Piperine: A Mini Review on its Pharmacological Profile and Synthetic Derivatives

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Abstract: Piperine, known for its vast biological profile, is obtained from black pepper (*Piper nigrum*, Family*: Piperaceae*) which is one of the most commonly used spice in major parts of the world and is known for its pungent taste. Piperine is also found to act as an important bioenhancer by increasing the bioavailability of drug molecules and reducing their dosing frequency and dosage. This review article aims at providing various biological activities exhibited by piperine and its numerous synthetic derivatives in order to get some potential lead molecule for future drug discovery.

Keywords: Piperine, Piper Nigrum, Piper longa, Anticancer, Antibacterial, Bioenhancer

1. Introduction

Discovery of pharmacologically active constituents from natural sources has been used throughout the world as significant approaches for the generation of lead molecules. Modifications of these lead structures could yield optimized potential molecules with a diverse activity profile. Spices holds an important position by getting not only used as flavoring agents but also as medicinally active molecules. Among all spices, black pepper (*Piper nigrum*, family *Piperaceae*) is a well-known characteristic spice which is also known as king of spices and finds use in Indian and Chinese traditional therapies (Chopra et al., 2016; Parasarathy et al., 2008). It was first isolated in the year 1819 by Hans Christian Ørsted as a yellow crystalline product which later on identified structurally as (*2E,4E*)-5-(benzo[d] [1,3] dioxol-5-yl)1-(piperidin-1-yl) penta-2,4-dien-1-one. Black pepper contains alkaloid Piperine as one of its most active constituents that gives it a pungent flavour along-with several volatile and essential oils (Pruthi, 19999). Other alkaloids present in black pepper were later identified as Piperanine, Piperettine, Piperylin, Piperolein and Pipericine (Tiwari et al., 2020). The concentration of piperine basically varies from 2% to 7.4% and can show variations by changing climatic conditions for cultivation, drying and source of origin (Sozi et al., 2012). Piperine basically exist in its various isomeric forms like *trans-trans* isomer (piperine), *cis-trans* isomer (isopiperine), *cis-cis* isomer (chavine) and *trans-cis* isomer (isochavine) (Figure 1 & 2) (Ravindran, 2000). These isomeric forms (conversion of piperine to other isomers) are brought about by light-induced isomerization and the extent of isomerization depends on intensity of light and its exposure (Kozukue et al., 2007).

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Piperine has displayed a vast biological profile which includes anti-cancer (Ferreira et al., 2020), anti-alzheimer (Yang et al., 2021), anti-parkinsonian (Wang et al., 2020), anti-filarial (Joardar et al., 2021), anti-leishmanial (Ferreira et al., 2011), trypnocidal (Da Silva et al., 2008), larvicidal (Tantawy et al., 2020), anti-inflammatory (Shahbazi et al., 2020), anti-convulsant (Khom et al., 2013), MAO inhibition (Chavarria et al., 2020), carbonic anhydrase inhibition (Elimam et al., 2021), anti-bacterial (Shivahsanmugam and Velmathi, 2022) and blood brain barrier permeation enhancer (Eigenmann et al., 2016) (Figure 3).

Piperine is found to acts as a bioenhancer by enhancing the absorption and bioavailability of certain therapeutic agents without getting involved in the said activity. Their mode of action as bioenhancer can be same or different. In this review article, we tried to focus on piperine and its synthetic derivatives as strong therapeutic potential agents and also to generate some lead molecules which can be explored in the near future as medicinal agents that are more efficacious with reduced toxicity profile. The patents on piperine are mentioned in Table 1.

