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Review Article

Biological Activities of Hispolon

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Abstract

Natural products are a great source for the discovery of new chemotherapeutic agents. Phenolic compounds are significant natural products, mostly from the source of microorganisms and plants. Among fungi, mushrooms are not only the source of nutrients but also many bioactive components. In this paper, the authors made a comprehensive review of the biological activities of hispolon. The biological activities like anticancer, antioxidant, anti-inflammatory, and antimicrobial are possessed by hispolon. Along with anti-tuberculosis properties, hispolon exhibited effectiveness in the treatment of metabolic disorders and functional as immunomodulators.

Keywords: Hispolon; Anticancer; Antioxidant; Anti-inflammatory; Antibacterial; Antitubercular.

Introduction

Natural products (NP) provide a wide range of sources in drug discovery and offer a key role in the therapeutics of different diseases. With structural diversity and a wide range of biological purposes, NP gained momentum in different industries including the pharmaceutical sector. Since ancient days, humans have had faith in nature for the healing of many diseases. Great history of research with nature revealed many diverse sets of molecules. Still a majority of unknown facts about natural products looking for answers. Many NP are known to have huge diversity in structure, and also highly effective in biological functions, minimally toxic, and are less expensive[1]. The safety profile of synthetic drugs always prompted to depend on NP. A statistical examination of drugs agreed by US-FDA from 1980-2010 exposed that only a quarter portion was from a synthetic source, and the majority are from natural or derivatives of NP[2]. After the discovery of penicillin, the thrive of the fungal metabolites increased over the years.

Phenolic compounds are important natural products, mainly from the source of microorganisms and plants. Mushrooms are not only the source of nutrients but also for many bioactive components. Certain species of genus *Phellinus* and *Inonotus* were demonstrated are the rich basis of different polyphenolic compounds with broad biological potential. A varied polyphenolicstyrylpyrone scaffolds from *Phellinus* and *Inonotus* showed pronounced potential for use in the discovery of drugs[3]. Hispolons are such bioactive styrylpyrone analogs exists in some mushrooms[4]. Over the decade, hispolon stands for its wide range of biological properties. Ali *et al.*[5] isolated hispolon and hispidin from fruit bodies of a mushroom, *Inonotus hispidus* (Bull. ex Fr.) Karst. The isolation of hispolon from *I. hispidus* was illustrated in **Figure 1**.

Hispolon is similar to a cinnamic acid derivative with -OH groups at *meta*- and *para*-positions in the aromatic ring and –OH by alkyl groups at the end of the chain as illustrated in figure 2, besides cinnamic acid hispolon was also structurally analogous to curcumin. Hispolon is a yellow pigment compound and exhibited distinctive physicochemical properties (**Table 1**). Different species of the Phellinus genus such as *Phellinus Ignatius*[6], *Phellinus merrillii*[7], *Phellinus lonicerinus*[8], and *Phellinus linteus*[9,10] are the natural source of hispolon (**Table 2**).

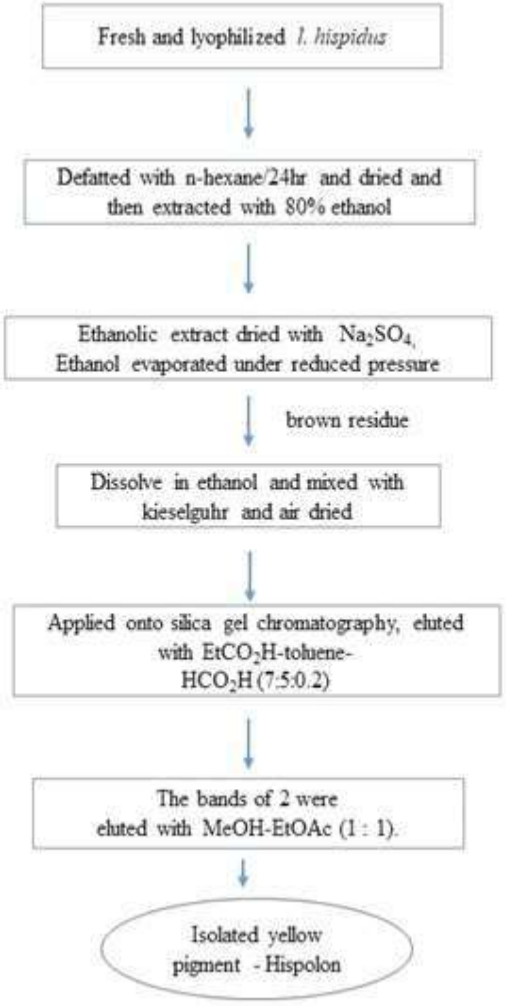


Figure 1: Isolation of hispolon from the fruit bodies of *I. hispidus*[5]

