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Review article

Hispolon: A natural polyphenol and emerging cancer killer by multiple cellular signaling pathways



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ABSTRACT

Nature as an infinite treasure of chemotypes and pharmacophores will continue to play an imperative role in the drug discovery. Natural products (NPs) such as plant and fungal metabolites have emerged as leads in drug discovery during recent years due to their efficacy, safety and selectivity. The current review summarizes natural sources as well as pharmacological potential of hispolon which is a major constituent of traditional medicinal mushroom *Phellinus linteus*. The study aims to update the scientific community about recent developments of hispolon in the arena of natural drugs by providing insights into its present status in therapeutic pursuits. Hispolon, a polyphenol has been reported to possess anticancer, antidiabetic, antioxidant, antiviral and anti-inflammatory activities. It fights against cancer via induction of apoptosis, halting cell cycle and inhibition of metastasis by targeting various cellular signaling pathways including PI3K/Akt, MAPK and NF-κB. The current review proposes that hispolon provides a novel opportunity for pharmacological applications and its styrlypyrone carbon skeleton might serve as an attractive scaffold for drug development. However, future researches are recommended to assess bioavailability, toxicological limits, pharmacokinetic and pharmacodynamic profiles of hispolon, in order to establish its potential as a potent multi-targeted drug in the near future.

1. Introduction

Natural products (NPs) have recently regained prominence in the arena of drug discovery due to increasing recognition of their pharmacological significance, biological functions and structural diversity (Schmidt et al., 2007). The term “natural product” encompasses all the chemical compounds isolated from natural sources as fungi, plants and microorganisms (Rasul et al., 2013). Humans have been extensively relying on nature for the fulfillment of their basic needs including food, shelter and cure of a wide spectrum of diseases (Cragg and Newman, 2001). Over the three billion years, mother nature has refined her chemistry and after a long history of extensive research on nature, we are still only scratching the surface for analyzing nature's molecular

diversity (Cragg and Newman, 2013). Structural diversity is not the only reason but high selectivity, efficacy, specific biological activities, safety and cost effectiveness are additional features behind emerging significance of NPs in drug development (Kennedy et al., 2009; Veeresham, 2012).

Although synthetic medicines gained popularity due to stringent regulation, time effectiveness and easy quality control, however, their potency and safety are always unreliable which led to the ultimate dependence of populations on NPs (Veeresham, 2012). An analysis of drugs approved by FDA from 1981 to 2010 revealed that only 36% medicines were derived from synthetic molecules while more than half are either natural or derivative of NPs (Atanasov et al., 2015). The most exciting nature-derived medicines including paclitaxel (anticancer

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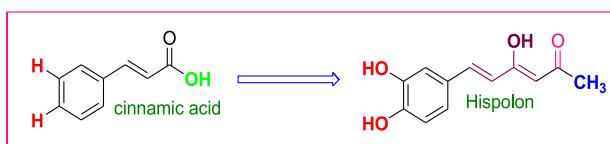


Fig. 1. Hispolon from cinnamic acid.

drug) derived from the leaves of *Taxus* species and artemisinin (anti-malarial drug) from *Artemisia annua* (L.) (Sarfraz et al. 2017). Folk medicine of European countries also uses fungus-derived medicinal substances to cure hepatitis, asthma and tumors. The fact that fungi could be a copious source of therapeutic molecules is affirmed from the discovery of penicillin (Sulkowska-Ziaja et al., 2005). Advanced screening approaches based on innovative biological and chemical strategies have led to the identification of potent fungal metabolites in the recent years (Schueffler and Anke, 2014).

Polyphenols are diverse group of naturally occurring compounds with high industrial and medicinal potential (Dos Santos et al., 2018). Mushrooms belonging to the genus *Phellinus* and *Inonotus* are identified as a good source of various polyphenolic compounds with a diverse pharmacological potential. Highly diverse and amply decorated mushroom-derived polyphenolic styrylpyrone scaffolds hold great promise for utilization in drug discovery (Lee and Yun, 2011). One such bioactive styrylpyrone polyphenolic entity present in several mushrooms is hispolon (Chethna et al., 2018a). Hispolon, a bioactive constituent of traditionally used medicinal mushrooms, exhibits a broad range of medicinal properties.

The current review aims to update the scientific research community about natural sources and pharmacological potential of hispolon. The literature was searched via several e-sites such as PubMed, Science Direct, Scopus and Elsevier. Keywords used for searching of data were “hispolon and anticancer”, “hispolon and anti-inflammatory”, “hispolon and antidiabetic”, and “natural sources of hispolon”.

1.1. Structure-activity relationship of hispolon and its derivatives

Basically hispolon is a natural bioactive compound similar to cinnamic acid derivative (by replacement of H with -OH groups at *meta* and *para*-position in aromatic ring and -OH by alkyl groups at the end of chain) as shown in Fig. 1 (Bisogno et al., 2007).

Structure-activity relationship (SAR) showed that the major factor responsible for greater activity of hispolon as compared to cinnamic acid is the -COCH₃ (Bisogno et al., 2007). Substitution of different groups in basic skeleton of hispolon especially in aromatic phenyl ring played an excellent role in enhancing the biological activity. For example placement of methoxy group (-OCH₃) in phenyl ring increase the cytotoxicity but in comparison, the presence of hydroxyl (-OH) group decrease the cytotoxicity and this has been supposed to be due to greater lipicity of methoxy (-OCH₃) as compared to hydroxyl (OH) (Bisogno et al., 2007; Gaoa et al., 2018; Rossia et al., 2019). Moreover, it has been observed that the position of substitution on hispolon skeleton also played a crucial role in enhancing its activity as shown in Fig. 2. It has been observed that gingerdione and its analogues showed a clear difference in their activity affected by substituents in phenyl ring and its terminal part. For example, gingerdione has 10% sweetness as compared to its dehydro-derivative (Rasul et al., 2013), -dehydrogingerdione that has 15% sweetness. Similar behavior has also observed in other gingerdione derivatives (Fig. 2). It means that unsaturation or olefinic double bond and aromatic ring are very important in enhancing the activity (Gaoa et al., 2018; Ley et al., 2019).