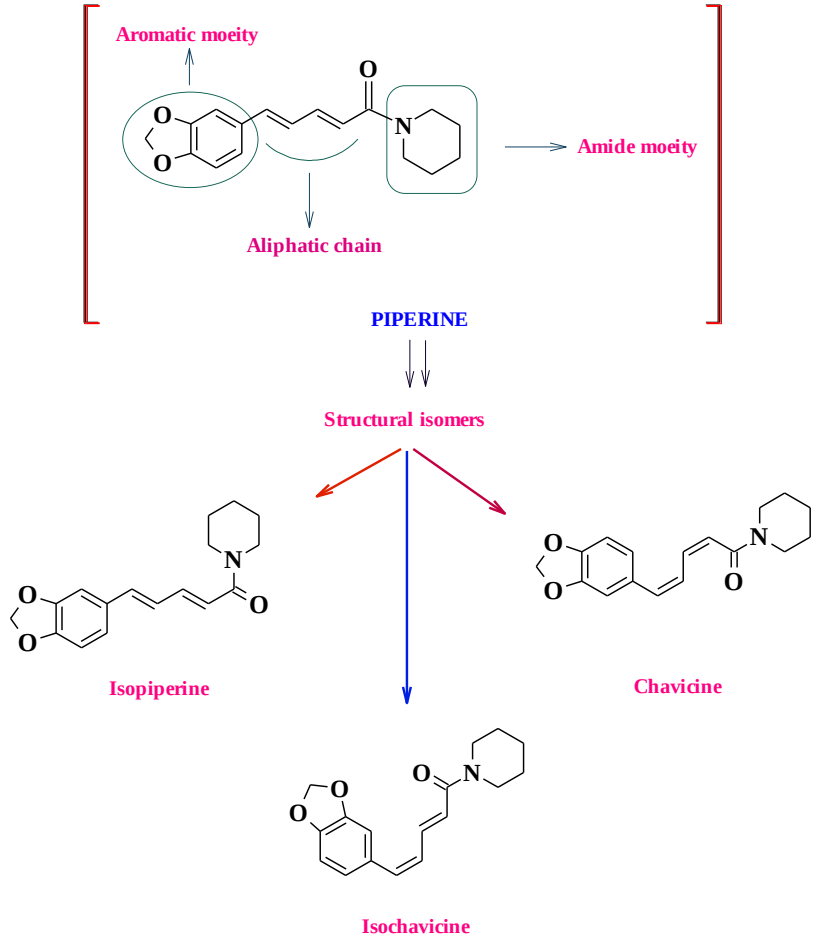


Figure 1: Piperine and its structural isomers.