Table 1: Physicochemical properties of hispolon

Physical State	Solid
Color	Yellow
Solubility	DMSO
Melting point	155.65 °C
Boiling point	~477.21 °C at 760 mmHg
Density	~1.3 g/cm^3
pKa	8.35

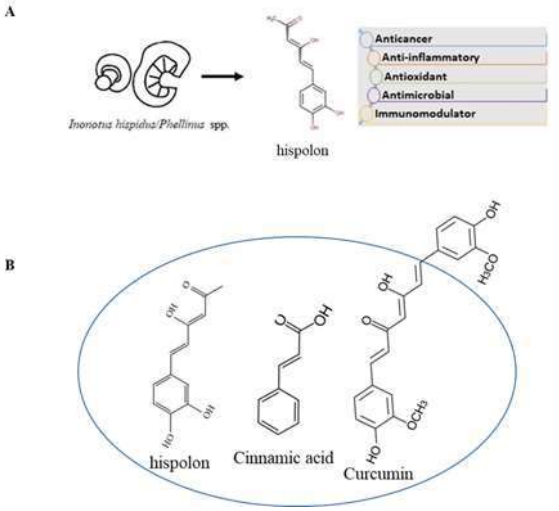


Figure 2: A. Hispolon from the species of certain mushrooms, and their biological activities, B. Structural relationship of hispolon with cinnamic acid and curcumin

Biological activities of hispolon

Anticancer

Naturally, occurring polyphenols are the best source for the discovery of novel drugs against different type's cancers. Polyphenols are present abundantly in dietary foods and other natural sources, and these natural compounds are more selective to cancer cells and less toxic to normal tissues. Hispolon is the potential inhibitor of metastatic properties like invasion and migration of cancer cells[11], downregulated the matrix metalloproteinase like MMP-2 and 9 further repressed the phosphorylation of PI3K/Akt, ERK1/2, and FAK. Hsiao *et al*[12] studied the anticancer effects of hispolon in acute myeloid leukemia (AML), and proved that hispolon efficiently caused apoptosis by the inhibition of caspases 3 and 9 expressions and PARP cleavage. Hispolon exhibited apoptotic effect in leukemia cells by arresting G0/G1-phase, which was linked to downregulation of p53 and cell cycle checkpoints like cyclin-dependent kinases, cyclins D1 and E, which in turn enhanced the expression of p27Kip1 and p21waf1/Cip1[13,14]. Hispolon has the potentiality to cure melanoma and hyper pigmentation by the over expression of apoptotic markers like caspase 3 and 9[15]. Hispolon might be helpful in the treatment of the estrogen shortage-

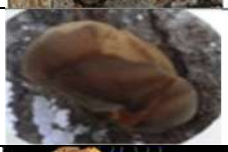
linked disease with antitumor effects and estrogenic agonist activity, moreover non-toxic to the normal cells[16].

Balaji *et al*[17] synthesized hispolon and 26 analogs assessed for their *in vitro* anticancer activities in a set of human cancer cell lines. Hispolon has modulated the ERα expression and inhibited its transcriptional activity, and exhibited anticancer activities on breast cancer cells. It could be a potential chemotherapeutic agent for human breast cancer management[18]. Metastatic properties like migration and invasion in breast cancer were greatly inhibited by hispolon at non-toxic concentrations and suppressed the release of matrix metalloproteinase-9 (MMP-9). Moreover, it suppressed the nuclear translocation of p65 phosphorylation and nuclear factor-κB (NF-κB)[19].

Additionally, hispolon repressed the metastatic ability of breast cancer cells via abrogating the E-cadherin pathway and may be advanced as a possible anti-metastatic agent to cure breast cancer[20]. Hispolon enhanced the susceptibility of cancer cells to the treatment of tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) by upregulating the apoptotic biomarkers such as Bax, caspase-3,8, and 9 and further suppressing the cell survival genes Bcl-xL and Bcl-2[21]. Hispolon has elevated the death receptors via p53-independent but connected to the initiation of CAAT enhancer-binding protein homologous protein (CHOP). Hispolon was well studied for its anti-metastatic properties, it prevented the invasion and migration of human nasopharyngeal carcinoma cells by suppressing the urokinase-plasminogen activator by the regulation of the Akt pathway[22].