DFT (density-functional theory) and docking studies displayed that the different types of alkyl groups in alcoholic moiety of hispolon and its analogues has a great influence on the increment of activity as an electron-donating moieties including -OME, -OH, -OAc increased the activity as compared to electron-withdrawing group as shown in Figs. 2 and 3 (Rossia et al., 2019; Weia et al., 2020). These groups have different influences on activity as calculated by DFT. Introduction of the ester group raise the activity initially but at a specific length of alkyl chain in ester group has decrease effect. With the increase of alkyl chain in place

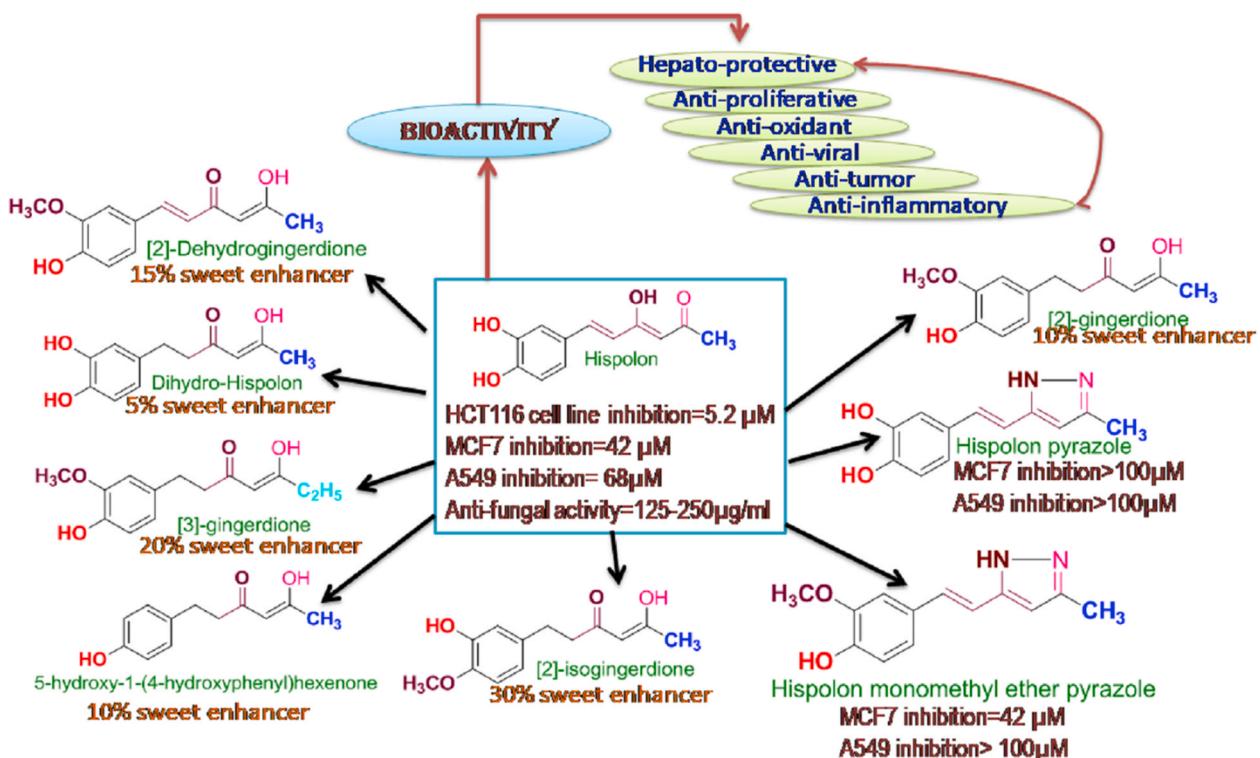


Fig. 2. Structure-Activity relationship (SAR) of hispolon and its analogues.

