mechanisms of the active compounds found in the selected functional foods.

Keywords

HIF, Functional food, Phyto-chemicals, Synergism, Cancer therapy.

Introduction

The present conventional monotherapies aim for targeting various Hallmark characters of cancer individually by various molecular means. This type of single-agent therapy led to the discovery of hundreds of medicines for targeting each and every molecular pathway of the cancer cells. It soon became apparent that single-agent application of these therapies, although sometimes showing remarkable antitumor effects, was still often not enough to eradicate disease [1]. Moreover, targeting different paths each with single-agent not only a tedious job, but also likely to weaken the goal of complete eradication of cancer cells. Therefore, instead of targeting individually the several hallmark characters of cancer, scientists now attempt to seek a multifaceted approach by targeting a dominant factor which acts as the master regulator gene (MRG). In this connection accumulating evidence has demonstrated that HIF-1α mediates different biological processes, including tumor angiogenesis, metastasis, metabolism, and immune evasion and therefore it may serve as potential targets for cancer therapies [2]. Over the past few decades, a number of HIF-1 inhibitors have been identified as potential therapeutic agents for various cancers. However, none of these inhibitors have been successfully translated into clinically available cancer treatments [3].

According to growing evidence, HIF1α signalling activation can be mediated by a number of hypoxia-dependent and hypoxia-independent pathways [4] and targeting this factor by any single mono-therapy approach may not yield desirable results [1]. This necessitates the need for finding out some treatment approach involving combinational therapies [1,5-7].

Recently, Bui et al., [3] tried to provide new insights into anticancer drug development targeting HIF-1 and suggested combination of

various HIC-1 inhibiting chemotherapy drugs targeting each stage of activation of HIF-1 under clinical trials. They [3] concluded the need for identification of hypoxic markers and genomic analyses are urgently required to allow HIF-1 inhibitors to be tailored to specific cancer types and individual patients. Bayat Mokhtari et al. [7] have listed the use of combinational therapy involving several natural pharmaceutical products and conventional therapeutic medicines targeting molecular pathways of cancer cells. Similarly, application of some medicinal herbal products and natural products in targeting HIF 1a has been reviewed by Li et al. [8] and Pandey et al. [2]. Such combination interventions target these pathways either synergistically, additively, or in a potentiating manner [8]. In this connection, it is reported that many functional foods having good amount of anti-cancer chemicals are recommended and consumed for combating against cancer [9-13]. Among the phytochemicals of the functional foods, Curcumin, resveratrol, gingerols, sulforaphane and vitamin D phytochemicals are said to be having specific inhibitors effect on HIF1 through different pathways [8-13]. Here we are going to analyse the relative efficacies of these phytochemicals in inhibiting HIF-1a, based on the UpToDate available research reports. The possible synergetic or additive effects of those drugs are also will be discussed.

In order to find out in which molecular pathway the said phytochemicals influence HIF-1a, it is necessary to understand the various molecular mechanisms involved in the production, stabilization and activation of the HIF-1α.

Molecular pathways involved in various regulations of HIF-1a

Koyasu et al. [14] reviewed and have given a detailed account of various mechanisms involved in the regulations of Stabilization, Nuclear translocation, Heterodimer formulation and Transactivation activities of HIF-1a. Since the anti- HIF-1α agents may act on any of these regulatory activities, it is essential to know the role of various genes involved in these regulations. These genes may act on HIF-1a either positively or negatively in the following molecular pathways:

Pathway regulating synthesis of HIF-1α

Transcription initiation is generally regarded as one of the most influential steps affecting the expression levels of genes. Transcription of the HIF-1α gene is a continuous process in Cancer cells, although basal levels of HIF-1α may be assured regardless of oxygen availability [14]. Many groups of genes which is composed of STAT1/STAT2/IRF9, STAT3, or NF-κB, bind to the promoter region of the HIF-1α gene and activate its transcription initiation [15-17].

PI3K/Akt/mTOR Pathway: Activation of PI3K leads to the activation of Akt and mTOR. mTOR promotes HIF-1α protein translation. This pathway is inhibited by the tumor suppressor PTEN [18].

RAS/RAF/MEK/ERK Pathway: Stimulated by growth factors, this cascade increases HIF-1α through both translation and transcription: In translation, ERK phosphorylates 4E-BP1, S6K, and MNK (which directly phosphorylates eIF-4E) to speed up protein synthesis [19,20].

Pathways regulating stability of HIF-1α

Under normal oxygen tension, HIF-1α protein expression is negatively regulated by proteasomal degradation and ubiquitination in a pathway involving von Hippel−Lindau protein (pVHL). In the presence of sufficient oxygen, hydroxylation of the two proline residues (P402/ P564) located in the HIF-1α protein occurs by PHDs (prolyl-4-hydroxylases). Another residue (lysine, K532) could be acetylated by an enzyme called arrest-defective-1 (ARD-1). Consequently, modified HIF-1α subunits with hydroxylated P402/P564 and acetylated K532 moieties are preferably recognized by pVHL and are tagged for ubiquitination and proteasomal degradation. Since both the hydroxylation and acetylation actions from PHDs and ARD-1 expression require the presence of oxygen, under hypoxic condition, neither hydroxylation nor acetylation of HIF-1α proline and lysine residues occurs, resulting in stabilization of HIF-1α protein [21].

In another pathway under normoxia conditions, HIF-1α binds to the p53 gene and allows Mdm2 (mouse double minute 2 homolog) mediated ubiquitination and proteasomal degradation of HIF-1α [22]. Heat shock protein 90 (Hsp90) is known to bind directly with HIF-1α inducing some conformational changes in its structure to fit and couple with HIF-1β initiating its transactivation. In addition, Hsp90 can stabilize HIF-1α against its non-VHL dependent degradation [23].

Pathway regulating nuclear translocation of HIF-1α

Translocation from the cytosol into the nucleus is another important regulatory step in HIF-1 activity. AMPK-HDAC pathway deacetylates the cytosolic molecular chaperone, HSP70, promotes the interaction between HIF-1α and HSP90, and facilitates the rapid nuclear accumulation of HIF-1α. MAPK has been reported to block export of HIF-1a out of nucleus thereby promoting nuclear accumulation and transcriptional activity [24].

Pathway regulating dimerization

After being stabilized, HIF-1α forms a heterodimer with the constitutively expressed binding partner, HIF-1β. Heterodimer formation is also an important regulatory step in the activation of HIF-1. CK1δ is negatively involved by inhibiting heterodimer formation with HIF-1β by Phosphorylating HIF-1α at S247 [25]. Degradation of ARNT (HIF-1β) inhibits dimerization [26].