Phytoestrogen is well known for hormone replacement therapy in many cases of breast cancers, during these hormone-dependent breast cancer therapies hispolon could be a good option due to its phyto-estrogenic properties[23]. Hispolon inhibits the proliferation of glioblastoma cells (U87MG), blocks the cell cycle at G2/M, and induces apoptosis through the upregulation of p53[24]. Hispolon were exhibited anti-metastatic potential towards cervical cancers and inhibited the expression of lysosomal protease Cathepsins which indeed crucial for the suppression of tumor cell metastasis. Moreover, hispolon enhanced the formation of acidic vesicular organelle and further autophagy[25]. Additionally, hispolon was also implicated in the abrogation of Epithelial-mesenchymal transition (EMT) which is essential for metastatic features like migration and invasion[26]. Paul *et al*[27] analyzed the derivatives of hispolons for NF-κβ by *In Silico* access of protein dynamics. Hispolon derivatives like methyl-hispolon exhibited profound anti-proliferative effects in estrogen-sensitive breast cancer cells through inhibition of oncogenic signals such as Ras, API, ERα, C-myc, and cyclinDl, besides their gene transcription.

Table 2: Natural sources of hispolon – types of mushrooms

Source – common name	Part used – Fruiting body	Reference
Inonotushispidus - shaggy bracket mushroom		Ali *et al.*[5]
Phellinus Ignatius- Willow bracket mushroom		Mo *et al.*[6]
Phellinus merrillii- Sangwhang mushroom		Chang *et al.*[7]
Phellinus lonicerinus		Wang et al. [8]
Phellinus linteus - black hoof mushroom		Lu *et al.*[9]

Rossia *et al*[28] studied the structure activity relationship (SAR) of hispolon for anti-proliferative action against HCT116 tumor, indicating the significance of the hydrogenation of hispolon bridge. Yun *et al*[29] analyzed the susceptibility of human renal carcinoma cells to hispolon, which was mediated by inducing apoptosis through TNF-related apoptosis-inducing ligand (TRAIL). Hispolon showed a significant impact on prostate cancer cell lines through the arrest of the S phase in the cell cycle, which was prompted by the reduction of cyclin B1, D1, and CDK4 along with overexpression of p21.

Additionally, hispolon caused apoptosis in a dose-response mode in prostate cancer cells (DU145) through the induction of apoptotic Bcl-2 family proteins and loss of MMP, further release of cytochrome c from mitochondria which enhances the caspases eventually triggering cell death[30]. The antitumor mechanism of hispolon has also evidenced the dysregulation of the STAT3 pathway and

potentially inhibited the phosphorylation of STAT3. Overall, the antitumor function of hispolon involved STAT3 through the mitochondrial pathway. Alongside antioxidant property, hispolon exhibited anti-melanoma effect likewise curcumin through the inhibition of Bcl2 and overexpression of Bax further enhancement of caspase 1 and 3, downregulation of mitochondrial complex 1 and 4 activities[31]. Hispolons were also shown to be potent anticancer agents in the management of glioblastoma[32], and prominently inhibited the proliferation of glioblastoma multiforme cells through activation of apoptic cascade such as caspase 3 and 9, and PARP cleavage. Alongside, hispolon abrogated the G2/M phase of the cell cycle through the reduction in the expression of cdc2, cyclin B1, and cdc25c proteins. The anticancer mechanism of hispolon was illustrated in figure 3.