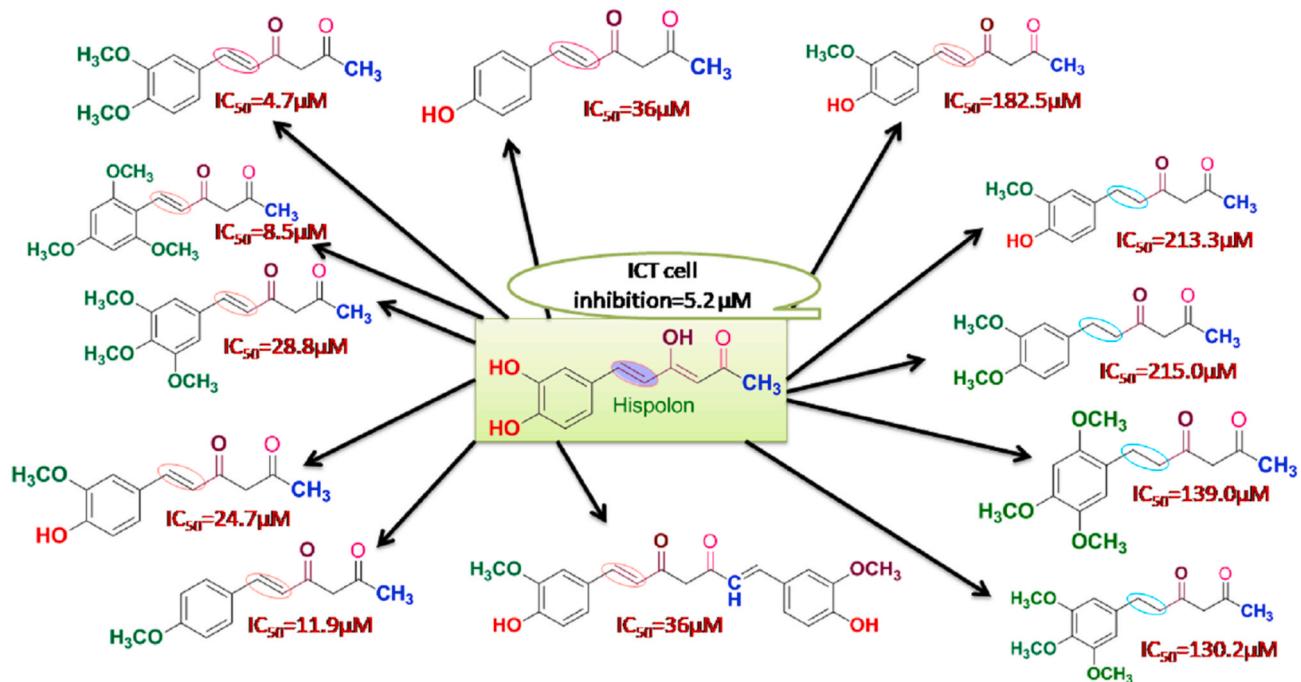


Fig. 3. Effect of substitution on activity of hispolon and derivatives.



Fig. 4. Illustration of natural sources of hispolon.

of -OMe, -OH or -OAc reduce the activity by enhancing non-polar and less polar effect as compared to methoxy, hydroxyl and acetate group (Figs. 2 and 3) (Zhou et al., 2017). Additionally, SAR studies displayed that the tertiary alkyl groups showed greater activity as compared to linear alkyl groups due to the stearic hindrance that leads to improve the activity. Similarly, phenyl substitution enhances the activity while cyclohexyl decreases the activity. Similarly, by comparison of benzyl

group and simple alkyl group, it has been observed that the benzyl group increases the activity more than a simple alkyl group (Chethna et al., 2018b; Weia et al., 2020).

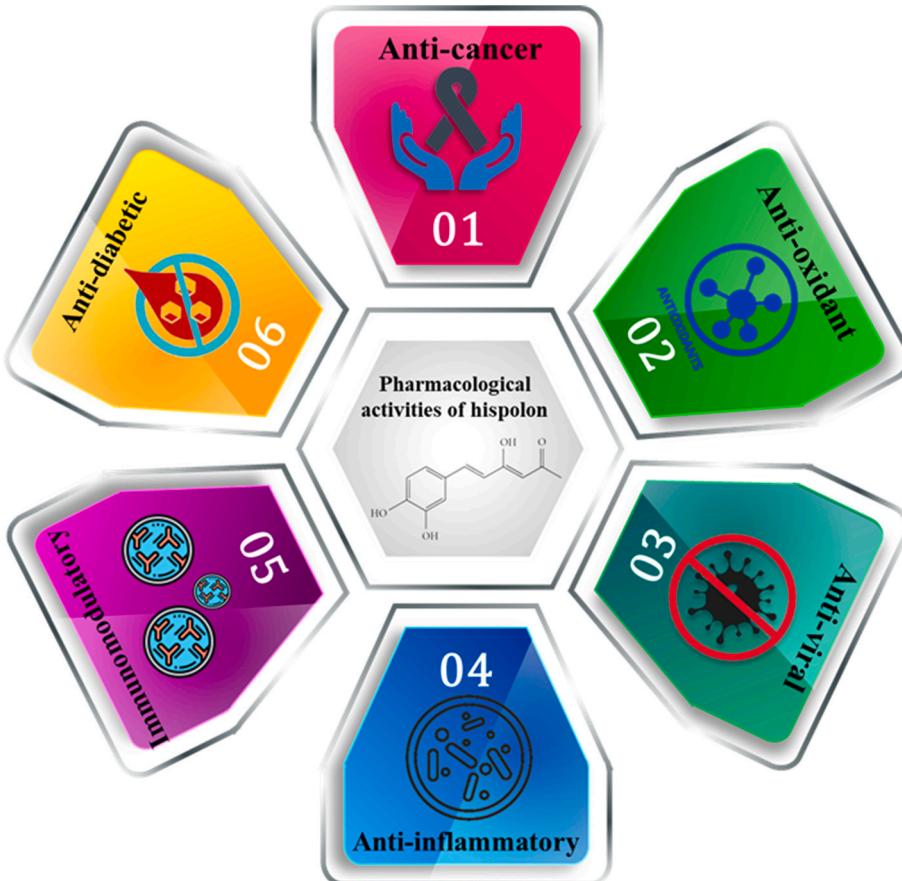
2. Natural sources of hispolon

The nature-derived pharmacologically active polyphenol, hispolon is

Table 1

Natural sources of hispolon, their biological activities.