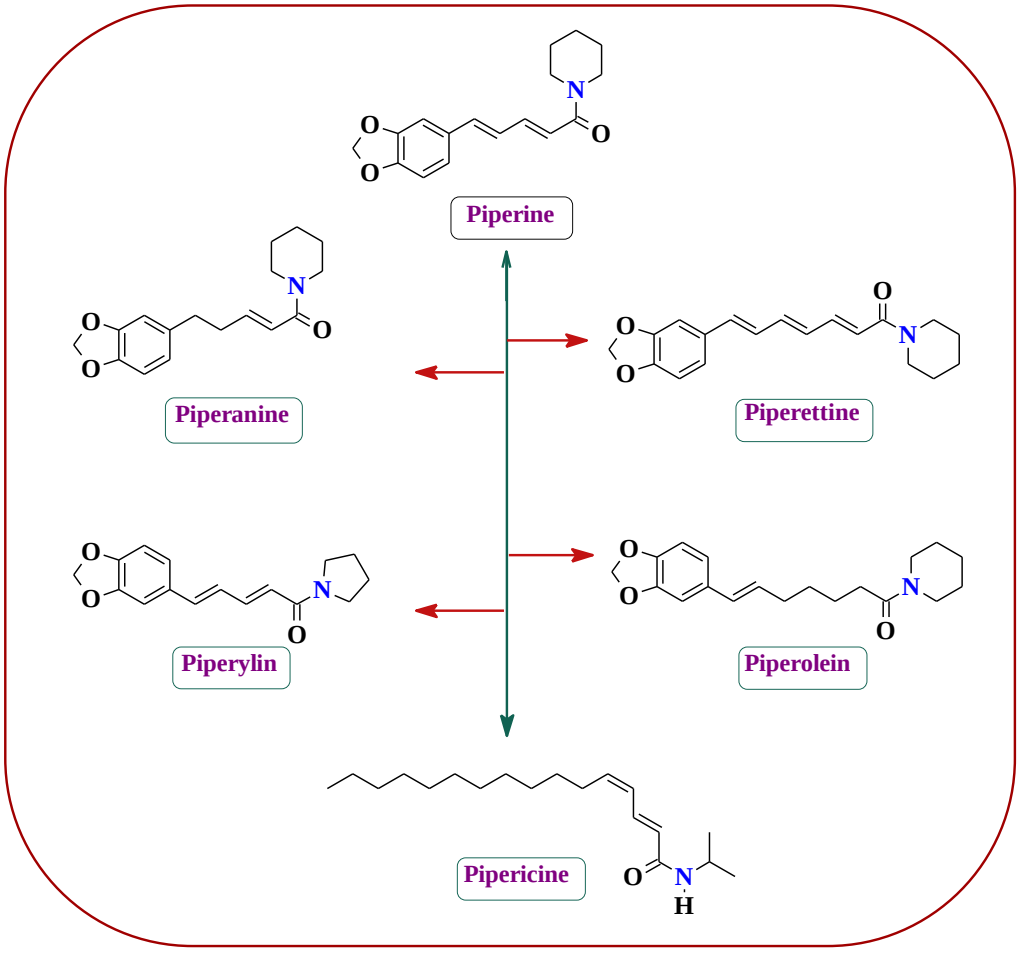


Figure 2: Piperine and other alkaloids present in black pepper.

Table 1: Patents on piperine.

S.No.	Patent no.	Patent date	Inventors	Description
1	WO2019073491 A1 (Phull et al., 2019)	18 April 2019	Manjinder Singh Phull, Dharmaraj Ramachandra Rao, Geena Malhotra, Dilip Ramdas Birari, Sachin Vasant Desai	Process for the preparation of piperine.
2	CA 2735844 (Amala and Zhixiu., 2013)	01 October 2013	Raman Amala, Lin Zhixiu	Use of Piperine and Analogues Thereof in the Prevention of Skin Cancer.
3	WO2003010159 A8 (Domany et al., 2004)	12 February 2004	Gyoergy Domany, Csilla Horvath, Sandor Farkas, Szalai Gizella Bartane, Jozsef Nagy, Sandor Kolok, Bozo Eva Kovacsne, Istvan Borza, Istvan Vago, Attila	Piperidine derivatives as nmda receptor antagonists.

			Bielik, Szendrei Gyoergyi Ignaczne, Gyoergy Keseru	
4	US6054585A (Majeed and Badmaev, 2000)	25 April 2000	Muhammed Majeed, Vladimir Badmaev	Process for making high purity piperine for nutritional use.
5	US5744161A (Majeed et al., 1988)	28 April 1998	Muhammed Majeed, Vladimir Badmaev, Ramaswamy Rajendran	Use of piperine as a bioavailability enhancer.