Pathway regulating Transactivation of HIF-1α

The transcriptional activation of HIF-1α target genes is initiated through the cooperative binding of C-TAD in the HIF-1α and the co-activator CBP/p300. In normoxia, factor inhibiting HIF-1 (FIH-1), also known as asparginyl hydroxylase, blocks the interaction between the two domains, abrogating the subsequent HIF-1α mediated gene transcription [27]. SIRT1 can bind to HIF-1α and deacetylate at lysine 674, which is acetylated by p300/CBP-related

factors (PCAF), thereby inhibiting HIF-1α through blocking the recruitment of p300 [28]. Factor-inhibiting HIF (FIH), which is able to block the interaction between HIF-1 and the transcriptional activators p300/CBP via the asparagine hydroxylation of HIF-1, attenuating HIF transactivation activity [29]. MAPK/ERK is known for its involvement in regulation of HIF-1α synthesis. In addition, it also involved in its transcriptional activation. ERK phosphorylates the co-activator CBP/p300 so it increases HIF-1α/p300 complex formation, and thus stimulates its transcriptional activation function [30]. XBP1 is positively regulating HIF-1 transcriptional activity by forming a transcriptional complex with HIF-1α and promoting the recruitment of RNA polymerase II [31]. Similarly, IDH3 activate transcription of HIF-1 by inactivating FIH-1 through a decrease in 2OG levels when overexpressed aberrantly [32].

A summary of sequence of various pathways is shown in Figure 1 and how these pathways act on the regulation of HIF-1α is shown Figure 2.

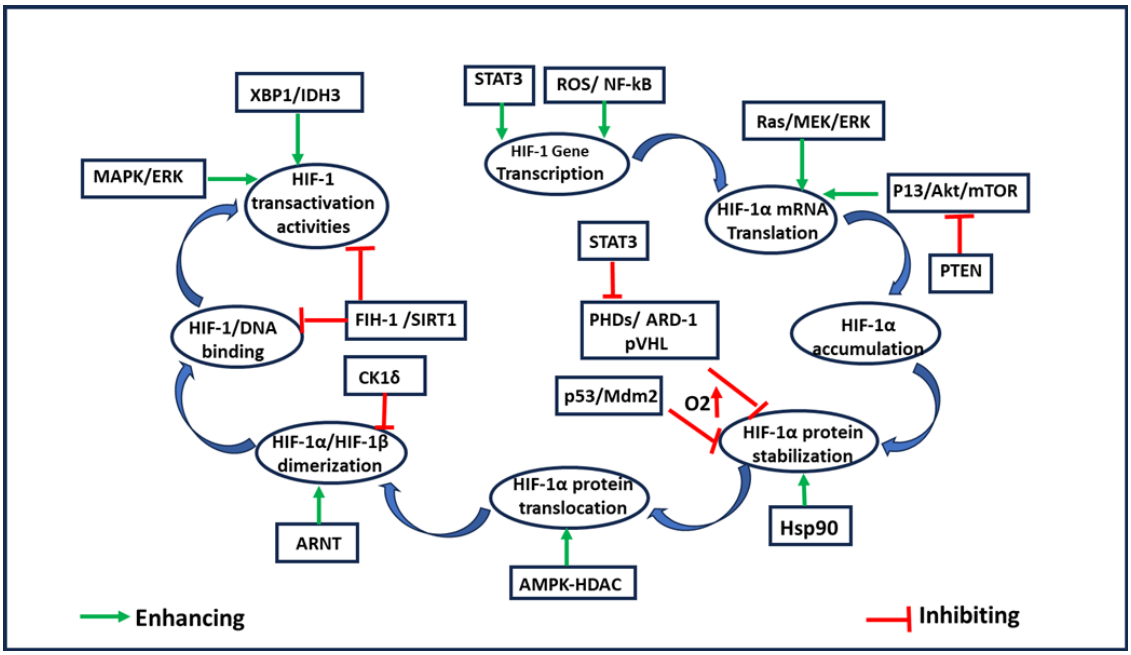

Figure 1: Molecular pathway sequences in HIF regulation and the mode of actions of different molecules in the regulatory process. (Refer text for the abbreviations).

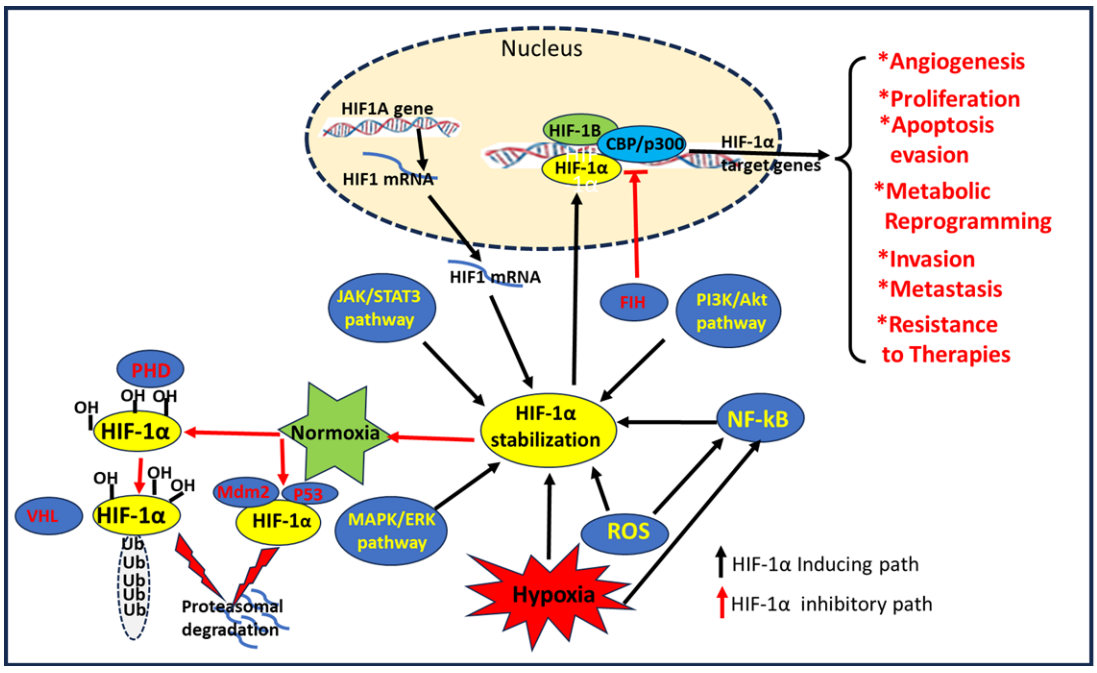

Figure 2: Graphical abstract: Picture showing different molecular pathways involved in influencing HIF-1α functioning. (Refer text for the abbreviations used).