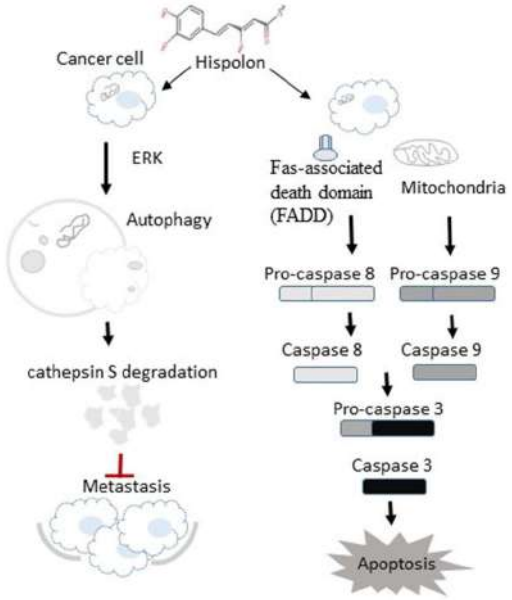


Figure 3: Anticancer mechanism of hispolon

Anti-inflammatory

Severe side effects are associated with the current regime of steroidal and non-steroidal anti-inflammatory drugs. Natural polyphenols are a significant source of anti-inflammatory properties. Hispolon possessed the ability to inhibit the early phase of the inflammation provoked by *Propionibacterium acnes* by abolishing the release of iNOS and COX-2[33]. The bioactive fraction isolated from *Phellinus linteus* that constituted hispolon exhibited an anti-inflammatory effect in macrophages through the reduction of TNFα and NFκB[34]. Data from Yang *et al.*[35] supported the anti-inflammatory activities of hispolon by inhibition of activator protein (AP)-1, c-JNK protein phosphorylation, and NF-κB activation. Hispolon inhibited lipoteichoic acid (LTA) and LPS associated nitric oxide synthase (iNOS) and nitric oxide production with upregulation of heme oxygenase-1(HO-1) in microglial cells. Additionally, hispolon protected the cells from apoptosis caused by LPS and LTA by suppressing caspase-3 and PARP cleavage[36]. Hispolon was suppressed LPS-induced ER stress through upregulation of PERK, CHOP, IRE1, GRP78, ATF6, and Bcl-2 protein expression and downregulation of caspase-3 and Bax[37]. Furthermore, autophagy was triggered by the reduction of Beclin-1 and LC3 II expression, hispolon showed inhibitory effect towards oxidative stress and inflammatory pathways. Together, hispolon could be the potential therapeutic agent in lung inflammation.

Al Saqr *et al.*[38] investigated the synergistic anticancer effects during combinatorial treatment of doxorubicin and hispolon by means of a liposomal method in melanoma cell lines. In this combinational approach, hispolon and doxorubicin improved apoptosis than in distinct treatment. Among various derivates of hispolon, dehydroxyhispolon methyl ether (DHME) exhibited strong anticancer activity in a group of colorectal cancer cell lines[39]. DHME was more effective than hispolon and a selective proapoptic agent through the downregulation of WNT/*β*-catenin signaling pathway.

Antioxidative and Cytoprotective

Polyphenols are well-known antioxidants, contribute significantly to free radical scavenging function, and defend the cells from the harm caused by reactive oxygen species (ROS). Hispolon was reported as hepatoprotectant, which abrogated the damage of the liver by CCl_4. Furthermore, hispolon reduced inflammatory markers like TNF-α, nitric oxide, cyclooxygenase-2 (COX-2), and inducible NO synthase (iNOS). Hispolon was kn[40]own to be a strong antioxidant agent, it has the ability to reduce Dr lipid peroxidation as well as superoxide radicals. Shaikh *et al*[41] synthesized various derivatives of hispolon and studied for their antioxidant properties. Authors confirmed that hispolon was a more potent antioxidant than its derivatives contained structural moiety of pyrazole and isoxazole. Hispolon and its derivatives such as hispolon monomethyl ether, hispolon pyrazole, and hispolon monomethyl ether pyrazole were exhibited antigenotoxic and cytoprotective effects.

Chethna *et al.*[42] proposed that diketo and phenolic groups were critical in protection of cells

and DNA from different toxins. Recently, Kou *et al.*[43] analyzed 14 metabolites isolated from an edible mushroom *Inonotus hispidus*. Among these metabolites, three novel hispolon analogs were identified which collectively processed the inhibitory effect on NO production by LPS stimulated microglial cells through the downregulation of the pathways like NF-κB and TLR-4, and abrogation of inflammatory markers comprising cyclooxygenase-2 (COX-2)and inducible nitric oxide synthase (iNOS). Cooperatively, these metabolites may be a novel source of protecting agents against neurodegenerative conditions. Thimmuri *et al*[44] first time reported the anti-osteoclastogenic effect of hispolon and revealed its mechanism of action. Hispolonreduced the RANKL expression that persuaded the differentiation of RAW 264.7 into osteoclasts, further downregulated the activation of NFkB and MAP kinase pathway. Additionally, hispolon also inhibited the expression of main transcriptional factors NFATc1 and c-FOS, which are necessary for osteoclast differentiation. Chien *et al*[45] suggested that hispolons were cardioprotective, it rescued from balloon injury-madeneointimal hyperplasia by reducing VSMC proliferation and migration, short of prompting apoptosis.