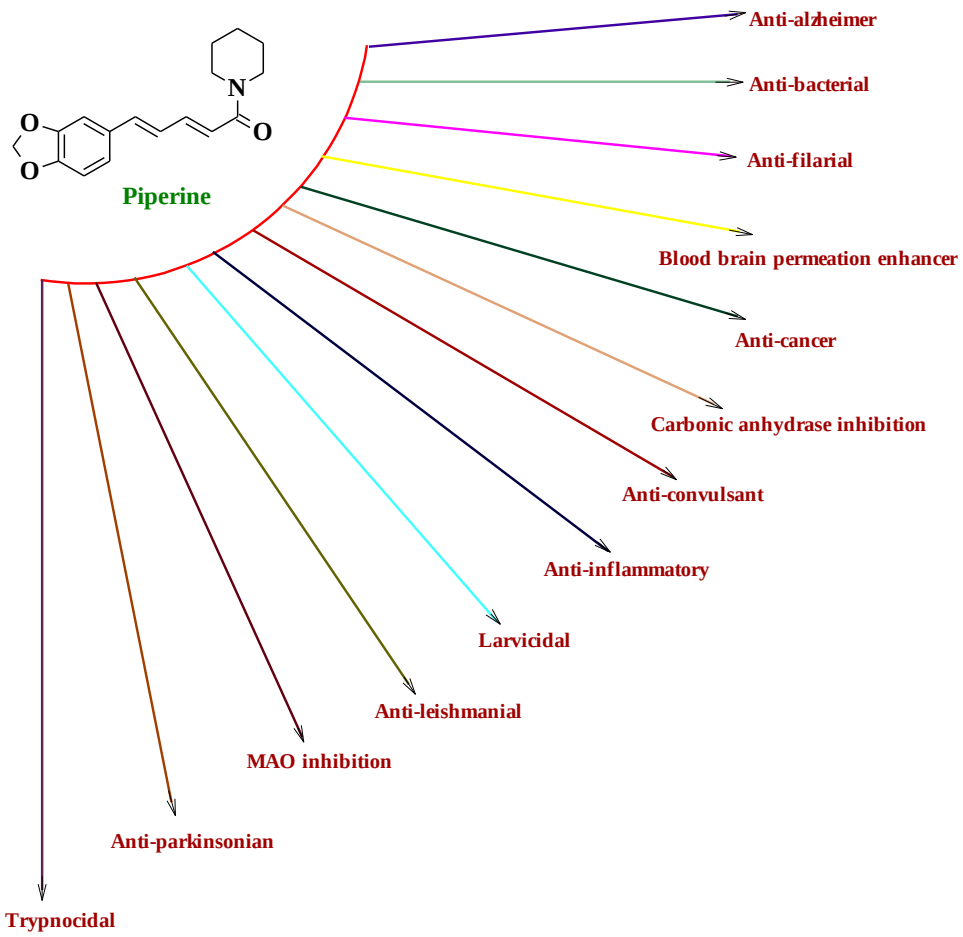


Figure 3: Pharmacological profile of piperine.

2. Pharmacological Profile of Piperine

2.1 Anti-alzheimer Activity

Yang et al. (2021) have reported a piperine derivative (1) N-(2-(7-fluorobenzo[d]oxazol-5-yl)-2-oxoethyl) morpholine-4-carboxamide and evaluated it for the inhibition of neuroinflammation (induced by Aβ1-42) and oxidative damage (via Keap1-Nrf2-TXNIP axis). The compound exhibited neuroprotective results in SH-SY5Y cells and experimental rats by reduction in apoptosis, neuroinflammation and oxidative stress mainly associated with Aβ1-42 and also inhibited formation of Keap1-Nrf2 complex. Yang et al. (2022) have synthesized a novel piperine derivative (2) 2-(4-

chlorobenzo[d]oxazol-6-yl)-N-(2-oxo-2-(piperidin-1-yl) ethyl) acetamide and assessed it for its binding ability to keap-1 (Kelch-like ECH associated protein), activation of keap-1-Nrf2 signaling pathway and investigation of its beneficial effects on Ibotenic acid (IBO) induced neurological disorders in rats. Compound 2 effectively ameliorated cognitive impairment (IBO-induced) in Morris water maze, Y maze and significantly inhibited apoptotic cell death (IBO-induced) to attenuate neuronal morphological changes and cholinergic dysfunction. It also inhibited keap-1-Nrf2 interaction, followed by upregulation of expression of nuclear Nrf2 leading to inhibition of oxidation stress and TXNIP mediated NLRP3 activation of inflammasome (Figure 4).

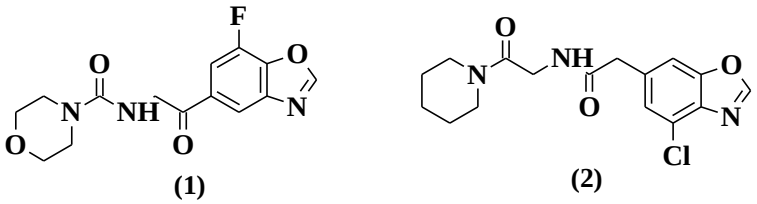


Figure 4: Piperine derivatives showing anti-alzheimer activity.

2.2 Anti-bacterial Activity

Shivahsanmugam and Velmathi (2022) have synthesized a series of piperic amide analogues and evaluated them for their anti-bacterial potential against E. coli, A. baumannii, S. aureus, E. faecalis and S. epidermidis. Compound 3 (trimethyl piperic amide analogue) and 4 (p-nitro piperic amide analogue) were found to be exceptionally active and showed the susceptibility to various strains as follows: S. epidermidis> S. aureus= A. baumannii> E. faecalis> E. coli (Figure 5).

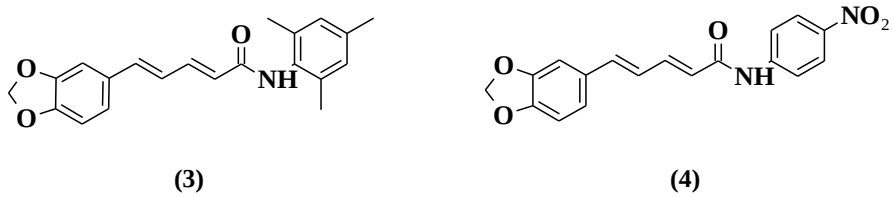


Figure 5: Piperine derivatives showing anti-bacterial activity.