ROS as a master regulator of HIF-1a through multiple inflammatory signalling pathways

ROS (Reactive Oxygen Species) play a central role as the second messenger in modifying a variety of signaling molecules to facilitates HIF-1α activities. Current development of ROS scavenging biomaterials for the treatment of inflammatory diseases has been rapid, offering countless possibilities for biomedicine as a promising therapeutic modality. Although some problems need to be carefully solved, the great possibilities of these biomaterials deserve further exploration [33]. They (ROS) control multiple inflammatory / HIF-1α stimulating pathways such as, the NF-κB signaling pathway [34-36], the MAPKs signaling pathway [37,38], the JAK/STAT signaling pathway [39], the PI3K/AKT signaling pathway [40], and the PHDs/ ARD-1/pVHL pathway [41].

Levels of ROS and oxygen decides HIF-1α activation—under hypoxia condition, the increased ROS level upregulate HIF1α, as PHD activity is downregulated [42-44], while under low ROS condition HIF1α is downregulated, as PHD activity is upregulated [45,46]. Qutub & Popel [47] discussed the molecular mechanisms involved in the differential actions of ROS under various oxygen levels. It is understood that targeting ROS is primary need before attempting targeting HIF-1α as ROS is the master regulator of many of the inflammatory pathways (Figure 3).

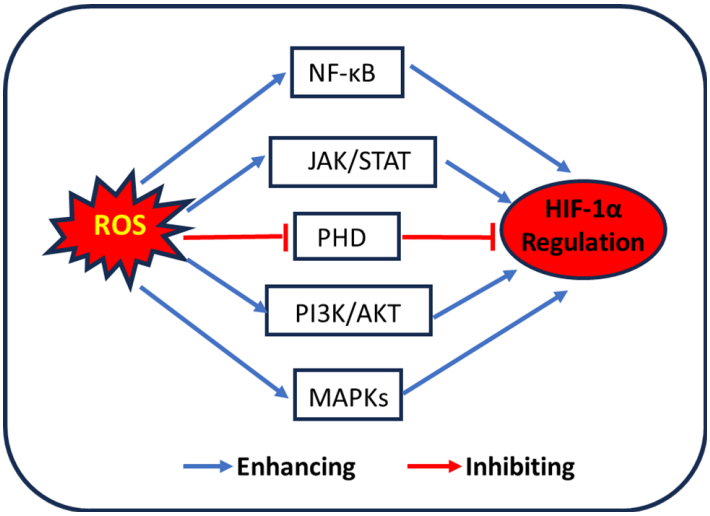

Figure 3: Action of ROS in HIF-1α regulation through various molecular pathways (Refer text for abbreviation).

Molecular Pathways exhibited by the Phyto-chemicals which target HIF-1a

A clear account of various regulatory molecular paths of HIF-1α are explained above. Now, it may be easy to understand on which of the molecular paths the said phytochemicals may express their inhibitory influence. A review of on the available UpToDate scientific findings on the molecular mechanisms of the phytochemicals in this respect is done here.

Curcumin

Curcumin is the major component of the rhizomes of Curcuma longa L. In the past 2 decades, curcumin and its derivatives have garnered much attention due to their antitumor qualities [48]. Bae et al. [49] and Choi et al. [50] were the pioneers who independently brought out the role of curcumin in inhibiting the activation of HIF in various types of cancers. The former reported inhibition of hypoxia-induced angiogenesis via down-regulation of HIF-1 by curcumin [49] while the latter [50] reported stimulation of the proteasomal degradation of ARNT (one of the sub-components of HIF), resulting in the inhibition of transcriptive function of HIF 1a protein.

Role of curcumin in inhibiting STAT3 pathway has been reported by [51-54]. Curcumin treatment significantly decreases HSP90 expression while promoting the ubiquitination and degradation of HIF-1α [55]. HDAC which involves in positive regulation of HIF-1a is inhibited by Curcumin [56]. Curcumin as one of the master regulators of ROS has been widely reported [57-64]. Many scientists started working on the role of curcumin in influencing the molecular mechanism involved in various regulations of HIF-1a and its value in cancer therapy [65-75].

Vitamin D3

Humans obtain vitamin D through dietary intake and exposure to sunlight. Egg and Mushrooms are the functional foods that are the main source of Vitamin D. 25(OH)D is the major circulating form of vitamin D and is used to determine vitamin D status. In order to be biologically active, additional hydroxylation in the kidneys is needed to form active 1,25-dihydroxyvitamin D [1,25(OH)2D] (calcitriol) [76].

Vitamin D has a great effect in forming and maintaining strong bones. It has also recently been found that vitamin D receptors exist in a variety of cells thus it has a biological effect on more than mineral metabolism [77]. The first study indicating that sunlight exposure may lower the risk of cancer was first made almost seven decades ago [78]. Garland and Garland [79] were the first to propose that vitamin D deficiency may contribute to a higher risk of colon cancer mortality since vitamin D is formed in the skin through solar UVB radiation. Many recent studies suggest that vitamin D deficiency may account for thousands of various types of cancer deaths every year [79-83].

Gkotinakou et al. [77] in their review provided substantial data indicating that calcitriol interferes with important signalling cascades that affect HIF-α mRNA expression. Among the signalling cascades, PI3K-AKT-mTOR pathway, which is a common feature of cancer cells, leads to the induction of HIF-1α. Calcitriol can indirectly influence HIF-1/2α synthesis by moderating PI3K activation by increasing the expression of PTEN in a VDR dependent manner [84,85]. It was observed that the expression of HIF-2α depends on AKT2 while the expression of HIF-1α on AKT3 [86,87]. In this pathway, calcitriol treatment resulted in decreased phosphorylation levels of AKT and downstream translation initiation factors [88]. Additionally, HIF1A mRNA translation rates are also dependent on PERK activation. Interestingly, calcitriol receptor MARRS/PDIA3 has been shown to prevent PERK kinase activation thereby, the translation of HIF1A mRNA is affected

[89]. Abu et al. [90] have given a detailed account of the adaptive role of HIF-1α in tumor metabolism and highlighted the inhibitive mechanism played by Vitamin D3 against HIF 1a in their review.

It is reported that the two moieties, HIF-1α and c-Myc, are involved in rewiring the tumor metabolism [91]. Reduction of the expression of both factors by 1,25(OH)2D3 in cancer cells has been reported by numerous studies [92-94], and the genes encoding these oncogenes have been shown to harbor putative vitamin D response elements (VDRE) [95,96].