Antimicrobial

Drug resistance developed by microorganisms like pathogenic bacteria and viruses is a biggest threat and creating pandemics to the world. In this scenario, searching for novel and safe antimicrobials is always a need in drug discovery. Apart from other biological activities, natural polyphenols also possessed potential antimicrobial activities. The phenolic compounds such as hispolon and hispidin isolated from the mushroom *Inonotushispidus*and tested for their antiviral activity towards Influenza viruses[46]. A set of hispolon analogs was synthesized and tested against a strain (H37Rv) *Mycobacterium tuberculosis* for their antitubercular activities[47]. Among the hispolon analogs, a derivative of dihydrohispolon was more potent and displayed synergism with other drugs including ciprofloxacin and rifampicin. Replacement of bioisosteric of 1,3-diketo scaffold in hispolons with isoxazole or pyrazole rings exhibited potent anti-tuberculosis molecules[48]. Along with antituberculosis activity, hispolon and its derivatives exhibited broad-spectrum antimicrobial potency against different bacteria and fungi[49]. The emergence of drug resistance in different microorganisms alarmed the importance of new antibiotics like hispolon.

Metabolic disorders

Diabetes mellitusis one of the biggest hurdles among metabolic disorders due to the poor current lifestyle. The evolving metabolic targets like aldose reductase and α-glucosidase are crucial for the management of patients with compromised glucose metabolism in diabetes[50]. Hispidin, hispolon, and inotilone were identified from the ethanolic extract of *Phellinus merrilliiand* showed inhibitory activity towards α-glucosidase and aldose reductase[51]. It proved hispolon has the potential for diabetic management.

Immunomodulators

Immunomodulators are significantly helped to maintain the health of immune cells and balance the immunity, mainly helpful in the management of patients with organ/tissue transplantation. Majority of current immunomodulators belong to the class of monoclonal antibodies and small molecules, but adverse effect associated with these agents limited the usage and encouraged the search for safe natural products. Hispidin and hispolon isolated from *Inonotus hispidus*were showed interference with the role of various immune cells, moreover possessed immunomodulatory function[52].

Moreover, all the hispolon group compounds are well related to curcuminoids as per structural relevance and these curcuminoids have lot of commercial importance[53]. So, improvement of more structural analogs and studies on biological activities to hispolon skeletal compounds may also lead to provide a prominent drug candidate.

Conclusion

In conclusion, natural polyphenols like hispolon are small molecules with significant potentiality in various biological activities. So far, hispolon was demonstrated as an anticancer agent in various cancers especially in breast cancers due to their anti-estrogenic perspective. Different oncogenic pathways were vulnerable to hispolon and furthermore possessed the anti-metastatic ability. As hispolon targets various immune-oncogenic pathways, it could be a promising and attractive scaffold for the management of autoimmune diseases. Moreover, the antioxidant nature of hispolon protects the cells from drug-associated toxicities. Additionally, hispolon possessed anti-inflammatory activities through the inhibition of pro-inflammatory cytokines. Antibacterial activities of hispolon towards the strains of *M. tuberculosis* proved its broad spectrum of biological activities. This review suggests that hispolon has substantial efficacy for pharmaceutical applications.

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Conflict of interest

There are no conflicts of interest.