Source	Common name	Parts used	Biological activities	Yield	References
<i>Phellinus</i> <i>linteus</i>	Black hoof mushroom	Fruiting body, mycelium	Anticancer, anti-inflammatory, immunomodulatory, antioxidant, antifungal antidiabetic, hepatoprotective, neuroprotective	0.1629 mg/g of dried mushroom powder (95% ethanol, 6 h extraction time)	(Sliva, 2010; Toopmuanga et al., 2014; Chen et al., 2019)
<i>Phellinus</i> <i>igniarius</i>	Willow bracket mushroom	Fruiting body	Antitumor, anti-oxidative, anti-inflammatory	–	(Kim et al., 2015; Suabjakyong et al., 2015)
<i>Inonotus</i> <i>hispidus</i>	Shaggy bracket mushroom	Fruiting body	Antimicrobial, antiviral, antioxidant, anti- inflammatory, immunomodulatory, antiproliferative	0.06% (60 mg/1 g EtOAc extract)	(An and Jia, 1987; Ali et al., 1996)
<i>Phellinus</i> <i>merrillii</i>	Sangwhang	Fruiting body	Hepatoprotective and antioxidant	–	(Chang et al., 2007; Huang et al., 2011a)
<i>Phellinus</i> <i>lonicerinus</i>	–	Fruiting body	Anti-tumor, anti-proliferation	–	Wang et al. (2014)

**Fig. 5.** Illustration of major biological activities of hispolon.

a yellow colored compound. It was firstly isolated in 1996 from *Inonotus hispidus* (Ali et al., 1996). Hispolon has also been isolated from various species of *Phellinus* genus (Fig. 4) such as *Phellinus* *linteus* (Lu et al., 2009; Paul et al., 2019), *Phellinus* *igniarius* (Mo et al., 2004), *Phellinus* *lonicerinus* (Wang et al., 2014) and *Phellinus* *merrillii* (Chang et al., 2007). Table 1 presents yield of hispolon from natural sources and their pharmacological properties.

3. Biological activities of hispolon

The bioactive natural compound, hispolon, has been reported to possess pharmacological activities such as anti-oxidant (Chen et al., 2014), anti-tumor (Hsin et al., 2017), antiviral (Awadh Ali et al., 2003), anti-inflammatory (Ravindran et al., 2010), hepatoprotective (Chang et al., 2007), immunomodulatory (Grundemann et al., 2016) and anti-diabetic (Chen et al., 2013). Fig. 5 presents the various

pharmacological activities of hispolon.

3.1. Anticancer activity

Cancer is a multi-factorial disease caused by genetic alterations as well as environmental factors which coordinately trigger neoplastic transformations via activation of oncogenes or inactivation of tumor suppressor genes (Khan et al., 2016). Current treatment opportunities for this deadly disease include chemotherapy which often exhibits high toxicity and low tumor specificity (Schirrmacher, 2019). Poor efficacy and non-selectivity of chemotherapeutics is a matter of great concern from several years (Huang et al., 2017). In this context, naturally occurring bioactive compounds are becoming a novel source for drug discovery against cancer due to their selectivity, safety and cost effectiveness (Huang et al., 2017).

From 136 approved drugs against cancer during 1981–2014, only

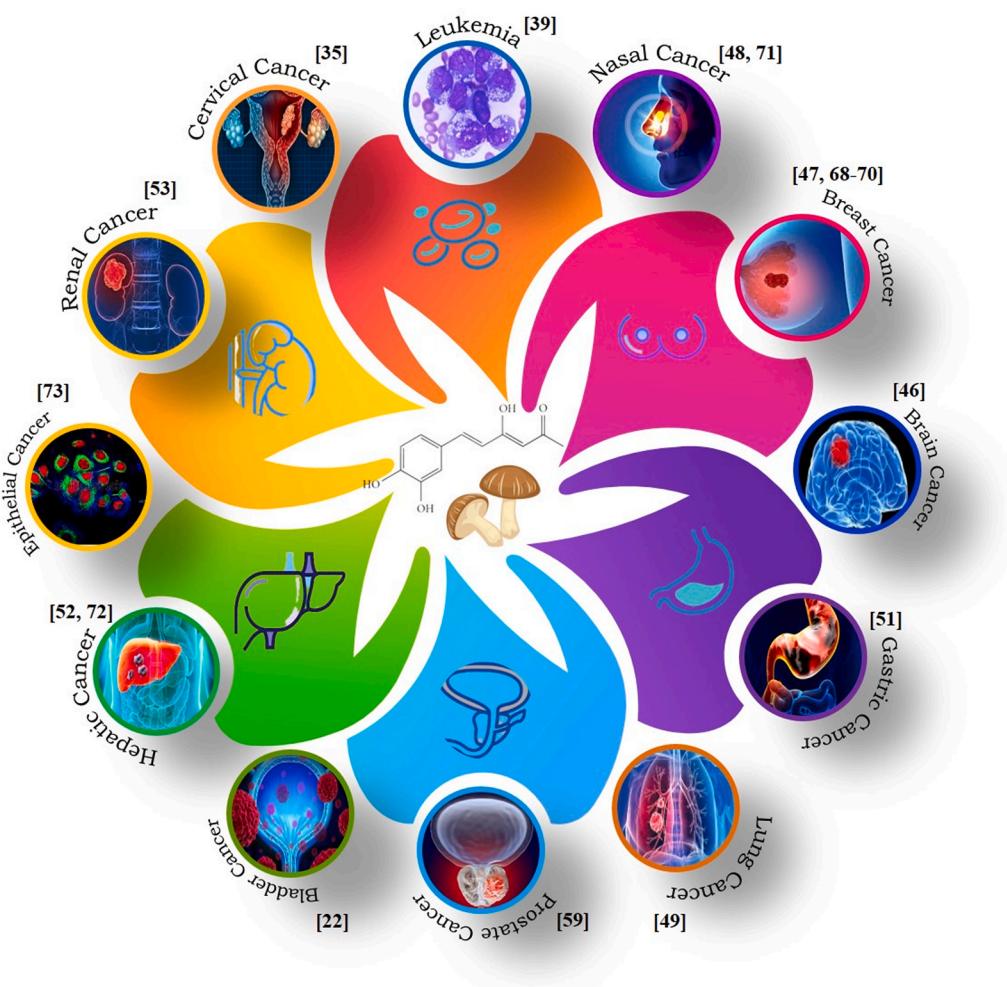


Fig. 6. Anticancer potential of hispolon against various types of cancer.