Gkotinakou et al. [88] reported recently the synthesis of the two sub-units of HIF, HIF-1α and HIF2a, is affected by calcitriol that inhibits the activation of PI3K/AKT/mTOR pathway and, thus, impairs the phosphorylation of critical components of the translational machinery responsible for HIF1A and EPAS1 mRNA translation. Down regulation of STAT3 by Calcitriol in Cancer cells has been reported. Interestingly, as an adaptation, the cancer cells employ the calcitriol deactivating enzyme, CYP24A1 to catalyse calcitriol's inactivation [97]. The role of vitamin D3 in neutralizing the oxidative damage caused due to ROS is discussed extensively by various authors [98-106].

Resveratrol

Resveratrol is a potential substance of stilbenes family that can be utilized in treatment of a large number of cancers and it is a promising substance which can be utilized in pharmaceutics, therapeutics and medicinal sectors to gain its multiple benefits [107]. It is abundantly found in dietary sources such as fruits and vegetables and especially in red wine [108]. It is reported in various research findings on the anti-cancer role of Resveratrol by acting on various molecular pathways which are leading to HIF-1 regulations [107]. The major pathways include: ROS/ HIF pathway [109], PI3K/Akt/mTOR pathway [110-113], STAT3 pathway [114-117], PI3K/Akt/ MAPK pathway [118,119], NF-kB pathway [120-123] and PHD/proteosome pathway [124]. The role of neutralizing the ROS effect by resveratrol has been extensively studied by many authors [125-138].

Sulforaphane

Sulforaphane (SFN), a member of the isothiocyanate (ITC) family, originates from cruciferous vegetables, including broccoli, cabbage, and kale [139]. SFN is a biologically active small molecule compound with anti-inflammatory and antioxidant properties [140,141]. Its anti-cancer properties include cancer prevention [142] and inhibition of tumor growth and progression [143-145]. Furthermore, several studies have reported that SFN can also be used as a natural dietary supplement taken with some norm chemotherapeutic medicines to increase therapeutic effectiveness while reducing their adverse side effects [146-148]. The inhibitory roles of SFN in various molecular pathways that lead to activation of HIF in various cancers both in vitro and vivo have been recently reviewed and reported by Liu et al. [149], specifically highlighting the role of SFN in the ROS/HIF pathway [150], the PI3K/Akt/mTOR pathway [151,152], the STAT3 pathway [153], the NF-kB pathway [154], and the PHD/proteasomal pathway [155-157]. Furthermore, sulforaphane inhibits pancreatic cancer through disrupting the Hsp90-p50(Cdc37) complex and direct interactions with amino acid residues of Hsp90 [158], and as an important antioxidant, its molecular mechanisms involved in neutralizing oxidative stress have been extensively discussed [159-166].

Ginger

Ginger (Zingiber officinale), belonging to the Zingiberaceae family, has been widely used as a spice in various foods and beverages worldwide. In Southeast Asia, ginger has long been used as a traditional medicine to treat digestive problems, sore throats, coughs, fevers, and so on [167]. The non-volatile components give ginger a pungent, spicy taste, including gingerol, shogaol, zingerone, and paradol. In fresh ginger, the main component is gingerol, which will then be converted to shogaol, zingerone, and paradol in ginger-based products [168].

The recent review by Mao et al. [167] discussed the bioactive compound and bioactivities of ginger, including antioxidant activity, anti-inflammatory activity, antimicrobial activity, neuroprotection, and protective effect against respiratory disorders. Anti-inflammatory role of Ginger products have been reviewed by Jalali et al. [169] and Morvaridzadeh et al. [170]. Cancer preventive role of ginger products and other functional foods has been discussed by several authors [171-174]. Natural compounds including gingerol as inhibitors of HIF-1α has been reviewed by Losso et al. [175], Li et al. [176], and Pandey et al. [177].

The major molecular pathways that influence HIF in which ginger products play a role include the ROS/HIF pathway [178-184], the PI3K/Akt/mTOR pathway [185-188], the NF-kB pathway [189,190], HIF stabilization [191], and the STAT3 pathway [192].

The role of Gingerol and shogaol biochemical compounds in controlling oxidative stress and ROS has been reported in various cancer lines [169,170,178-184] and their pharmacological applications have been recently reviewed by Abdul et al. [193] and Xicen [217]. The various mechanism followed by ginger compound in neutralizing the oxidation stress has been explained in various reports [193-199].

Inhibitory potential of the phytochemicals against the pro-active HIF-1α molecules

It has been already pointed out in the foregoing sections that all the five phytochemicals are involved in controlling HIF-1 through the following major six molecular pathways: ROS pathway, PI3K/Akt/mTOR pathway, NF-kB pathway, STAT3 pathway, MAPK-RAS-RAF-MEK-ERK pathway and PHD/ proteasomal pathway. Understanding how specific pathways regulate HIF-1α is essential for leveraging functional foods as targeted, non-toxic interventions in cancer therapy. This section evaluates the inhibitory potential of the phytochemicals against the pro-active HIF-1α molecules through a comparative lens.

ROS regulation

Bioactive compounds found in functional foods—curcumin,

vitamin D, resveratrol, sulforaphane, and gingerols—play a significant role in neutralizing Reactive Oxygen Species (ROS). By mitigating oxidative stress, these compounds effectively inhibit the ROS-driven activation of HIF-1, thereby curtailing its downstream effects (as already discussed above).

Good antioxidant effect can be achieved by promoting the production and activity of antioxidant enzymes (Nrf2 Pathway Activation) and by neutralizing free radicals directly [194]. In this respect, all the above said phytocompounds exhibit both promotion of antioxidant enzymes and direct radical scavenging except sulforaphane that does not perform scavenging free radical directly.

Although all the above five bioactive compounds follow similar molecular paths in targeting ROS, their efficacy may vary. As judged from the number of research findings which support their respective anti-ROS role, the efficacy of directly neutralizing the free radicals, Resveratrol, curcumin and Vitamin D3 stands highest. Among these three, resveratrol efficacy has been specially highlighted by research findings in respect of free radial scavenging [125]. In respect of the activity, promotion and production of antioxidant enzymes, sulforaphane (SFN) is rated top by the scientific findings [149-153]. SFN not only modifies Keap1 cysteine residues, resulting in Nrf2 activation, but also restores Nrf2 expression through epigenetic mechanisms, including inhibition of DNMTs and HDACs [200]. Su et al. [165] consider that the epigenetic restoration of Nrf2 by SFN as an important strategy against oxidative damage-related diseases, including cancer, which may provide new research directions and preventive approaches for oxidative damage-related diseases. There is ample evidence that sulforaphane is a very potent inducer of Phase II enzymes and also raises cellular glutathione levels [201]. Kensler et al. [202] and Su et al. [165] considered that targeting Keap1-nrf2 signalling by SFN is one of the main anticancer mechanisms.