2.3 Anti-filarial Activity

Joardar et al. (2021) have synthesized novel piperine derivatives and evaluated them for anti-filarial (macrofilaricidal & microfilaricidal) activity against Setarai cervi. Compound 5 showed highest efficacy amongst all synthesized derivatives in a time and dose dependent manner against all developmental stages of filarial worm with MIC of 3.05 ± 1.07µg/ml, IC50 of 6.09 ± 1.45µg/ml and LC50 of 24.38 ± 2.69µg/ml for macrofilaricidal activity and MIC of 1.58 ± 1.07µg/ml, IC50 of 3.25 ± 1.45µg/ml and LC50 of 15.68 ± 1.02µg/ml for microfilaricidal activity (Figure 6).

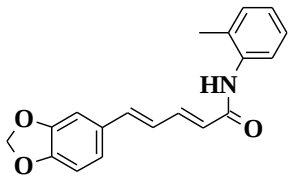
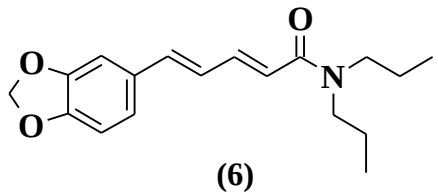


Figure 6: Piperine derivatives showing anti-filarial activity.

2.4 Blood Brain Barrier Permeability Enhancer

Eigenmann et al. (2016) have evaluated various piperine analogues for their blood brain barrier permeability using three models i.e. human model with immortalized hBMEC cells, human brain like endothelial cells model and a primary animal model. UHPLC-MS/MS methods were developed and permeability coefficients were evaluated. Compound 6 showed highest potential for blood brain barrier permeation (Figure 7).



(6)

Figure 7: Piperine derivatives showing blood brain permeation enhancing activity.

2.5 Anti-cancer Activity

Ferreira et al. (2020) have synthesized several piperine analogues and evaluated them for toxicity (in zebra fish and mice) and anti-tumor potential (Ehrlich ascites carcinoma model in mice). Compound 7 (butyl-4-(4-nitrobenzoate)-piperinoate) showed not only reduced toxicity (LC50 > 100µg/ml and LD50≥ 1000mg/kg), but also displayed significant anti-tumor activity by modulating tumor micro-environment. It showed significant decrease in cell viability in Ehrlich tumor model with reduction in peritumoral micro vessels density and enhanced ROS production (Figure 8).

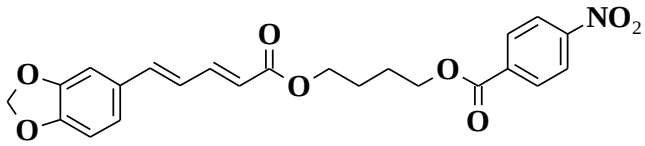


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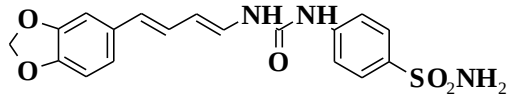
Figure 8: Piperine derivatives showing anti-cancer activity.

2.6 Carbonic Anhydrase Inhibition

Elimam et al. (2021) have reported a series of piperine analogues and evaluated them for carbonic anhydrase inhibition against four human (h) CA Isoforms-I, II, IX & XII. Compound 8 and 9 as para-regioisomers appeared as most potential inhibitors against hCA II (kIs= 93.4 & 88.6 nM), hCA IX (kIs= 38.7 & 68.2 nM) and hCA XII (kIs= 57.5 & 45.6 nM respectively) (Figure 9).



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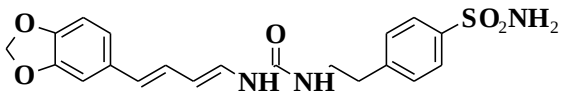


(9)

Figure 9: Piperine derivatives showing carbonic anhydrase inhibition activity.

2.7 Anti-Convulsion Activity

Khom et al. (2013) have reported a piperine derivative (10) ((2E,4E)-5-(1,3-benzodioxol-5-yl))-N,N-diisobutyl-2,4-pentadienamide) and assessed for its action on GABAA (gamma amino butyric acid) and TRPV1 (transient receptor potential vanilloid-1) receptors. GABA modulation was determined using GABAA induced chloride channels and activation of TRPV-1 was evaluated using microelectrode voltage clamp technique and fast perfusion. Compound 10 have effectively brought down the interaction with TRPV-1 receptors, heightened GABAA modulation and induced γ2 subunit dependence in comparison to piperine. Compound 10 may be considered as an important scaffold for novel GABAA receptor modulators along with anxiolytic and anticonvulsant activity

Wimmer et al. (2015) have synthesized a series of piperine derivatives through Heck cross coupling reactions of conjugated dienamides and evaluated them GABAA (gamma amino butyric acid) and TRPV1 (transient receptor potential vanilloid-1) receptors modulation. Compound 11 showed significant GABAA modulation (970 ± 244%) whereas compound 12 showed enhanced TRPV-1 modulation (88 ± 22%) (Figure 10).