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References

1. Cragg, G.M.; Newman, D.J. *Biochim. Biophys. Acta*, **2013**, *1830(6)*, 3670. DOI: 10.1016/j.bbagen.2013.02.008
2. Atanasov, A.G.; Waltenberger, B.; Pferschy-Wenzig, E.M.; Linder, T.; Wawrosch, C.; Uhrin, P.; Temml, V.; Wang, L.; Schwaiger, S.; Heiss, E.H.; Rollinger, J.M.; Schuster, D.; Breuss, J.M.; Bochkov, V.; Mihovilovic, M.D.; Kopp, B.; Bauer, R., Dirsch, V.M.; Stuppner, H. *Biotechnol. Adv.,* **2015**, *33(8)*, 1582. DOI:https://doi.org/10.1016/j.biotechadv.2015.08.001
3. Lee, I.K.; Yun, B.S. *J. Antibiot. (Tokyo),* **2011**, *64(5)*, 349. DOI: 10.1038/ja.2011.2
4. Chethna, P.; Iyer, S.S.; Gandhi, V.V.; Kunwar, A.; Singh, B.G.; Barik, A.; Balaji, N.V.; Ramani, M.V.; Subbaraju, G.V.; Priyadarsini, K.I.. *ACS Omega*, **2018**, 30, 5958. DOI: 10.1021/acsomega.8b00415.
5. Ali, N.A.A.; Jansen, R.; Pilgrim, H.; Liberra, K.; Lindequist, U. *Phytochemistry*, **1996**, *41*, 927. DOI: 10.1016/0031-9422(95)00717-2.
6. Mo, S.; Wang, S.; Zhou, G.; Yang, Y.; Li, Y.;Chen, X.; Shi, J.; Phelligridins, C.-F. *J. Nat. Prod.,* **2004**, *67(5)*, 823. DOI: 10.1021/np030505d.
7. Chang, H.Y.; Peng, W.H.; Sheu, M.J.; Huang, G.J.; Tseng, M.C.; Lai, M.T.; Ho, Y.L.; Chang, Y.S. *Am. J. Chin. Med.,* **2007,** *35(5)*, 793. DOI: 10.1142/S0192415X07005272.
8. Wang, J.; Hu, F.; Luo, Y.; Luo, H.; Huang, N.; Cheng, F.; Deng, Z.; Deng, W.; Zou, K. *Fitoterapia,* **2014**, 95, 93. DOI:10.1016/j.fitote.2014.03.007
9. Lu, T.L.; Huang, G.J.; Lu, T.J.; Wu, J.B.; Wu, C.H.; Yang, T.C.; Iizuka, A.; Chen, Y.F. *Food Chem. Toxicol.*, **2009**, *47(8)*, 2013. DOI:10.101/j.fct.2009.05.023
10. Paul, M.; Kumar, Panda.; M., Thatoi, H. *J. Biomol. Struct. Dyn*., **2019**, *37(15)*, 3947. DOI:10.1080/07391102.2018.1532321.
11. Huang, G.J.; Yang, C.M.; Chang, Y.S.; Amagaya, S.; Wang, H.C.; Hou, W.C.; Huang, S.S.; Hu, M.L. *J. Agric. Food Chem.,* **2010**, *58(17),* 9468. DOI: https://doi.org/10.1021/jf101508r
12. Hsiao, P.C.; Hsieh, Y.H.; Chow, J.M.; Yang, S.F.; Hsiao, M.; Hua, K.T.; Lin, C.H.; Chen, H.Y.; Chien, M.H. *J. Agric. Food Chem*., **2013**, 61, 10063.
13. Wu, Q.; Kang, Y.; Zhang, H.; Wang, H.; Liu,Y.; Wang, J. *BiochemBiophys Res Commun.,* **2014**, *453(3)*, 385. DOI:10.1016/j.bbrc.2014.09.098
14. Chen, Y.C.; Chang, H.Y.; Deng, J.S.; Chen, J.J.; Huang, S.S.; Lin, I.H.; Kuo, W.L.; Chao, W.; Huang, G.J. *Am. J. Chin. Med.,* **2013**, *41(6)*, 1439. DOI:10.1142/S0192415X13500961
15. Chen, Y.S.; Lee, S.M.; Lin, C.C.; Liu, C.Y. *Int. J. Mol. Sci.,***2014**, 15, 1201.
16. Wang, J.; Hu, F.; Luo, Y.; Luo, H.; Huang, N.; Cheng, F.; Deng, Z.; Deng, W.; Zou, K. *Fitoterapia,* **2014**, 95, 93. DOI:10.1016/j.fitote.2014.03.00
17. Balaji, N.V.; Ramani, M.V.; Viana, A.G.; Sanglard, L.P.; White, J.; Mulabagal, V.; Lee, C.; Gana, T.J.; Egiebor, N.O.; Subbaraju. G.V.; Tiwari, A.K.*Bioorg Med Chem.*, **2015**, *23(9)*, 2148. DOI: 10.1016/j.bmc.2015.03.002
18. Jang, E.H.; Jang, S.Y.; Cho, I.H.; Hong, D.; Jung, B.; Park, M.J.; Kim, J.H. *Biochem. Biophys. Res. Commun.,* **2015**, *463(4),* 917. DOI: 10.1016/j.bbrc.2015.06.035
19. Sun, Y.S.; Zhao, Z.; Zhu, H.P. *Oncol Lett.*, **2015**, *10(1),* 536. DOI: 10.3892/ol.2015.3220
20. Zhao, Z.; Sun, Y.S.; Chen, W.; Li, L.X.; Li, Y.Q. *Oncol. Rep*., **2016**, *35(2)*, 896. DOI:10.3892/or.2015.4445
21. Kim, J.H.; Kim, Y.C.; Park, B. *Oncol. Rep*., **2016**, *35(2)*, 1020. DOI: https://doi.org/10.3892/or.2015.4440
22. Ho, H.Y.; Ho, Y.C.; Hsieh, M.J.; Yang, S.F.; Chuang, C.Y.; Lin, C.W.; Hsin, C.H. *Environ. Toxicol.*, **2017**, *32(2)*, 645. DOI: 10.1002/tox.22266
23. Wang, J.; Chen, B.; Hu, F.; Zou, X.; Yu, H.; Wang, J.; Zhang, H.; He, H.; Huang, W. *Int. J.*