Synergism in the combined action of curcumin and resveratrol in translocation Nrf2 protein into the nucleus and activate it to initiate transcription of antioxidant genes against oxidative stress has been studied and reported [203]. In this connection, it is noteworthy to know that Synergistic action of Resveratrol and sulforaphane in cancer prevention has been reported [204]. Uberti et al. [205] have analysed the synergism seen in the combination of resveratrol and vitamin D3 and reported that both in *in vitro* and *in vivo* experiments, resveratrol exerts more evident effects when administered in combination with vitamin D showing a common biphasic cooperative effect. Zhou et al. [206] have worked out the synergistic effects of Turmeric and Ginger combination in enhancing the activity of Nrf2 protein, and found that Ginger-Turmeric combination boosted the Nrf2 upregulation by 18.89 ± 1.32-fold which was significantly higher than that of Ginger or Turmeric. Tuttis et al. [207] reported that Sulforaphane combined with vitamin D upregulated NRF2 (Nrf2) expression. Vitamin D and Sulforaphane Decrease Inflammatory Oxidative Stress synergistically [208].

As far as activation of NRF2 is concerned, all the above phytochemicals are said to involve in the activation of NRF2 which helps to reduce oxidative stress. Although this action helps in prevention of origin of tumour cells, in the case of established cancer cells, it acts negatively and encourage their survival by protecting them from excessive oxidative stress. Baie et al. [209] studied Hypoxia, oxidative stress, and the interplay of HIFs and NRF2 signalling in cancer and analysed the dual role of NRF2 and concluded that activation of NRF2 in established cancer environment encourages cancer growth. Further it is reported that Overactivated NRF2 induces pseudohypoxia in hepatocellular carcinoma by stabilizing HIF-1α [210].

PI3K/Akt/mTOR & HIF pathway

Activation of this pathway (common in many cancers) increases the rate of HIF-1α protein synthesis (translation) [211]. This pathway mechanism is responsible for the development of resistance to the therapies and therefore this warrants further investigation and provides a possible approach to reverse resistance to chemo/radiotherapy [212]. As pointed out earlier all the said phytochemicals are involved in controlling this pathway and therefore some sort of synergism or cumulative effects might be there while using all these chemicals combined together for cancer control. In this connection, the synergetic action of curcumin and resveratrol was reported in controlling PI3K/AKT pathway [213]. Curcumin together with resveratrol causes a greater inhibition of growth of colon cancer cells *in vitro* than either agent alone.

The study by He et al. [214] demonstrated an advanced effect of Cur and Res in combination to attenuate fatty liver diseases, and the mechanism is at least partly associated with the modulation of the PI3K/AKT/mTOR and HIF-1 signaling pathways. Individual treatments of Curcumin and Resveratrol produced a moderate inhibition of PI3K, AKT, mTOR and STAT3 compared to the model group, while Cur+Res showed a greater inhibitory effect on all these key gene targets than Cur and Res alone with the exception for STAT3 where the Cur+Res' effect was only significantly greater than that of Curcumin. Muhanmode Y et al. [215] have reported that Curcumin and resveratrol inhibit chemoresistance in cisplatin-resistant epithelial ovarian cancer cells via targeting P13K pathway.

Similarly, synergism of curcumin and 6-shogaol is reported in down-regulating the Resveratrol mediated PI3K/AKT and MAPK signalling pathways [216]. Combinational treatment with resveratrol and sulforaphane increases the activation of intracellular signalling proteins, such as proliferating cell nuclear antigen (PCNA), cyclin D1, phospho-Akt, Akt, and caspase-3 in human U251 glioma cells [217].

NF-kB pathway

There have been several studies demonstrating cross-talk between the NF-κB and HIF signalling pathways, including shared target genes. NF-κB can directly modulate the HIF-1α pathway, and that this modulation was sufficient to alter HIF target gene expression *in vivo* [218-220].

Regarding the role of NF-κB and HIF 1a in cancer initiation and growth, both are acting independently [221,222] or combining by cross-talk method [218,219]. Considering the therapeutic value for the cancer control, there is a need for attending both, NF-κB and HIF 1a [221,222].

As far as the phytochemicals discussed here are concerned, we have seen that all are involved in controlling the NF-κB pathway effectively [223,224], thereby involved in controlling the HIF 1a as well as several tumour genes [220].

Regarding synergistic effects of these phytochemicals in controlling the NF-κB effects, the existence of synergism has been studied among curcumin and Resveratrol by Csaki et al. [122]. According to their [122] study, it is revealed that both resveratrol and curcumin inhibited NF-κB activation in a concentration-dependent and time-dependent manner. The inhibition of NF-κB activation by resveratrol occurred mainly through the accumulation of phosphorylated IκBα, ubiquitinated IκBα and inhibition of proteasome activity—in contrast to this, in the case of curcumin it was mainly caused through inhibition of IKK activation. Thus, we could observe a higher synergistic value of these two compounds as they affect NF-κB through two different molecular pathways. These two compounds not only inhibit the action of NF-κB by deactivation but also inhibit the translocation of NF-κB into the nucleus and thereby prevent its transcription activity [122].

Xian et al. [225] have studied the true synergistic interaction of Ginger and Turmeric extracts and demonstrated that the synergistic mechanism was associated with downregulation of the miRNA-155-5p and key proteins in the TLR4-TRAF6-MAPK and NF-κB pathways. According to them, their study results establish a scientific basis for the combined application of Ginger and Turmeric as an advanced therapeutic candidate in inflammatory diseases with broad and synergistic anti-inflammatory activity and multi-targeted mechanisms.

Similarly, Adrianta et al. [226] reported that the combination of curcumin and gingerol showed synergistic activity in increasing antioxidant and anti-inflammatory capacities. Raahim et al. [227], in their review, reported that Curcumin, gingerol, and shogaol reduced cell inflammation by impairing the NF-kB signalling pathway and emphasised the need for additional studies exploring the synergistic anticancer effects of these bioactive compounds. A synergistic effect in down-regulating inflammation markers like TNF, IL-1, NO, PGE2 by curcumin plus Sulforaphane has been reported by Cheung et al. [228].

STAT3 / HIF-1α pathways

Niu et al. [229] discussed the role of STAT3 in HIF-1α pathway. According to them, consistent with a role of STAT3 in regulating HIF-1α RNA transcription, elevated STAT3 activity increases HIF-1α promoter activity, and STAT3 protein binds to the HIF-1α promoter in both transformed cells and in growing tumors. Control of this STAT3 pathway by the phytochemicals individually has been mentioned elsewhere above.