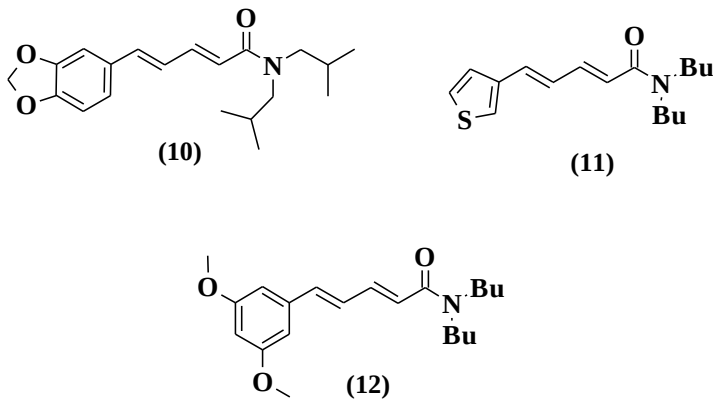


Figure 10: Piperine derivatives showing anti-convulsant activity.

2.8 Anti-Inflammatory Activity

Shahbazi et al. (2020) have developed a novel piperine derivative 13 (((2E,4E)-5-(benzo[d] [1,3] dioxol-5-yl)-N-(4-(hydroxymethyl) phenyl) penta-2,4-dienamide and evaluated them for anti-inflammatory potential against CHME3 and SVG cell lines which corresponds to human microglia and astrocytes. Results revealed that compound 13 significantly inhibited NF-kB translocation pathway and brought down levels of pro-inflammatory cytokines in comparison to aspirin. It also showed excellent oral bioavailability and high anti-neuroinflammatory potential. Ali et al. (2015) have synthesized novel piperine based triazole derivatives using click chemistry approach and assessed for in vivo anti-inflammatory potential. Compound 14 (80.40% inhibition) and 15 (76.71% inhibition) showed significant inhibition in comparison to piperine which showed 54.72% inhibition and reference drug indomethacin which showed 77.02% inhibition (Figure 11).

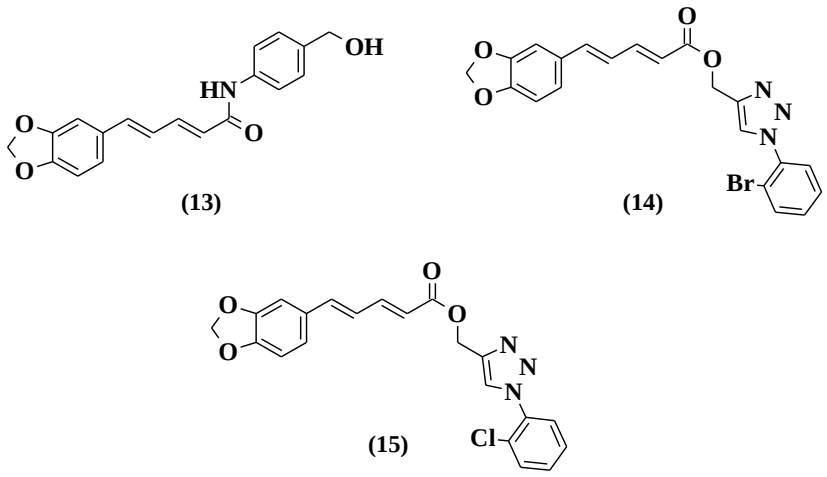


Figure 11: Piperine derivatives showing anti-inflammatory activity.

2.9 Larvicidal Activity

Tantawy et al. (2020) have designed and synthesized a series of piperine-dienehydrazide derivatives and evaluated them for their insecticidal potential against Culex pipiens (at third-instar larval stage) at 0.1-1.2 mg/mL concentration. Among all synthesized derivatives; compound 16 displayed significant insecticidal potential with a mortality rate of 80-80.33% at a concentration of 0.75 mg/mL after 48 hrs of treatment and a LC50 values of 0.221-0.094 mg/mL (Figure 12).