Med., **2017**, *19(3)*, 233. DOI:10.1615/IntJMedMushrooms.v19.i3.50
24. Arcella, A.; Oliva, M.A.; Sanchez, M.; Staffieri, S.; Esposito, V.; Giangaspero, F.; Cantore, G. *Environ. Toxicol.*, **2017**, *32(9)*, 2113. DOI:10.1002/tox.22419
25. Hsin, M.C.; Hsieh, Y.H.; Wang, P.H.; Ko, J.L.; Hsin, I.L.; Yang, S.F. *Cell Death Dis.*, **2017**, 8, 3089. DOI:https://doi.org/10.1038/cddis.2017.459
26. Hong, D.; Park, M.J.; Jang, E.H.; Jung, B.; Kim, N. J.; Kim, J.H. *Oncol Lett.*, **2017**, *14(4)*, 4866. DOI:10.3892/ol.2017.6789
27. Paul, M.; Kumar Panda, M.; Thatoi, H.*J. Biomol. Struct. Dyn*. **2019**, *37(15)*, 3947. DOI:10.1080/07391102.2018.1532321
28. Rossia, M.; Carusoa, F.; Costanzinia, I.; Kloera, C.; Sulovaria, A.; Montic, E.; Gariboldic, M.; Marrasc, E.; Balajid, N.V.; Ramanid, M.V.; Subbaraju, G.V. *Bioorg. Med. Chem.*, **2019**, *27(17)*, 3805. DOI:10.1016/j.bmc.2019.07.008
29. Yun, J.M.; Min, K.J.; Kwon, T.K. *J Cancer Prev.*, **2019**, *24(3)*, 155. DOI: 10.15430/JCP.2019.24.3.155
30. Masood, M.; Rasul, A.; Sarfraz, I.; Jabeen, F.; Liu, S.; Liu, X.; Wei, W.; Li, J.; Li, X. *Pak. J. Pharm. Sci.*, **2019**, *32(5)*, 2237.
31. Al Saqr A.; Aldawsari, M.F.; Alrbyawi. H.; Poudel, I.; Annaji, M.; Mulabagal, V.; Ramani, M.V.; Gottumukkala, S.; Tiwari, A.K.; Dhanasekaran, M.; Panizzi, P.R.; Arnold, R.D.; Babu, R.J. *AAPS PharmSciTech.*,**2020**, *21(8)*, 304. DOI: 10.1208/s12249-020-01846-2.
32. Liao, K.F.; Chiu, T.L.; Chang, S.F.; Wang, M.J.;Chiu, S.C. *Molecules*, **2021**, *26(15)*, 4497. DOI:10.3390/molecules26154497
33. Tsai, H.H.; Lee, W.R.; Wang, P.H.; Cheng, K.T.; Chen, Y.C.; Shen, S.C. *J Dermatol Sci.*, **2013**, *69(2)*, 122. DOI: 10.1016/j.jdermsci.2012.10.009
34. Lin, C.J.; Lien, H.M.; Chang, H.Y.; Huang, C.L.; Liu, J.J.; Chang, Y.C.; Chen, C.C.; Lai, C.H. *J. Biosci. Bioeng*., **2014**, *118(1)*, 88. DOI:10.1016/j.jbiosc.2014.01.001
35. Yang, J.; Nie, J.; Ma, X.; Wei, Y.; Peng, Y.; Wei, X. *Mol. Canc.*, **2019**, *18(1)*, 26. DOI: 10.1186/s12943-019-0954-x
36. Wu, Q.; Kang, Y.; Zhang, H.; Wang, H.; Liu, Y.; Wang, J. *Biochem. Biophys. Res. Commun.*, **2014**, *453(3)*, 385. DOI:10.1016/j.bbrc.2014.09.098
37. Huang, C.Y.; Deng, J.S.; Huang, W.C.; Jiang, W.P.; Huang, G.J.*Nutrients*, **2020**, *12(6)*, 1742. DOI:10.3390/nu12061742
38. Al Saqr, A.; Majrashi, M.; Alrbyawi, H.; Govindarajulu, M.; Fujihashi, A.; Gottumukkala, S.; Poudel, I.; Arnold, R.D.; Babu, R.J.; Dhanasekaran, M. *Life Sci.*, **2020**, *256*, 117702. DOI: 10.1016/j.lfs.2020.117702