The review by Golmohammadi et al. [230] demonstrates that CUR directly inhibits the phosphorylation of STAT3, preventing its movement into the nucleus and its ability to bind to DNA, thereby hindering the survival and proliferation of cancer cells. Similarly, Kohandel et al. [114] reported the role of resveratrol in inhibiting the activity of STAT3. Synergism in curcumin + resveratrol in inhibiting the STAT3 pathway is reported by He Y, et al. [214]. Therefore, the combination treatment exhibits promise in modulating the STAT3 pathway, which is essential for cancer prevention and treatment [231].

MAPK-RAS-RAF-MEK-ERK pathway

The Ras-Raf-MEK-ERK pathway, also known as the extracellular signal-regulated kinase (ERK) pathway or mitogen-activated protein kinase pathway (MAPK), is a transduction cascade that carries extracellular signals into the nucleus of cells, where specific genes are triggered for cellular survival, proliferation, and differentiation [232]. The role of Curcumin as an important inhibitor of MAPK pathway molecule in cancer control has been reviewed by Ameer et al. [233]. Inhibition of MEK/ERK pathway has been studied in resveratrol [234], sulforaphane [235], vitamin D [236] and in gingerol [237] in various cancer lines.

Actions of Synergism in MEK/ERK path inhibition have been reported in Curcumin – Sulforaphane [238], in Curcumin - Gingerol/ Shogaol [239], in Resveratrol - vitamin D [240,241], and Ginger- Turmeric [242]. Thus, it is observed that these phytochemicals could control this MAPK path effectively both individually and synergistically.

PHD/ HIF-1α pathways

Inhibition of HIF-1α by its degradation occurs during normal oxygen supply by two pathways: by the hydroxylation and acetylation actions from PHDs and ARD-1 expressions respectively involving pVHL (as already discussed). In this pathway, except vitamin D3, all other four phytochemicals are involved (as already discussed). However, no combination treatment studies involving these phytochemicals for testing their synergistic efficacies in HIF-1α degradation activities are available.

Where and how the phytochemicals target the regulatory pathways of HIF-1α

Considering the profound impacts of HIF-1α on cancer progression via gene expression and the unsatisfactory efficacy of chemotherapy, there has been enormous growing interest in the biology of HIF-1α pathway and the development of direct or indirect HIF-1 inhibitors [4]. It is clear that the HIF-1α regulation pathway is a highly complex network involving several signaling cascades and overlapping mechanisms, each of which could serve as a promising target or step to intervene selectively [4]. They suggested that HIF-1α inhibition can usually be achieved through modulation of several key steps, including HIF-1α mRNA expression, the HIF-1α protein level via translation or degradation, HIF-1α/HIF-1β dimerization, HIF-1α-DNA binding at the HIF-1α/HRE site, and HIF-1α transcriptional activity involving the CH-1

of p300 or the C-TAD of HIF-1α.

A clearer understanding of these mechanistic relationships is critical for fully elucidating when, where, and how HIF-1 becomes active and applying this information to the development of novel therapeutic strategies for cancers [14]. Masoud et al. [4] have identified many small molecules reported as HIF-1α inhibitors in literature and categorized them based on their targets, structures and putative mechanisms of action. Li RL et al. [8] attempted to find out the use of active molecules from some Traditional Chinese herbal products that could target molecular pathways of HIF-1α. However, most studies only focus on the inhibitory effects on HIF-1α, and few go deep into the specific step affected.

Following this, Ikeda et al. [243] suggested some natural products for targeting HIF-1α. Lasso et al. [175] are the pioneers in pointing out that phytochemicals of some functional foods could affect the regulation of HIF, though they were not then able to identify the exact molecular pathways. The different molecular pathways targeted by phytochemicals have been discussed already above. Accordingly, it is critically analysed here how these phytochemical molecules express control on the different regulatory pathways and how a therapeutic strategy could be developed.

Regulating synthesis of HIF-1α at transcription level

Two pathways are identified. The ROS/NF-κB pathway involves enhancing HIF-1α synthesis by activating the transcription of HIF-1 RNA. Here, ROS induces NF-κB activation in a canonical pathway and NF-κB functions as a critical transcriptional regulator primarily by binding to the promoter region of the HIF-1A gene [33]. All phytochemicals discussed here are involved in controlling the NF-κB pathway [as explained already]. Synergistic effects have been reported between curcumin and Resveratrol, curcumin and gingerol, and curcumin and sulforaphane. Thus, the combination of these phytochemicals may be more effective in inhibiting HIF-1α at the transcription level.

Regulating synthesis of HIF-1α at translation level

Once HIF-1 mRNA is produced, it must be translated into protein. The pathways involved are PI3K/Akt/mTOR [244] and MAPK/ERK/STAT3 [245]. In another pathway, STAT3 is involved in enhancing translation of HIF-1α protein and is needed for HIF-1α RNA expression under both hypoxia and growth signalling conditions [246]. The role of the five phytochemicals in controlling these pathways has been dealt already above. Thus, all the five phytochemicals are involved in controlling translation of HIF-1α mRNA either individually or synergistically.

Regulating stability of HIF-1α

PHDs/ ARD-1/pVHL and p53/Mdm2 are the two main pathways through which the stability of HIF-1α is inhibited. Curcumin, Resveratrol and sulforaphane are involved in PHD/ proteasomal degradation of HIF-1α. Synergistic or additive actions of these three phytochemicals may be considered more effective in the destabilization of HIF-1α. The most distinct mechanism for 6-gingerol is its ability to downregulate HSP90, a chaperone protein that normally protects HIF-1α from degradation. By disrupting this interaction, 6-gingerol promotes the rapid proteasomal degradation of HIF-1α [247]. Thus, the stability of HIF-1α is checked by multiple ways and thereby the efficacy of this action through the combination of these phytochemicals could be improved.

Regulating nuclear translocation of HIF-1α

Translocation of the stabilized HIF-1α is another important checking path for inhibiting its action. HDAC is involved in translocating HIF-1α into the nucleus and accumulating it there for initiating transcription of target genes. As an enhancer of nuclear translocation, any inhibitor of HDAC will have an inhibitory effect on HIF-1α function. In this respect, among the five phytochemicals discussed, curcumin [248], Resveratrol [249], sulforaphane [250], and Ginger [251] have been reported to act as HDAC inhibitors and have anticancer actions. Therefore, some sort of synergistic or additive action may be expected in controlling the action of HIF-1α if all these are taken together.

Regulating dimerization

Dimerization of HIF-1α - HIF-1β is another step required for HIF-1α to initiate its translational activities. Inhibition of this action leads to dysfunction of HIF-1α. As far as inhibition of dimerization is concerned, although direct inhibition by these phytochemicals is not reported, curcumin indirectly inhibits dimerization by destroying one of its cofactors, HIF-1β (ARNT), thereby stopping dimerization [252-254].