17% were of synthetic origin while 83% of these drugs were derived from natural compounds or based on natural scaffolds (Demain and Vaishnav, 2011). Several natural compounds such as taxols, brassinosteroids and polyphenols possess high efficacy to fight various cancers (Greenwell and Rahman, 2015). Polyphenols are significantly abundant in dietary foods and their contribution in the prevention of cardiovascular diseases and cancer is emerging now a days (Manach et al., 2004).

Hispolon has been affirmed to possess antiproliferative activity against U87MG (glioblastoma) (Arcella et al., 2017), HeLa, SiHa (cervical cancer) (Hsin et al., 2017), MCF-7, MDA-MB-231 (breast carcinoma) (Wang et al., 2017), NPC-39, HONE-1, NPC-BM, NPC-039 (nasopharyngeal cancer) (Ho et al., 2017), A549, H661 (lung cancer) (Wu et al., 2014), DU145, LNCaP, PC3 (prostate cancer) (49318940), MV4-11, HL-60, U937, THP-1 (leukemia) (Hsiao et al., 2013), SGC-7901, MKN-45, MGC-803 (gastric cancer) (Chen et al., 2008), T24, J82 (bladder cancer) (Lu et al., 2009), Hep3B, SK-Hep1 (hepatocellular carcinoma) (Huang et al., 2011b), TCMK-1 (renal cancer) (Yun et al., 2019) and KB (human epidermoid) (Chen et al., 2006) cancer cells. The anticancer efficacy of hispolon against several cancers types is shown in Fig. 6.

3.1.1. Hispolon and cell cycle arrest

Cell cycle is an extremely controlled process involving complex cascade of events and dysregulation of this control leads to the development of cancer (Bailon-Moscoso et al., 2017). Cell cycle progression is under control of regulatory proteins such as cyclins, CDKs (cyclin-dependent kinases) and tumor suppressor genes such as p53 (Sanchez and

Dynlacht, 2005; Wang et al., 2015). Nature-derived bioactive compounds have promising ability to modulate the expression of various cyclins, CDKs and CDK inhibitors (CKIs), thus, halting proliferation in human cancers (Johansson and Persson, 2008).

Hispolon has potential to halt cell cycle in several cancer cells at G0/G1 and G2/M phase. In the human NB4 (promyelocytic leukemia) cells, hispolon caused cell cycle arrest at G0/G1 with a marked reduction in CDK4, CDK2, cyclin E and cyclin D1 levels (Chen et al., 2013). Hispolon induced G2/M arrest and inhibited the cell viability of glioblastoma U87MG cells by increasing the level of CDK inhibitor, p21 (Arcella et al., 2017). Down-regulation of cyclins A and E contributed towards hispolon-stimulated S phase arrest with up-regulation of p27kip1 and p21waf1/Cip1 expression in Hep3B cells (Huang et al., 2011b). Hispolon has also been reported to induce S phase arrest in DU145 cells by downregulating cyclin B1, cyclin D1 and CDK4 (Masood et al., 2019). The distribution of hispolon treated lung cancer cells (A549 and H661) in different phase of cell cycle showed that hispolon treatment increased the accumulations of these cells in G0/G1 phase (Wu et al., 2014). However, there is lack of evidences about phase specific cell cycle inhibitory potential of hispolon in various cancers such as whether hispolon halted cell cycle at G2, M, G0 or G1 phase which needs to be investigated in future studies.

3.1.2. Hispolon and apoptosis

Apoptosis is a highly systemized mode of cell death that is characterized by energy-dependent biochemical events and distinct morphological characteristics (Elmore, 2007). Defective apoptotic pathways have critical