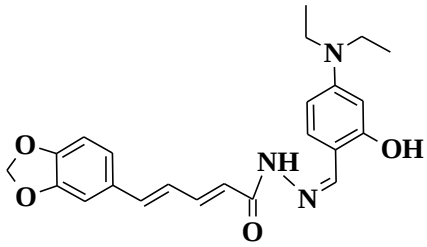


Figure 12: Piperine derivatives showing larvicidal activity.

2.10 Anti-leishmanial Activity

Ferreira et al. (2011) have reported some piperine derivatives and analogues and assessed them for leishmanicidal potential on Leishmania amazonensis. Compound 17 was found to be active against promastigotes and amastigotes in infected macrophages. It also affected the cell cycle of promastigote with an increased G1 phase and reduction in S phase. Their toxicity to macrophages was determined by XTT (sodium2,3-(bis(2-methoxy-4-nitro-sulfophenyl)-5-[(phenylamino)-carbonyl]-2H-tetrazolium inner salt), Trypan blue exclusion and phagocytosis assays and was found to be non-toxic at a concentration of 50 μM. Compound 17 showed 83% inhibition of leishmaniasis after 48 hrs of treatment (Figure 13).

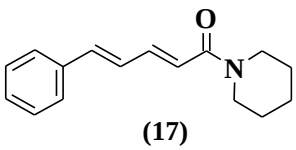
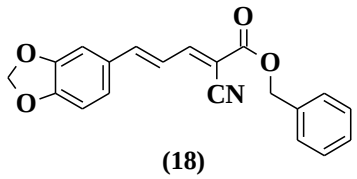


Figure 13: Piperine derivatives showing anti-leishmanial activity.

2.11 MAO Inhibitors

Chavarria et al. (2020) have designed and synthesized a library of various piperine derivatives and evaluated them for inhibition of human MAO (monoamine oxidase) isoforms (hMAO-A and hMAO-B) to get effective anti-parkinsonian agents. Compound 18 with an α-cyano group and benzyl ester appeared as the most potential and competitive hMAO-B inhibitor with an IC50 value of 47.4 nM. Also, at a concentration of 10 μM, compound 18 significantly decreased P-gp efflux in Caco-2 cells (Figure 14).

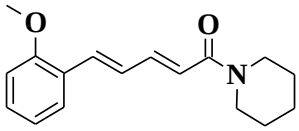


(18)

Figure 14: Piperine derivatives showing MAO inhibitory activity.

2.12 Anti-parkinsonian Activity

Wang et al. (2020) have reported several piperine analogues and evaluated them for their neuroprotective effects hydrogen peroxide damage in PC12 cells. Compound 19 exhibited most potential neuroprotection and its ROS scavenging and cytoprotection is might be due to Nrf2 activation and upregulation of phase-II antioxidant enzymes like HO-1 and NQO1. At a dose of 100 mg/kg, compound 19 attenuated Parkinson diseases associated behavioral deficits (Figure 15).

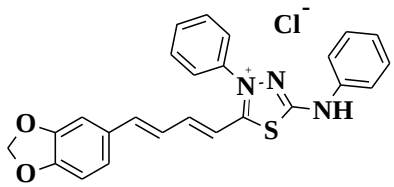


(19)

Figure 15: Piperine derivatives showing anti-parkinsonian activity.

2.13 Trypnocidal Activity

Da Silva et al. (2008) have synthesized and characterized mesoionic 1,3,4-thaidiazolium-2-phenylamine chloride derivatives of piperine and assessed them for trypnocidal activity against Trypanosoma cruzi and host murine macrophage cells. Compound 20 showed most potent activity (Figure 16).



(20)

Figure 16: Piperine derivatives showing trypnocidal activity.

3. Conclusion

Natural products are an important source of molecules for rapid drug discovery to find newer/ novel chemical entities. Black pepper (Piper nigrum and Piper longum) as an important source of piperine plays an essential role as a bioenhancer by increasing the bioavailability, reducing the therapeutic dose as well as dosing frequency and minimizing the side effects and toxicity of the concerned drug molecule. Also, its vast pharmacological profile makes it effective in variety of diseases. This scaffold can further be explored in the synthesis of its various derivative with enhanced efficacy and potency and can prove to be a landmark in the process of drug discovery.

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