Regulating HIF-1/DNA binding

The HIF-1α/p300 complex is a precondition for the initiation of Transactivation of HIF-1. In this respect, ERK1/2 phosphorylates the co-activator CBP/p300, which increases the production of the HIF-1α/p300 complex [255]. MAPK signaling has been shown to facilitate the physical interaction between p300 and the HIF-1α C-TAD, promoting transactivation even under normoxic conditions in certain cancer cell types [256].

Inhibition of the ERK/MAPK pathway by the phytochemicals has been indicated in the foregoing. Thus, the phytochemicals affect the transactivation process by inhibiting the interaction of p300 with HIF-1α. Another way of reducing the interaction of p300 is blocking its recruitment. In this connection, SIRT1 is said to block the recruitment of p300 by binding to HIF-1α and deacetylating it at lysine 674, which is acetylated by p300/CBP-related factors [257]. Curcumin increases SIRT1 through activation of small molecules, and SIRT1 has a vital role in the inhibition of cancer cell growth [258]. Resveratrol is also said to use the SIRT1 pathway to inhibit HIF-1/DNA binding [259]. Thus, both curcumin and resveratrol are found to inhibit regulation of HIF-1/DNA binding.

Regulating Transactivation of HIF-1α

This is the final part of the regulatory path of HIF-1α; controlling it will affect the transcription of many target genes responsible for

cancer growth and metastasis. It is reported that the ERK/MAPK path leads to the transcriptional activation function of HIF-1 [256]. Thus, we observe that through the modulation of the above seven regulatory pathways, the five phytochemicals successfully inhibit HIF-1 transactivation and the expression of various genes responsible for cancer growth (Figure 4).

Improving the efficacy of the phytochemicals

We have shown that all the phytochemicals discussed here are very effective in inhibiting the action of the master factor, HIF-1α at various levels under various experimental conditions. But their bioavailability and reachability in vivo in human body is a major drawback in effectively using them as anticancer agents. Most of them are metabolized and lose their characters before reaching the target sites. They don't reach the expected therapeutic value unless they are effectively absorbed and made more functional in their original form. Therefore, scientists now work on improving their bioavailability and effective dosages.

Curcumin

The pharmacological challenges associated with curcumin, such as its limited solubility and rapid metabolism, have a significant impact on its absorption within the body's digestive system [260,261]. The challenge of curcumin's limited bioavailability poses a barrier to its effective use in cancer treatment. However, there are various strategies available to overcome this hurdle. These include the development of novel curcumin derivatives with enhanced bioavailability, the utilization of nanoparticles for curcumin delivery, the implementation of combination therapy involving curcumin and other substances, and the adoption of other tactical approaches to address this issue [262].

Emerging evidence suggests that synthesized curcumin analogs exhibit improved solubility, enhanced bioavailability, and greater efficacy against cancers compared to curcumin itself [263,264].

Nanomedicine provides advanced methods for targeting cancer, allowing for precise delivery of treatment to the blood vessels within the tumor, the immediate surroundings of the tumor, and individual cancer cells [265] and various nanomaterials have been suggested by Kydd J et al. [265]. The various benefits of using these nanomaterials have been listed out by Amekyeh et al. [266].

Recently Bertoncini-Silva et al. [267] worked out several Curcumin nanoformulation strategies to enhance bioavailability and bioactivity, and improve solubility, stability, absorption, and targeting of specific cells. Thus, there are many possibilities for getting the maximum potency of curcumin for using it as an effective therapeutic agent against cancer if the above discussed more active forms are put under use.

Resveratrol

One of the natural chemotherapeutic agents that has garnered attention in research is Resveratrol (RSV). As cancer research evolves, its value is growing in interest due to increased interest in natural compounds and their role in integrative oncology, as evidenced by the increasing number of preclinical and clinical studies supporting its potential role in cancer treatment [268].

Although RSV has shown promising chemopreventive effects, its clinical translation is impeded by poor aqueous solubility, rapid metabolism, and minimal systemic bioavailability (0.5%) [269]. However, recent advancements in drug delivery systems and the development of RSV analogs, such as hydroxylated and fluorinated

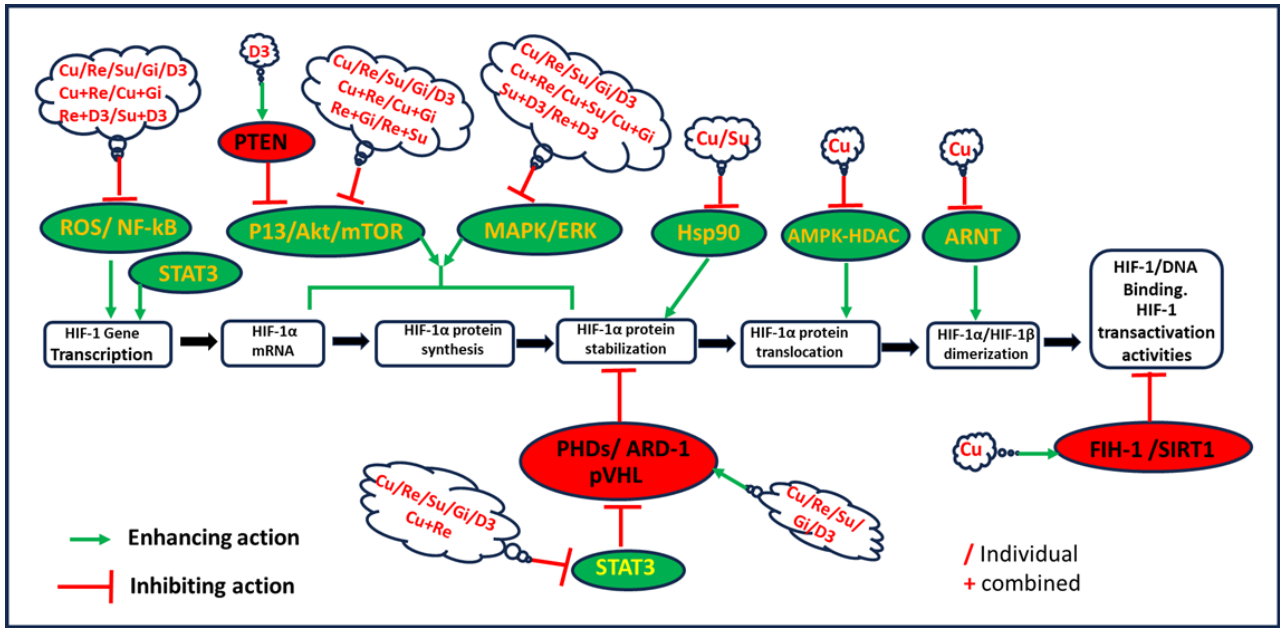

Figure 4: HIF regulation molecular pathways sequence and the mode of actions of the phytochemicals of the functional foods at different levels either as individual or in combined actions. Refer text for all abbreviations. (Cu=Curcumin; Re= Resveratrol; Su= Sulforaphane; Gi=gingerol; D3= Vitamin D3).