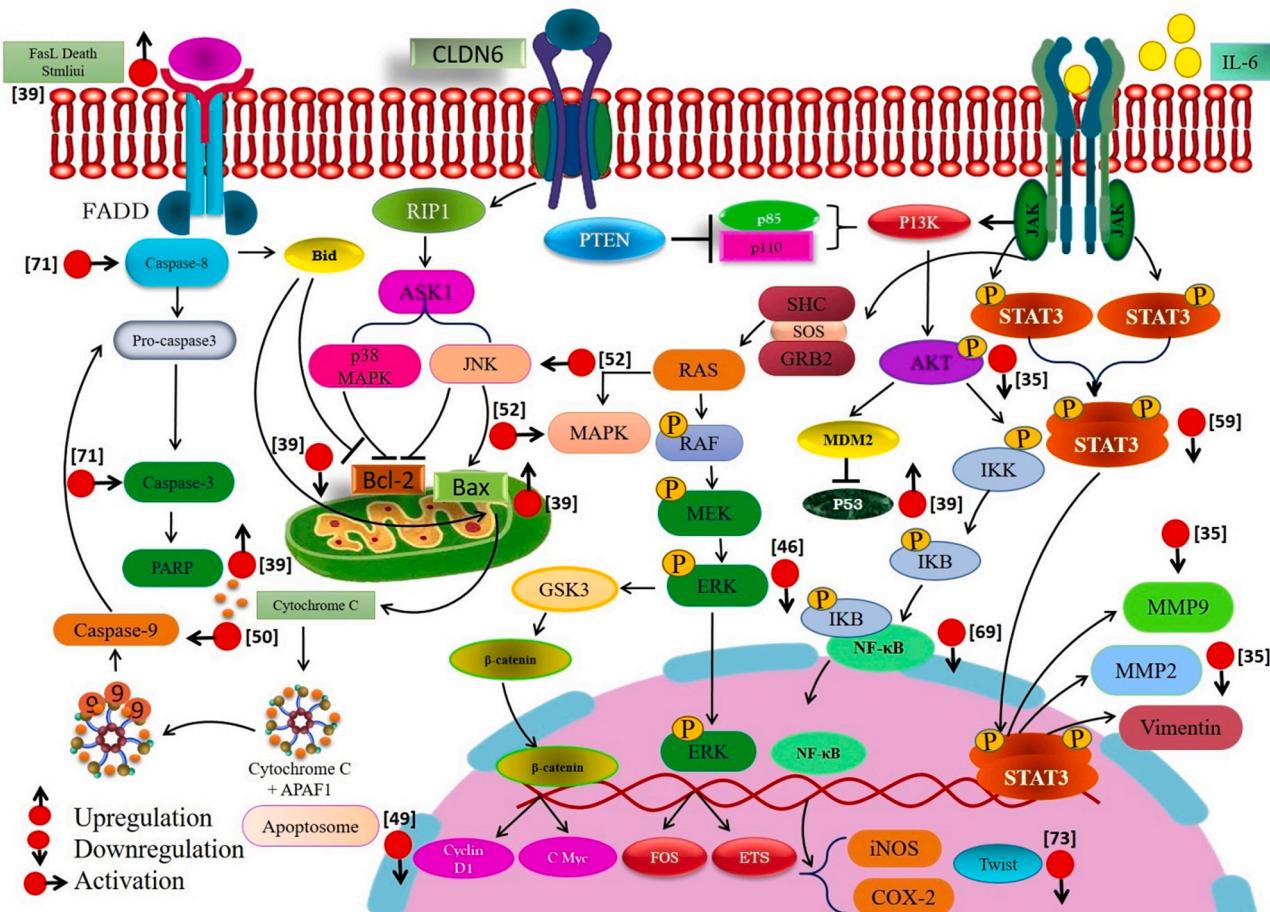


Fig. 7. Diagrammatic representation of hispolon's anticancer mechanism of action. Hispolon targets various nuclear, cytoplasmic and membranous proteins to induce apoptosis, halt metastasis and cell cycle in several cancer types.

role in the onset and pathogenesis of cancer, thus, induction of apoptosis is a feasible and targeted treatment in various types of cancer (Wong, 2011). The two majorly described apoptotic pathways are extrinsic/death receptor pathways and intrinsic/mitochondrial-mediated pathway (Baig et al., 2016). Extrinsic cellular pathway is characterized by the activation of death signalling ligands such as Fas-L (Fas ligand) (Jan and Chaudhry, 2019). The intrinsic pathway is mediated by Bcl-2 (B-cell lymphoma 2) family members such as activation of mitochondrial membrane bounded Bax (Bcl2-associated X protein) and inactivation of Bcl-2 stimulate the discharge of cytochrome c which in turn activates initiator and effector caspases to induce the apoptosis (Loreto et al., 2014).

Natural bioactive compounds induce the activation of apoptotic pathways in cancer cells (Safarzadeh et al., 2014). Hispolon, an active polyphenolic compound sensitizes cancer cells to trail by activating caspase-3, -8 and -9, reducing Bcl-2, Bcl-xL while upregulating Bax protein (Kim et al., 2016). In DU145 cells, hispolon modulates Bcl-2 family proteins leading towards the discharge of cytochrome c that ultimately triggers the cascade of caspases (Fig. 7) (Masood et al., 2019). Anticancer efficacy of hispolon is linked with the upregulation of Fas and Fas ligand that stimulates extrinsic apoptotic pathway (Chen et al., 2013; Hsieh et al., 2018). Molecular targets of hispolon, model cell lines used in experimentation, IC₅₀ and treatment conditions are presented in Table 2.

3.1.2.1. Hispolon and NF-κB (nuclear factor-κB) signaling pathway. NF-κB, family of transcriptional factors serve as master regulators of immune and inflammatory processes (Napetschnig and Wu, 2013). This five membered family is identified as a crucial player in many games of

cancer progression (Hoesel and Schmid, 2013). An inhibitor protein known as IκB interacts with NF-κB in cytoplasm to control the translocation and subsequent activity of NF-κB. Activation of NF-κB and its translocation towards nucleus is controlled by IκB phosphorylation and degradation. Once in the nucleus, NF-κB binds to target DNA and induce transcriptional activation of various genes involved in cell growth and inflammation, thus, playing an imperative role in cancer and inflammatory disorders (Baldwin, 1996). In tumor cells, NF-κB is found to be constitutively activated and its suppression leads to tumor regression (Xia et al., 2014).

Hispolon reduced the phosphorylation of IκBα which suppressed the translocation of NF-κB towards nucleus. Inhibition of NF-κB translocation down-regulated the expression of its down-stream encoded protein, MMP-9 (matrix metalloproteinase-9) which reduced the invasive capabilities of MDA-MB231 cells (Sun et al., 2015). Although inhibition of IκB has been reported as a possible mechanism of hispolon induced NF-κB inhibition, however the alteration in phosphorylation of p65 or p50 subunits by hispolon to deactivate NF-κB translocation needs to be investigated.