39. Fan, H.C.; Hsieh, Y.C.; Li, L.H.; Chang, C.C.; Janoušková, K.; Ramani, M.V.; Subbaraju, G.V.; Cheng, K.T.; Chang, C.C. *Int J Mol Sci.*, **2020**, *21(22)*, 8839. DOI: 10.3390/ijms21228839.
40. Huang, G.J.; Deng, J.S.; Chiu, C.S.; Liao, J.C.; Hsieh, W.T.; Sheu, M.J.; Wu, C.H. *Altern. Med.,* **2012**, 480714. DOI:10.1155/2012/480714
41. Shaikh, S.A.; Barik, A.; Singh, B.G.; Modukuri, R.V.; Balaji, N.V.; Subbaraju, G.V.; Naik, D.B.; Priyadarsini, K.I. *Free Radic Res.*, **2016**, *50(12)*, 1361. DOI:10.1080/10715762.2016.1247955
42. Chethna, P.; Iyer, S.S.; Gandhi, V.V.; Kunwar, A.; Singh, B.G.; Barik, A.; Balaji, N.V.;Ramani, M.V.; Subbaraju, G.V.; Priyadarsini, K.I. *ACS Omega.*, **2018**, *3(6)*, 5958. DOI: 10.1021/acsomega.8b00415
43. Kou, R.W.; Du, S.T.; Xia, B.; Zhang, Q.; Yin, X.; Gao, J.M.*J Agric Food Chem.*,**2021**, *69(2)*, 668. DOI: 10.1021/acs.jafc.0c0682243.
44. Thimmuri, D.; Khan, A.; Gawali, B.; Rajdev,B.; Adhikari, C.; Sharma, P.; Naidu, V. *Immunol Lett.*, **2021**, *231*, 35. DOI: 10.1016/j.imlet.2021.01.003
45. Chien, Y.C.; Huang, G.J.; Cheng, H.C.; Wu, C.H.; Sheu, M.J. *J Nat Prod.*, **2012**, *75(9)*, 1524. DOI: 10.1021/np3002145
46. Awadh Ali, N.A.; Mothana, R.A.; Lesnau, A.; Pilgrim, H.; Lindequist, U. *Fitoterapia*., **2003**, *74(5)*, 483. DOI: 10.1016/s0367-326x(03)00119-9
47. Balaji, N.V.; Hari Babu, B.; Subbaraju, G.V.; PurnaNagasree, K.; Murali Krishna Kumar, M.. *Bioorg Med Chem Lett.*, **2017**, *27(1)*, 11. DOI:10.1016/j.bmcl.2016.11.047
48. Balaji, N.V.; HariBabu, B.; Rao, V. U.; Subbaraju, G.V.; Nagasree, K.P.; Kumar, M.M.K. *Curr Top Med Chem.*, **2019**, *19(9)*, 662. DOI:10.2174/1568026619666190305124954
49. Raju, P.V.S.N.; Saketi, J.M.R.; Balaji, N.V.; Kurmarayuni, C.M.; Subbaraju, G.V.; Hari Babu, B.*J. Mex. Chem. Soc.*, **2021**, *65(2)*, 237. DOI: 10.29356/jmcs.v65i2.1458.

50. Grewal, A.S.; Bhardwaj, S.; Pandita, D.; Lather, V.; Sekhon, B.S. *Mini Rev. Med. Chem.*, **2016**, *16(2)*, 120. DOI:10.2174/1389557515666150909143737.
51. Huang, G.J.; Hsieh, W.T.; Chang, H.Y.; Huang, S.S.; Lin, Y.C.; Kuo, Y.H. *J. Agric. Food Chem.*, **2011**, *59(10)*, 5702. DOI:10.1021/jf2003943
52. Grundemann, C.; Arnhold, M.; Meier, S.;Backer, C.; Garcia-Kaufer, M.; Grunewald, F.; Steinborn, C.; Klemd, A.M.; Wille, R.; Huber, R.; Lindequist, U. *Planta Med.*, **2016**, *82(15)*, 1359. DOI:10.1055/s-0042-111693.
53. Balaji, N.; Mohan, K. C.; Babu, A.V.; Bollikolla, H. B. *Caribbean Journal of Sciences and Technology (CJST)*, **2017**, *5*(1), 80.