derivatives, have significantly improved the compound's stability, potency, and selectivity, addressing many of these limitations. Recent developments in nanoformulations, liposomal systems, and chemically modified analogs, have demonstrated improved pharmacokinetic profiles, enhanced tumor targeting, and synergistic antitumor effects *in vitro* and *in vivo* [270]. The latest developments in the field of improving the effectiveness of resveratrol have been discussed in depth.

in the review paper of Ogedjo, et al. [268]. In an enriched review article, they have highlighted on various updated strategies towards responding to the poor bioavailability, rapid metabolism, and potential antagonism with ROS dependent therapies challenges of RSV. These include structural modification, nanocarrier-based delivery, prodrug design, alternative formulations, and rational combination therapies, and combinations with nutraceuticals are being employed. These approaches aim to maximize RSV's therapeutic index, improve patient outcomes, and bridge the gap between preclinical promise and clinical application. As a result, it is believed that, Resveratrol holds considerable promise for enhancing the effectiveness of existing treatments and potentially providing a novel, less toxic alternative in cancer care [269].

Sulforaphane

The dietary sources of sulforaphane include mainly the plants (especially cruciferous vegetables) of the genus Brassica such as broccoli, brussels sprouts, kale, and cauliflower [3]. As per a recent review, broccoli sprouts are the chief source of sulforaphane and are 20 to 50 times richer than mature broccoli as they contain 1,153 mg/100 g, whereas the concentration of sulforaphane in mature broccoli is 44–171 mg/100 g. Sulforaphane is significantly effective as it is readily available in blood because of its high bioavailability (80%). The higher bioavailability is due to its lighter molecular weight in comparison to other polyphenols [270-272]. Recently, the trend of nanoencapsulation of various bioactive components to gain maximum benefits is increased. Nanoencapsulation of sulforaphane using a triblock copolymer PCL-PEG-PCL, enhanced the ant-cancer effects more efficiently than the free sulforaphane in the *in vitro* and in *vivo* trial and can be used safely for effective and targeted sulforaphane delivery to cancerous cells [273]. A study made by Azarashkan et al. [274] on the effect of basil seed gum-encapsulated broccoli sprout extract disclosed that encapsulation helped in the controlled release of sulforaphane, which is more effective in the treatment of cancer than free sulforaphane. Encapsulation of sulforaphane in broccoli membrane vesicles (BM vesicles) in vitro analysis revealed that BM vesicles containing sulforaphane had high absorption and metabolism in cancerous cells and reduced cancer and its markers [275]. Asif et al. [276] in their recent review listed out several ongoing and completed clinical trials aim to investigate the chemoprotective and preventive effects of sulforaphane and concluded that there is still a need for further investigation on the sulforaphane cancer protective/preventive potential and mechanisms.

Considering everything together, the results of preclinical and clinical studies point to new therapeutic perspectives towards the possible development of new sulforaphane-based anticancer drugs [276].

Gingerol

Ginger has great potential for application as a bioactive ingredient in food, supplements, or pharmaceutical formulations. However, its widespread application as a bioactive is currently limited because of its relatively low water-solubility, stability, and bioavailability [277]. To overcome these barriers, innovative drug delivery systems are currently being developed to improve absorption and therapeutic efficacy of ginger bioactives. Jalali-Jivan et al. [278] and Joanna Szymczak et al. [279] in their latest review papers have given a comprehensive analysis on the latest developments in overcoming these challenges using well designed technologies currently available. Jalali-Jivan et al. [278] have discussed different technologies for encapsulating Ginger bioactive compounds including lipid-based, surfactant-based, and biopolymeric carriers. In addition, different equipment available for fabricating carriers of GBCs, including spray drying, spray chilling, electrospinning, homogenization, and crystallization have also been overviewed by them. While, Joanna Szymczak et al. [279] have discussed the chemical and biological properties, metabolism, and delivery systems for gingerols, shogaols, and ginger extracts (e.g., liposomes, transfersomes, transethosomes, phytosomes, solid lipid nanoparticles, and nanostructured lipid carriers), niosomes, emulsion-based systems (nanoemulsions and microemulsions), self-emulsified drug delivery systems, polymeric systems (such as polymeric nanoparticles and micelles), metallic nanoparticles, nanofibers, hydrogels, and cyclodextrin inclusion complexes, to increase the bioavailability and thus the biological activity of ginger polyphenols. Further they have pointed out in most cases, the use of drug delivery systems resulted in improvements in biological effects, such as selective cytotoxicity against cancer cell lines, and anti-inflammatory and anti-bacterial activities. The likelihood of synergistic effect benefits while combining these different delivery systems is also worth investigating to improve the efficacy of the existing system further [279].

Vitamin D3

As far as this nutrient is concerned, unlike other bioactive compounds, it is easily absorbed and also synthesised by the body and stored. It very easy way to keep the optimum requirement of this vitamin by taking vitamin D foods or by taking readily available D3 supplements. In general, the majority of disease-specific recommendations to date have set a lower limit of 75 nmol/L and an upper one of about 125 nmol/L for optimal 25(OH) D levels. [280].

Conclusion

Bioactive compounds of the functional foods, curcumin, resveratrol, sulforaphane, gingerol and vitamin D3 are found to be effective in inhibiting the pro-cancer activities of the HIF-1α by targeting its various regulatory pathways either individually or by synergistic actions. The HIF-1α being a master regulator of most of the cancer promoting genes, curtailing the activities of

this factor using the said bioactive compounds may be one of the effective therapeutic methods to be attempted for fighting against cancer. The other advantages of selecting and using the said functional food bioactive compounds as anti-cancer therapeutic agents are: (i) they are used as a part of our regular diets and have least side-effects (ii) they are all proved to be as effective anti-cancer agents by many scientific findings, (iii) All of them were underwent various clinical trials and their efficacies as anti-cancer agents have been tested, (iv) they are able to show their anti-cancer properties both individually and synergistically, (v) their bio-availabilities are being made increased by latest techniques so as to improve their efficacies (vi) they could be used both for preventing the origin of tumour and for treating developed cancer and (vii) cost-effective ant-cancer drugs could be produced using these bioactive compounds.

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