3.1.2.2. Hispolon, MAPK and PI3K/Akt signaling pathways. The MAPKs (mitogen activated protein kinases) mediate several cellular activities involved in the cancer progression such as evading apoptosis, inducing proliferation and immune escape (Cargnello and Roux, 2011; Peluso et al., 2019). MAPK family includes following members: c-Jun N terminal kinase (JNK), ERK (extracellular signal-regulated kinase) and the p38 MAPK (Soares-Silva et al., 2016). Phosphatidylinositol 3-kinase (PI3K)/Akt is one of the most important intracellular pathway that

Table 2
Molecular targets of hispolon in various cancer types.

Cancer type	Cell line	No. of cells/well	Treatment time	IC ₅₀	Molecular targets	Cell cycle arrest	References
Glioblastoma	U87/MG	1 × 10 ⁴	24, 48, 72 h	—	Cyclin D4↑, p21↑, p53↑; CDK4↑, p-ERK 1/1	G2/M	Arcella et al. (2017)
Cervical Breast	HeLa, SiHa MCF-7, T47D, MDA-MB-231	7 × 10 ⁴ 5 × 10 ³ , 5 × 10 ⁴	24 h 24 h	— 70 Mm	p-AKT1, ERK ^{Act} , IC3-II↑, MMP-2/1, MMP-9↓ ERK1, PARP↑, Bcl-2↓, E-cadherin↓, MMP-9↓, p-IκBα [↓] , p-NF-κB [↓]	—	Hsin et al. (2017); Jiang et al. (2015); Sun et al. (2015); Zhao et al. (2016); Wang et al. (2017)
Naso-pharyngeal	HONE-1, NPC-39, NPC-BM, NPC-039	5 × 10 ⁴	—	—	p-Akt [↓] , uPA [↓] , MMP-2/1, MMP-9↓, caspase-3 ^{Act} , caspase-8 ^{Act} , caspase-9 ^{Act}	—	(Hsieh et al., 2014; Ho et al., 2017)
Lung	A549, H661	1 × 10 ⁴	24, 48, 72 h	35.9 ± 6.9, 28.8 ± 3.1, 8.1 ± 2.3 μM	Cyclin D1↑, CDK2/1, CDK4/1, cyclin E1, CDK6/1, p27↑, p21↑ cyclin B1, cyclin D1, CDK4/1, p21↑, p-STAT3↓ Fast↑, FasL↑, Bcl-2↑, PARP↑, caspase-9↑, Bax↑, caspase-3↑ p53↑, p27↑, p21↑, CDK2/1, CDK4/1, cyclin E1, cyclin D1, Caspase-3 ^{Act} , caspase-8 ^{Act} , caspase-9 ^{Act} , PARP↑	G0/G1 S phase G0/G1	Wu et al. (2014); Masood et al. (2019); Chen et al. (2013)
Prostate Leukemia	DU145, LNCap, PC3 NB4, OCL-AML3	— 1 × 10 ⁴	— 12, 24, 48 h	25 Mm	cyclin B1, cyclin D1, CDK4/1, p21↑, Bcl-2↑, caspase-3↑ p53↑, p27↑, p21↑, CDK2/1, CDK4/1, cyclin E1, cyclin D1, Caspase-3 ^{Act} , caspase-8 ^{Act} , caspase-9 ^{Act} , Bax↑, Bcl-2↑, Bcl-xL↓, ROS↑	—	Hsiao et al. (2013); Chen et al. (2008)
Acute myeloid Leukemia	MOLM-13, HL-60, MV4-11, U937, THP-1	1 × 10 ⁵	24 h	15.6, 11.4, 7.5 μg/mL	Caspase-3 ^{Act} , caspase-9 ^{Act} , Bax↑, Bcl-2↑, Bcl-xL↓, ROS↑	—	—
Gastric	SGC-7901, MGCG-803, MKN-45	—	—	—	—	—	—
Bladder	T24, J82	2 × 10 ⁴	—	10 μg/mL, 40 ng/mL	p-21↑	G2/M	Iu et al. (2009)
Hepatocellular	Hep3B, SK-Hep1	2 × 10 ⁵	24 h	—	cyclin A1, cyclin E1, CDK2/1, JNK ^{Act} , p38 MAPK ^{Act} , MMP-2/1, MMP-9↓, uPA↑, FAK↑, Snail↓, Twist↓, TRAIL↑	S phase	(Huang et al., 2010, 2011b; Hsieh et al., 2010b; Huang et al., 2011b)
Epithelial	TCMK-1	1 × 10 ⁴	24 h	—	—	—	Hong et al. (2017)
Renal	Human Epidermoid	5 × 10 ³	—	4.62 ± 0.16 μg/mL	Caspase-3 ^{Act}	—	Yun et al. (2019); Chen et al. (2006)

Cyclin dependent kinase 4 (CDK4); Protein kinase B (Akt); lightchain 3 (LC3); matrix metalloproteinase (MMP); poly-ADP ribose polymerase (PARP); Fas ligand (FasL); Mitogen activated protein kinase (MAPK); Reactive oxygen species (ROS); Zinc finger protein SNAI1 (Snail); TNF-related apoptosis-inducing ligand (TRAIL); Focal adhesion kinase (FAK).

perform several important roles in proliferation, cell growth and survival which makes it an attractive target for cancer therapy (Yang et al., 2019).

Polyphenols have been known for their potential of targeting protein kinases *via* interacting with the ATP-binding sites (Guerra and Issinger, 2019). Hispolon inhibited NPC cell metastasis by downregulating Akt signaling pathway (Ho et al., 2017). Hispolon treatment leads toward increased phosphorylation of p38 MAPK, JNK and ERK1/2 in HONE-1 and NPC-039 cells (Hsieh et al., 2018).

3.1.3. Anti-metastatic effects of hispolon

Metastasis is a primary cause of mortalities and most complicated obstacle in the development of effective cancer therapies (Zhao et al., 2016). Metastasis is characterized by four important steps: detachment, migration and adhesion of cancer cells to secondary sites. Cancer cell motility, extracellular matrix degradation, angiogenesis and epithelial mesenchymal transition (EMT) serve as initiating factors for metastatic transformations (Guan, 2015). Thus, targeting metastatic niche, EMT and other metastasis initiating factors could lead towards successful cancer therapies (Yoo et al., 2018).

Hispolon treatment inhibited the invasive capabilities of HeLa and SiHa cells *via* blocking ERK pathway (Hsin et al., 2017). Hispolon exerts anti-metastatic effects by the inhibition of uPA (Urokinase plasminogen activator) *via* the Akt pathway in nasopharyngeal cancer cells (Ho et al., 2017). By reducing the expression of MMP-2, MMP-9 and uPA, hispolon inhibited the metastasis in SK-Hep1 cells (Huang et al., 2010). Furthermore, hispolon suppresses invasive potential of cancer cells *via* EMT inhibition. Therefore, hispolon may be a novel anti-metastatic agent (Hong et al., 2017). As EMT has close association with drug resistance, further studies should also investigate whether hispolon has potential to sensitize cancer cells towards chemo-drugs.

3.2. Antioxidant activity

Overproduced ROS (reactive oxygen species) and free radicals cause DNA damage, induce mutations, impair proteins and react with membranes that serve as predisposing factor for age-related diseases and cancer (Khansari et al., 2009). Antioxidants derived from mushrooms, cereals, spices, vegetables and traditional medicinal herbs exhibit a broad range of biological activities such as anticancer, anti-aging and anti-inflammatory (Zhang et al., 2015; Xu et al., 2017). Therefore, antioxidants could save human body from the harmful effects of free radicals by scavenging and neutralizing powers. Hispolon isolated from *Inonotus hispidius* shows a strong antioxidant activity (Venkateswarlu et al., 2010). Recently, hispolon and its derivatives have also been reported to exhibit ROS scavenging activities in cell-free systems (Chethna et al., 2018a), affirming its potential as antioxidant agent.

3.3. Antiviral activity

The emergence and re-emergence of viral epidemics arouses the urgent need to develop effective anti-viral therapeutics (De Clercq, 2004). In addition, viruses also contribute to 15% of the total human cancers (Liao, 2006). In this context, nature-derived agents have potential to prevent and treat viral infections (Sencanski et al., 2015). It has been reported that hispolon exhibits significant anti-viral activity (Chen et al., 2008; Yang et al., 2014). Hispolon, isolated from ethanolic extracts of *Inonotus hispidus* fruiting bodies, showed potent anti-viral activity against influenza virus A and B (Awadh Ali et al., 2003). Thus, the antiviral activity of this phenolic compound recommends that its efficacy against other viruses such as coronaviruses should also be investigated.

3.4. Anti-inflammatory activity

Inflammation is a response of the body defense system against

infections and tissue damage (Punchard et al., 2004). Adverse effects associated with non-steroidal anti-inflammatory drugs (NSAIDs) arouse the need to develop safe alternatives for the treatment of chronic inflammations (Sostres et al., 2010). Hispolon induces potent anti-inflammatory response by suppressing TNF- α (tumor necrosis factor- α) (Lin et al., 2014), and decreasing MMP-9 via inhibition of NF- κ B pathway (Sun et al., 2015). Anti-inflammatory actions of hispolon occur via inhibition of JNK phosphorylation (Yang et al., 2014). Hispolon possesses inhibitory activity against LPS-induced inflammation via inhibiting JNK and NF- κ B while upregulating HO-1 (Heme oxygenase-1) protein in BV-2 cells (Wu et al., 2017).

3.5. Antidiabetic activity

Diabetes mellitus is characterized by hyperglycemia which is caused by defects in insulin secretion, its action or both (Kharroubi and Darwish, 2015). Alpha-glucosidase and aldose reductase are emerging metabolic targets for the treatment of patients with impaired glucose tolerance and diabetes (Grewal et al., 2016). Herbal medicines have a long history for the treatment of diabetes as compared to conventional medicine (Choudhury et al., 2018). Hispolon, a natural polyphenolic compound possesses strong antidiabetic properties (Chen et al., 2013). Hispolon exhibited potent activity against α -glucosidase ($IC_{50} = 12.38 \mu\text{g/mL}$) and aldose reductase ($IC_{50} = 9.47 \mu\text{g/mL}$). These findings suggest that hispolon might serve as an attractive scaffold for anti-diabetic drugs (Huang et al., 2011a).

4. Conclusions

Conclusively, hispolon is a smaller molecule with greater potential and more cell specificity. Since its first isolation in 1996 till now its cytotoxic potential against thirteen different types of cancers has been reported. As more than 200 types of cancers are known, thus, its efficacy against other cancers should also be investigated. Critical analysis of IC_{50} of hispolon against cancers revealed that it possess very good efficacy against breast cancer, suggesting that further studies should be conducted to validate its potential against breast cancer. Hispolon targets multiple pathways including PI3K/Akt, MAPK and NF- κ B in cancer cells to induce apoptosis and reduce their metastatic capabilities. Regarding the disease complexity, cancer is more likely to be alleviated or healed though simultaneous modulation of multiple targets, in this context hispolon might emerge as an attractive scaffold for the development of a multitargeted anticancer drug. The reported data suggests that hispolon possess significant efficacy as well as safety for its pharmacological applications. Thus, it would be worthwhile to conduct further studies to determine the bioavailability, toxicological limits and ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) profile of hispolon to fill the room of knowledge for its validation as a potential anticancer agent.

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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